STRIDER Canada: A Randomized Controlled Trial of **S**ildenafil **T**herapy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction

Version: 2.3
Date: November 20, 2015

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STRIDER CANADA STUDY PROTOCOL DETAILS

PROTOCOL DETAILS

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

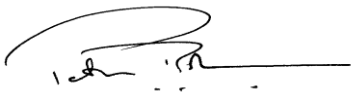
Short study title: **STRIDER Canada**

University if British Columbia REB Reference Number: H15-00899
Clinicaltrials.gov Number: NCT02442492

Sponsor(s): Funding for this study is provided by **Canadian Institutes of Health Research** (CIHR) to the University of British Columbia; Vancouver, BC, Canada, V6T 1Z3

INVESTIGATOR DECLARATIONS

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

Investigator Signature:  **Date: May 01, 2015**

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This trial will be conducted in accordance with the Health Canada Division 5 - Drugs For Clinical Trials Involving Human Subjects.

Current Protocol Version: 2.3

Current Protocol Date: November 20, 2015

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Document History

Document	Date of Issue	Summary of Change
Original protocol	May 01, 2015	Not applicable
Protocol version 2.0	June 21, 2015	• Added clinicaltrials.gov number • Reformatted/reworded inclusion/exclusion criteria • Added more details for safety information for sildenafil in section 4.3 • Added additional information to recruitment section 7 • Updated the Table 4 to highlight any interventions that will be different from standard care as a result of participating in the study. • Added section11.8 on bio-banking • Deleted section 13.5 on observation group • Added additional information on power calculation for section 14
Protocol version 2.1	August 05, 2015	• Moved inclusion criteria question related to EFW <700g from checkbox option to yes/no option. • Updated Table 1 to reword the inclusion/exclusion criteria for Canada so that it matches the protocol
Protocol version 2.2	September 16, 2015	• Updated contact information for Drs. Peter von Dadelszen and Laura Magee • Corrected typographical error on Table 1 for NZ/Australia
Protocol version 2.3	November 20, 2015	• Typographical error under section 12 “Safety Assessment and Monitoring”, pg 45. Combined two sentences and deleted word “not”. Revised bullet point is: Maternal prolonged hospital stay antenatal or post-natal related to the diagnosis of IUGR

TRIAL SYNOPSIS

FULL TITLE OF STUDY:	**STRIDER Canada**: A Randomized Controlled Trial of **S**ildenafil **T**herapy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction
SHORT TITLE:	STRIDER: Sildenafil for Early-Onset IUGR
TRIAL ACRONYM:	STRIDER Canada
PROTOCOL NUMBER:	STRCA15
CLINICAL TRIALS.GOV ID:	NCT02442492

BACKGROUND: Early-onset placental intrauterine growth restriction (EO IUGR) is associated with a high risk of perinatal morbidity and mortality. In association with reduced circulating placental growth factor (PLGF) EO IUGR results from abnormal placentation with inadequate remodelling of the maternal uteroplacental arteries. There is no known treatment for placental IUGR. Management involves intensive fetal surveillance with delivery with evidence of serious fetal compromise. However, remote from term, delivery is associated with significant perinatal mortality and morbidity. Sildenafil vasodilates the uteroplacental vessels of IUGR-affected pregnancies and may represent a novel therapy. Sildenafil has been used in pregnant women with pulmonary artery hypertension without adverse events, and has a good fetal safety profile from animal studies and a randomised controlled trial (RCT) of 17 women who received sildenafil (18 placebo-treated; non-significant increase in median birth weight of 367g after median 4.5d). We used sildenafil in a cohort of 12 women with severe EO IUGR as compassionate therapy. Compared with 17 sildenafil-naïve EO IUGR pregnancies, sildenafil appeared to improve daily fetal growth velocity (92% vs 41%, Fisher's p=0.008; OR 16 [95% CI 2, 151]) and were more frequently live born (75% vs 35%, p=0.042, OR 6 [1.1, 28])). *Therefore*, there are sufficient data to support an RCT. We will target the fetus as patient.

STRIDER Canada is one of a consortium of STRIDER randomised controlled trials (RCTs) each of which is designed to determine whether or not maternal treatment with sildenafil citrate improves markers of perinatal wellbeing.

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

PRIMARY OUTCOME: The primary outcome will compare the gestational age at delivery (d) between sildenafil- and placebo-treated groups.

SECONDARY OUTCOMES: Will sildenafil (vs. placebo) increase (or decrease) the likelihood of

i) live birth
ii) Survival to hospital discharge
iii) intact survival (defined as survival to EDD without evidence of severe central nervous system [CNS] injury [by ultrasound and/or magnetic resonance imaging (MRI)])
iv) combined non-CNS severe morbidity (one/more of bronchopulmonary dysplasia, ≥grade 3 retinopathy of prematurity, or necrotising enterocolitis)

OTHER OUTCOMES

Maternal

i) Symptomatic hypotension symptoms;
ii) uterine artery Doppler indices
iii) maternal plasma PLGF
iv) pregnancy outcomes

Perinatal

i) fetal growth velocity
ii) fetal Doppler
iii) Amniotic fluid
iv) Fetal heart rate indices

TRIAL DESIGN: STRIDER Canada is designed as investigator-initiated double-blind, randomised placebo-controlled trial of 90 women with a diagnosis of early-onset intrauterine growth restriction with an intention-to-treat analysis.

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

All legally adult women with a diagnosis of a pregnancy affected by early-onset IUGR between 18^{+0} and 27^{+6} weeks of gestation will be considered for randomisation.

Inclusion criteria

- Maternal age of 18 years or older
- Singleton pregnancy between 18^{+0} and 27^{+6} weeks of gestation age
- ultrasound (U/S) estimate of fetal weight (EFW) <700g
- E O IUGR, defined as at least ONE of following:
    - U/S measurement of the fetal abdominal circumference (AC) <10^{th} percentile for gestational age
    - reduced fetal growth velocity (AC interval growth less than 50% of expected) & abnormal uterine artery waveform
    - reduced fetal growth velocity (AC interval growth less than 50% of expected) & a prior pregnancy with EO IUGR with adverse perinatal outcome
- Serum PLGF < 5^{th} percentile for gestational age
- a clinical decision to manage expectantly

Exclusion criteria

- Prior participation in a STRIDER trial
- Decision made to terminate pregnancy
- Maternal
    - Pre-eclampsia or gestational hypertension (current pregnancy)
    - HIV positive status
    - Significant maternal heart disease
    - Current prescription or illicit drug therapy

- Receiving Prazosin or another peripheral alpha-blocker
- Treatment with Nitrates
- Current Cocaine, crystal meth or another vasoconstrictor use

  - Allergy to sildenafil or another contraindication not listed above

- Fetal

  - Aneuploidy
  - Anomaly/syndrome/congenital infection confirmed at the time of enrolment

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 British Columbia and Child and Family Research Institute (CFRI), Vancouver, Canada and conducted in hospitals across Canada. 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 18^{+0} and 27^{+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**	90
NUMBER OF CENTRES	MAX 25	**PLANNED TRIAL START:**	September 2015
PLANNED DATE OF LAST PATIENT ENROLMENT:	June 2019	**PLANNED DATE OF LAST OUTCOME:**	December 2019

TRIAL SCHEMATIC

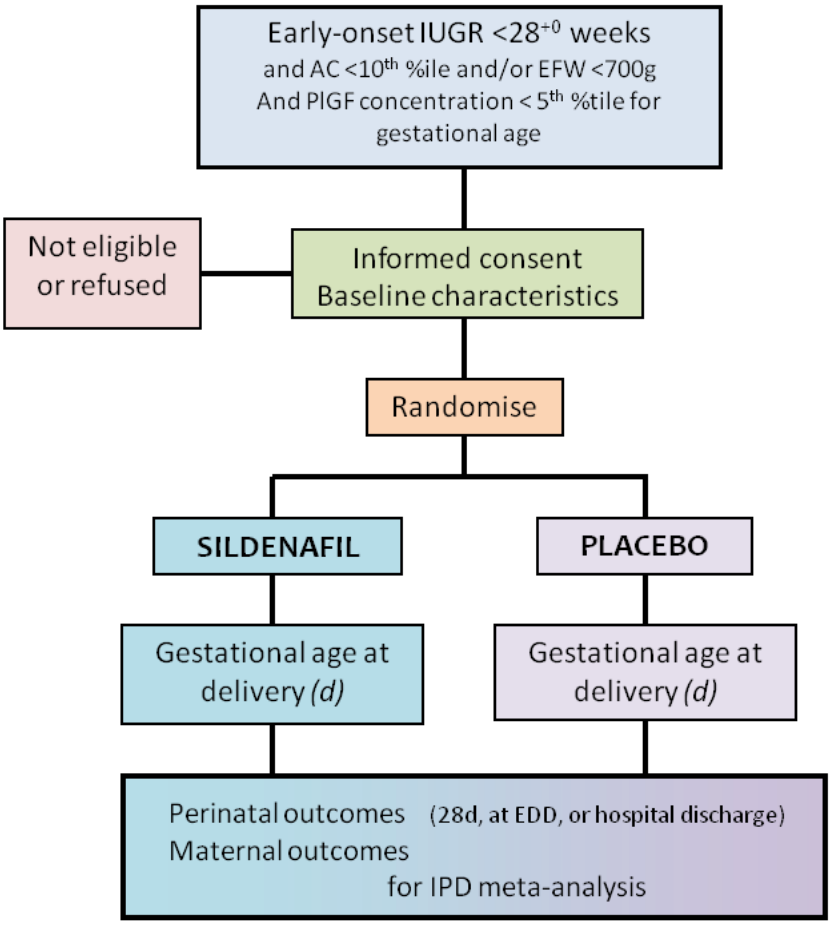


Figure 1: STRIDER Canada CONSORT diagram

AC, abdominal circumference; **d**, days; **EDD**, expected date of delivery; **EFW**, estimated fetal weight; **IPD**, individual patient data; **IUGR**, intrauterine growth restriction; **PLGF**, placental growth factor

ACCRONYMS & ABBREVIATIONS

Early-Onset	EO
Abdominal Circumference	AC
Adverse Event	AE
Alanine Transaminase	ALT
Amniotic Fluid Index	AFI
Angiotensin Converting Enzyme	ACE
Aspartate Transaminase	AST
BC Women's	BCW
Biparietal Diameter	BPD
Blood Pressure	BP
Canadian HIV Trials Network	CTN
Canadian Institute of Health Research	CIHR
Canadian Perinatal Network	CPN
Cardiotocography	CTG
Case Report Form	CRF
Central Nervous System	CNS
Centre for Health Evaluation And Outcome Sciences	CHÉOS
Child and Family Research Institute	CFRI
Cytochrome P450	CYP
Data Safety Monitoring Board	DSMB
Date of Birth	DOB
decidual Natural Killer Cells	dNK
Deepest Vertical Pool	DVP
Ductus Venosus	DVP
Electronic Case Report Form	eCRF
End Diastolic Flow	EDF
Estimate of Fetal Weight	EFW
Evaluating Maternal Markers Of Adverse Placental Outcomes	EMMA
Expected Date of Delivery	EDD
Extravillous Trophoblast	EVT
Femur Length	FL
Gestational Age	GA
Global Obstetric Network	GONet
Good Clinical Practice	GCP
Head Circumference	HC
Human Immunodeficiency Virus	HIV
In Vitro Fertilization	IVF
Individual Patient Data	IPD
Intrauterine Growth Restriction	IUGR
Last Menstrual Period	LMP
Magnetic Resonance Imaging	MRI

Middle Cerebral Artery	MCA
Millimetres of Mercury	mmHg
Neonatal Intensive Care Unit	NICU
New York Heart Association	NYHA
Nitrous Oxide	NO
Nonarteritic Anterior Ischemic Optic Neuropathy	NAION
Paper Case Report Form	pCRF
Participant Symptom Diary	PSD
Persistent Pulmonary Hypertension of The Newborn	PPHN
Phosphodiesterase-5	PDE-5
Placental Growth Factor	PLGF
Pre-Eclampsia & Eclampsia Monitoring, Prevention & Treatment Clinical Trials Unit	PRE-EMPT CTU
Principal Investigator	PI
Provincial Health Services Authority	PHSA
Randomised Controlled Trial	RCT
Randomization And Study Drug Allocation Website	RAW
Research Electronic Data Capture	REDCap
Republic of Ireland	Eire
Research Ethics Board	REB
Reversed Umbilical Arterial End Diastolic Flow	REDF
Standard Deviation	sd
Serious Adverse Event	SAE
Serious Adverse Reaction	SAR
Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction	STRIDER
Site Master Files	SMF
Small-For-Gestational Age	SGA
Society of Obstetricians and Gynaecologists of Canada	SOGC
Therapeutic Abortion	TA
Three Times Daily	tds
Ultrasound	U/S
Umbilical Artery	UmAD
University of British Columbia	UBC
Uterine Artery	UtAD

1. INTRODUCTION

1.1 Background

'Idiopathic' early-onset intrauterine growth restriction (EO IUGR) is associated with a high risk of perinatal morbidity and mortality. The overarching concept underlying the international STRIDER (**S**ildenafil **T**he**R**apy **I**n **D**ismal prognosis **E**arly-onset intrauterine growth **R**estriction) trials initiative is that maternal uteroplacental arterial dilatation with sildenafil citrate will permit recovery of fetal growth velocity for sufficient duration and degree to improve perinatal survival, and increase the quality of that survival. For the international STRIDER consortium (Table 1), our hypothesis is that sildenafil citrate (vs. placebo) therapy will be both more effective (result in fewer fetal/neonatal losses or sick babies), less costly (result in use of fewer health care resources), and safe (minimal maternal and perinatal side effects and risks). We have preliminary clinical data that support this hypothesis (Table 2, Figure 2) [1,2].

STRIDER Canada is one of a consortium of STRIDER randomised controlled trials (RCTs) each of which will be designed to determine whether or not maternal treatment with sildenafil citrate improves markers of perinatal wellbeing (Table 1). The three out of four other STRIDER trials (STRIDER NZAus (ANZCTR: 12612000584831), STRIDER UK (ISRCTN: 39133303), and Dutch STRIDER (EudraCT Number: 2012-004112-63)) have started recruitment and STRIDER Ireland is scheduled to commence recruitment in August/September 2015).

For STRIDER Canada, eligible women will have a pregnancy complicated by i) early-onset IUGR (either an ultrasound measurement of the fetal abdominal circumference (AC) <10th percentile for gestational age and/or documented reduced fetal growth velocity complicating either a pregnancy of a woman with a prior history of early-onset IUGR with adverse perinatal outcome or abnormal uterine artery Doppler in the index pregnancy); ii) ultrasound estimate of fetal weight (EFW) <700g, and iii) low plasma placental growth factor (**PLGF**) concentration[3].

This reflects a new international approach to distribute the funding burden between agencies to derive collectively the data required to address issues of morbidity and mortality. In combination, the international STRIDER consortium will contribute data for a planned individual patient data (IPD) meta-analysis, the primary outcome of which will be survival to the expected date of delivery without adverse perinatal outcomes in pregnancies complicated by severe early-onset IUGR.

The following make the ***STRIDER Canada unique***, and strengthen the international consortium: (i) the lower gestational age for eligibility and (ii) the requirement for low **PLGF** as an entry criterion (Table 1).

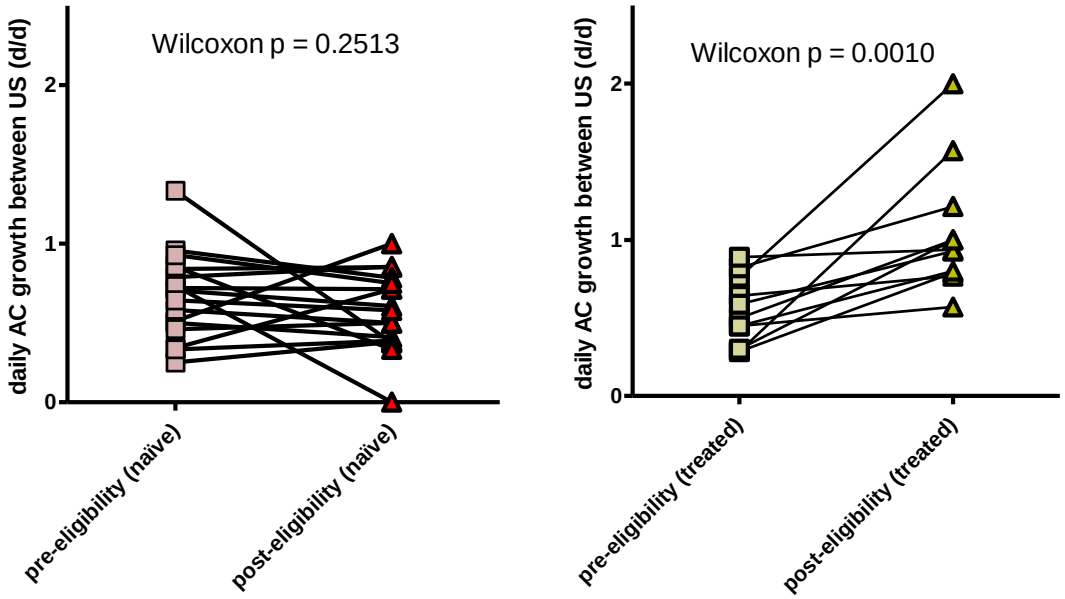
Table 1: Summary of the STRIDER consortium RCTs

	NZ/Australia	UK	Eire	Dutch	Canada
(n)	122	112	104 (aiming to recruit 130 to account for drop-outs)	354	90
Approximate number of centres	10	20	6	10	16
Eligibility criteria	•Singleton pregnancy. •At >22^{+0} - 27^{+6}wk: AC ≤3^{rd} %ile for GA •At 28^{+0} – 30^{+0}wk: U/S EFW <700g.	•Singleton pregnancy with severe, early-onset IUGR, 22^{+0} - 29^{+6}wk **AND** clinical decision to manage expectantly •IUGR defined as EFW **OR** AC <10^{th} centile **AND** absent or reversed EDF in the umbilical artery •Participants aged ≥16yr	•Singleton pregnancy with severe, early-onset IUGR, 22^{+0} - 29^{+6}wk **AND** clinical decision to manage expectantly •IUGR defined as EFW **OR** AC <10^{th} centile **AND** absent or reversed EDF in the umbilical artery •Participants aged ≥16yr	•Singleton pregnancy •20^{+0}-27^{+6}wk •U/S measurement of AC <3^{rd} %ile for GA or an EFW <5^{th} %ile **OR** •28^{+0}-29^{+6}wk •U/S EFW <700g **AND** •Likely placental origin defined by (a AND/OR b AND/OR c AND/OR d) a. the presence of uterine artery notching b. abnormal flow velocity patterns of the umbilical artery or middle cerebral artery c. maternal hypertensive disorders d. low PLGF in point-of-care assessment	•Singleton pregnancy •GA: 18^{+0} - 27^{+6}wk •ultrasound estimate of fetal weight <700g •EO IUGR defined as ((a) either U/S measurement of AC <10^{th} %ile for GA and/or reduced fetal growth velocity (AC interval growth less than 50% of expected) & abnormal uterine artery waveform and/or a prior pregnancy with EO IUGR with adverse perinatal outcome •serum PLGF levels < 5^{th} %tile for gestational age
GA (wk)	22^{+0} – 29^{+6}	22^{+0} – 29^{+6}	22^{+0} – 29^{+6}	20^{+0} – 29^{+6}	18^{+0} – 27^{+6}
GA range for randomisation	22^{+0} – 27^{+6} 28^{+0} – 29^{+6}	-	-	20^{+0} – 27^{+6} 28^{+0} – 29^{+6}	-
Treatment period (last dose)	Until delivery, or **31^{+6}** weeks of gestation, whichever comes first	Until delivery, or **31^{+6}** weeks of gestation, whichever comes first	Until delivery, or **31^{+6}** weeks of gestation, whichever comes first	Until delivery, or **31^{+6}** weeks of gestation, whichever comes first	Until delivery, or **31^{+6}** weeks of gestation, whichever comes first

Stratification criteria	i. Umbilical artery EDF ii. GA range < 24 weeks vs ≥ 24 weeks	i. Centre ii. GA range ($22^{+0} – 25^{+6}$) vs ($26^{+0} – 29^{+6}$)	i. Centre ii. GA range ($22^{+0} – 25^{+6}$) vs ($26^{+0} – 29^{+6}$)	i. Centre	i. Centre
Primary Outcome	Increase in fetal growth velocity determined by AC	Prolongation of pregnancy for one week as a surrogate for long term morbidity	Prolongation of pregnancy for one week as a surrogate for long term morbidity	Intact perinatal survival until term age. This is defined by the survival to term age without evidence of either severe CNS injury or non-CNS severe morbidity	GA at delivery (d)

%ile, percentile; **AC**, abdominal circumference; **CNS**, central nervous system; **EDF**, end diastolic flow; **EFW**, estimated fetal weight; **EO**, early-onset; Eire, Republic of Ireland; **GA**, gestational age; **IUGR**, intrauterine growth restriction; **NZ**, New Zealand; **PLGF**, Placental Growth Factor; **UK**, United Kingdom; **US**, ultrasound

Figure 2: Change in daily AC growth between pre-eligibility and post-eligibility epochs (data from BC Women's cohort[1], adding 2 unpublished cases)



a. Sildenafil-naïve

b. Sildenafil treated

AC, abdominal circumference; **US**, ultrasound

Table 2: Demographics & outcomes (median [interquartile range]) or (n (%))

Data for sildenafil-treated group include 2 unpublished cases managed after published BC Women's cohort

Variable	Sildenafil-naïve (n=17)	Sildenafil-treated (n=13)	P (MWu or Fisher's exact)
Demographics			
Maternal age at EDD (yr)	33 [28, 36.5]	33 [27.5, 38]	1.00
Nulliparous (n (%))	8 (47%)	6 (46%)	1.00
GA at eligibility (days since LMP)	148 [137.5, 163]	158 [148, 165]	0.13
Uterine artery notching at eligibility (n (%))	10 (59%)	11 (85%)	0.23
AC <1st percentile at eligibility (%)	10 (59%)	9 (69%)	0.71
AC discrepancy at eligibility(d) #	21 [11.5, 25]	19 [14.5, 24]	0.87
Umbilical artery Doppler EDF present (n (%))	13 (76%)	6 (46%)	0.26
Amniotic fluid index >50mm (n (%))	15 (88%)	7 (54%)	0.049
Outcomes			
Secondary development of pre-eclampsia (n (%))	5/9 (1 x IUFD)	3/13 (5 x TA)	0.23
Increased AC growth velocity post-eligibility/on Sildenafil	7 (41%)	11 (85%)	***0.026***
Eligibility-to-delivery interval (d)	42 [17, 55]	38 [20.5, 67]	0.90
GA at delivery (days since LMP)	180.5 [165.5, 208]	192 [182.5, 222]	0.13
Live birth (n (%))	6 (35%)*	8 (62%)†	0.23
Survival	6 (35%)*	6 (46%)†	0.71
Intact survival	5 (29%)	6 (46%)	0.45

*5 stillbirths due to late termination; 6 permissive stillbirths (EFW <500g)

† 1 stillbirth occurred within 48h of starting sildenafil (reversed end-diastolic flow on day of prescription), 1 stillbirth occurred during *in utero* transfer to USA (NICU occupancy), 1 permissive stillbirth (EFW <500g); 1 neonatal death due to ELBW (birth weight = 345g; not resuscitated); 1 stillbirth related to concerns about fetal skeletal dysplasia (not confirmed) with late termination; 1 neonatal death due to nosocomial fungaemia at 2 weeks of age

AC discrepancy: GA (by scan-confirmed GA; in days) – equivalent GA of AC at eligibility (50th percentile; in days)

AC, abdominal circumference; **EDF**, end diastolic flow; **EFW**, estimated fetal weight; **GA**, gestational age; **LMP**, last menstrual period (scan-confirmed); **MWu**, Mann-Whitney u test; **TA**, therapeutic abortion

1.2 The problem of severe early-onset IUGR

In the absence of an abnormal fetal karyotype, fetal anomaly, fetal syndrome, or congenital infection, severe early-onset IUGR results from abnormal formation and function of the placenta (placentation) with inadequate remodelling of the maternal spiral (uteroplacental) arteries. Normally, the smooth muscle of these medium-size resistance vessels is 'bored out' by invading trophoblast, but with early-onset IUGR, this process is incomplete (in terms of vessel

numbers and depth of invasion [Figure 3]), leading to ischaemic placental disease[4,5]. Such ischaemic placental diseases, including IUGR, pre-eclampsia, and placental abruption, have been implicated in more than 50% of induced premature birth[6].

Early-onset IUGR complicates approximately 60,000 pregnancies annually in Canada, approximately 0.2% of pregnancies. Although not a common pregnancy complication, the clinical outcome can be devastating. Severe early-onset IUGR increases the risk of perinatal morbidity and mortality, particularly due to premature delivery, both for fetal and for secondary maternal indications such as the development of pre-eclampsia [7-15]. These complications occur more commonly in the face of changing maternal demographics (advanced maternal age) and maternity care (enhanced use of artificial reproductive technologies [e.g. in vitro fertilization and use of donor gametes])[4,5,16-26]. Severe early-onset IUGR is very costly to the health care system and to families.

The effect of severe early-onset IUGR is particularly significant. From the experience at BC Women's Hospital, less than a third of these fetuses, generally born $<30^{+0}$ weeks gestation, will survive their neonatal intensive care unit (NICU) stay (if they are born alive) without significant sequelae (immediate and long term)[27]. Survival rates for severely growth-restricted fetuses remote from term (<28 weeks gestation) are dismal (between 7-33%)[11,12,28,29]. To have at least a 50% chance of intact survival, a newborn must be both 28^{+0} weeks at birth and weigh 700g[30]. Being able to defer delivery until around 30 weeks reduces the mortality risk to around 20%[29], and improves perinatal outcomes[30]. The direct costs of maternal and neonatal care contribute to a vastly disproportionate level of investment in these pregnancies. The direct costs include the increased cost of intensive antenatal surveillance (with or without a period of hospitalization), Caesarean delivery (if live born), NICU care, routine post-NICU follow-up, and, often, specialised neurodevelopmental assessments and interventions. In addition, the indirect costs to families include lost wages, supportive services, and relationship stress.

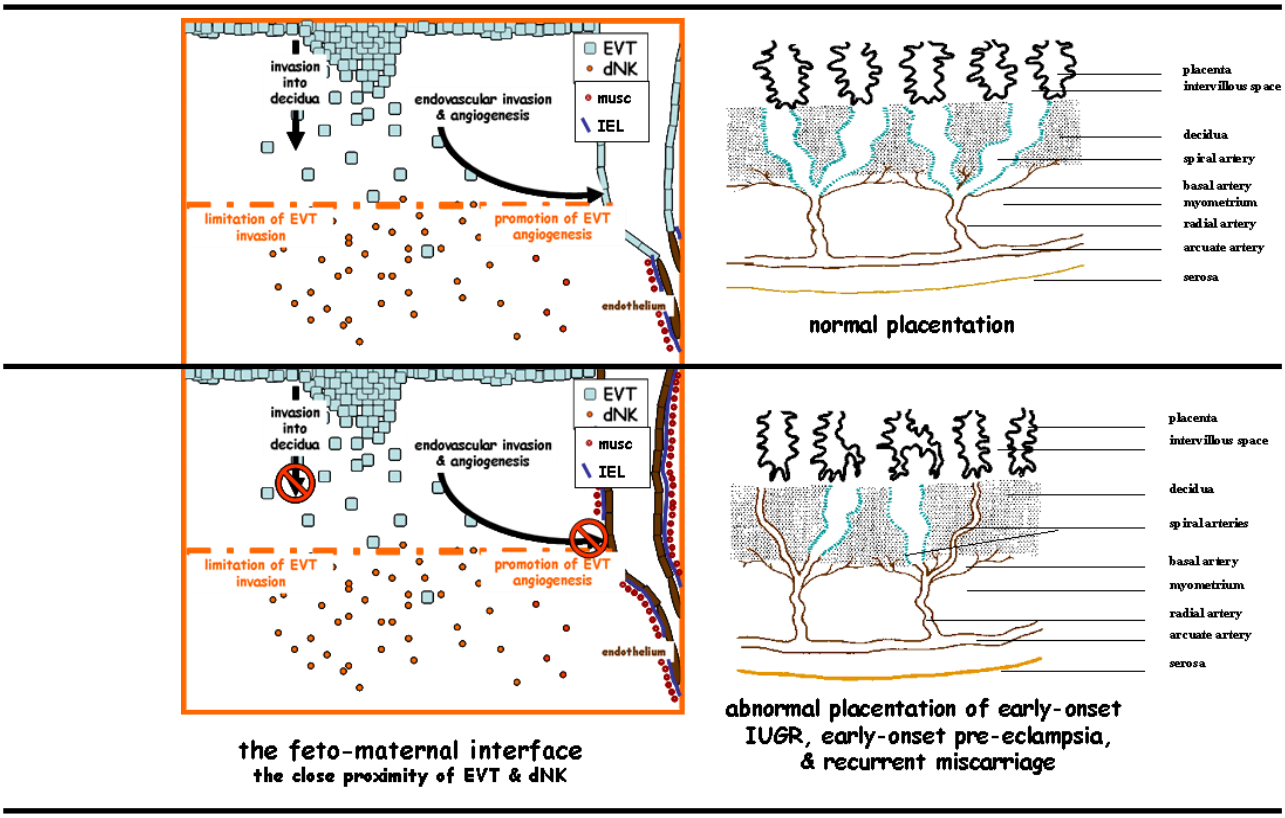
Expectant management and safe pregnancy prolongation is associated with significant societal and financial savings. We hope to determine whether or not sildenafil citrate will increase maternal blood flow to the placenta, allow for pregnancy prolongation and delivery of a baby who is 'less sick' in NICU and suffers fewer complications.

1.2.1 The origin of early-onset IUGR: normal and inadequate placentation problem of severe early-onset IUGR

In the absence of other causes, severe early-onset IUGR results from inadequate remodelling of the uterine spiral arteries that form the placental blood supply. The normal process of human placentation, central to reproductive success, is complex and poorly understood. Inadequate placental invasion has been associated with IUGR, pre-eclampsia, failed *in vitro* fertilization (IVF), and recurrent pregnancy loss[31]. The interaction between maternal immune surveillance by a specific population of natural killer cells, decidual natural killer cells (dNK), and invading fetal cells from the placenta, extravillous trophoblast (EVT), is crucial to successful placentation. We have reviewed the clinical relevance and biology of this relationship[31]. dNK, a distinct population of CD56brightCD16- lymphocytes, are key regulators of placentation. These cells account for more than 40% of cells in the decidua during early pregnancy and are found in direct contact with fetal trophoblast. dNK regulate trophoblast invasion and migration, and are involved in the process of spiral artery remodelling [31]. The process of normal spiral artery remodelling includes the removal of the nitrous oxide (NO)-producing endothelium, the internal elastic lamina and

the NO-responsive muscularis layers to the depth of the inner third of the myometrium (Figure 3).

Figure 3: Placentation



Normal placentation involves the replacement of NO-producing (endothelium) & -responsive (muscularis) elements in the spiral arterial wall across the placental bed. The spiral arteries are the small muscular arteries that regulate endometrial blood flow in non-pregnancy. Abnormal placentation related to poor extravillous trophoblast invasion and arterial remodelling retains both elements of NO-mediated arterial control that would be, and are (*ex vivo*), susceptible to sildenafil therapy.
dNK, decidual natural killer cell; **EVT**, extravillous trophoblast; **IEL**, internal elastic lamina; **musc**, muscularis

The removal of these layers by EVT converts a narrow bore, high resistance, low flow circulation to the wide bore, low resistance, high flow circulation of pregnancy that is unresponsive to normal regional vascular control and is largely modulated through changes in mean arterial pressure and regional blood flow diversion (e.g., to the thighs and buttocks during exercise). When this process is incomplete, then the NO-modulating/ NO-modulated elements of endothelium and muscularis remain partially intact in all vessels and fully intact in some; the intact muscularis and endothelium that will be responsive to an NO donor such as sildenafil.

1.2.2 Using placental growth factor (PLGF) to identify early-onset IUGR of placental origin

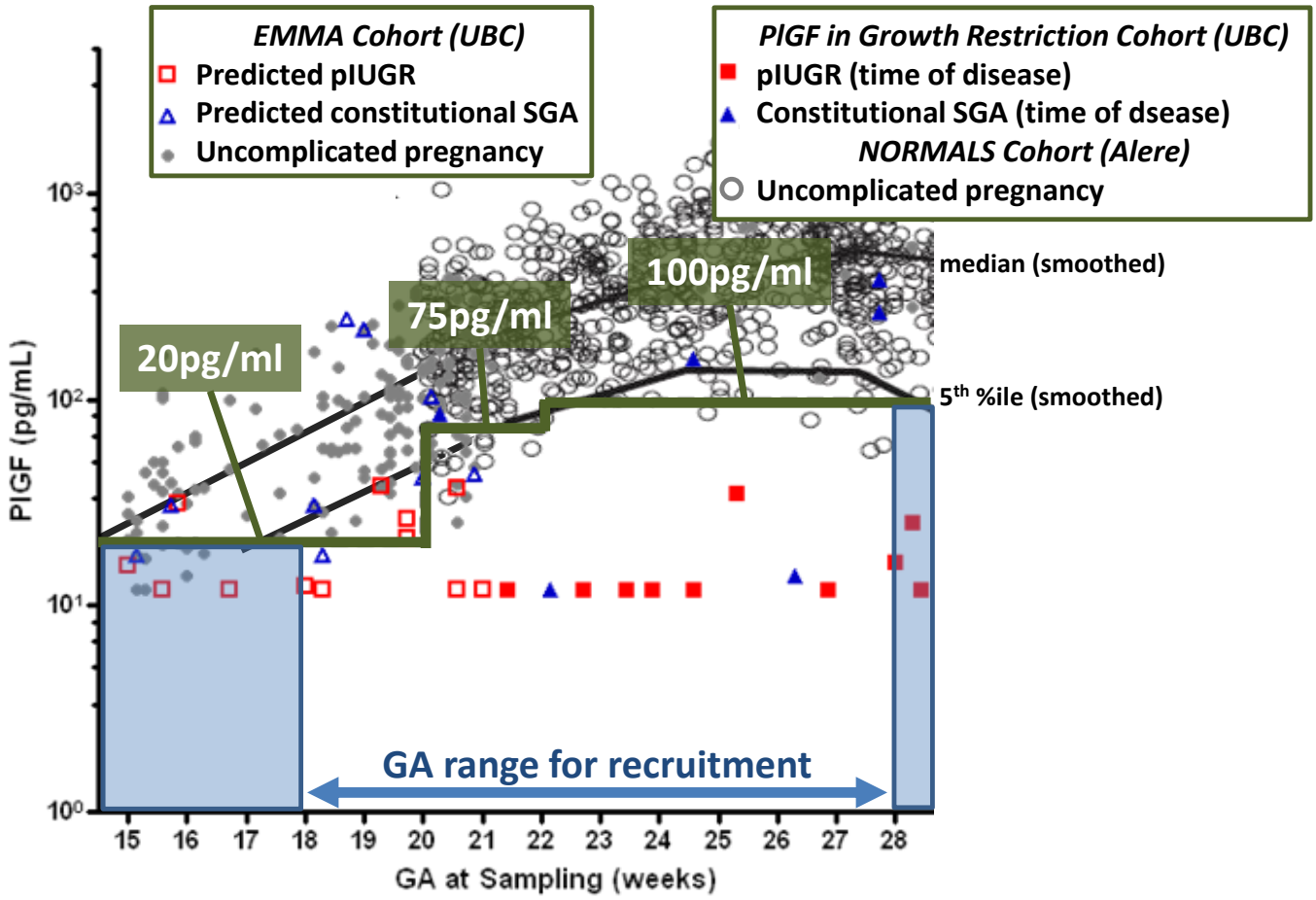
It is possible to discriminate between IUGR resulting from inadequate placentation and that due to normal population spread of fetal growth and birth weights, so-called constitutionally small fetuses[3] (see appended papers). STRIDER Canada is the only trial within the consortium to use

PLGF as an eligibility criterion; all other trials are collecting plasma samples for secondary analysis of PLGF concentrations.

Data from our ongoing CIHR-funded PLGF in Fetal Growth Restriction study in Vancouver, Ottawa and London (UK confirm the findings of our pilot project (Figure 4). In 104 women with an ultrasound estimate of the fetal AC <10th percentile for gestation age (BC Women's criterion for suspected IUGR), a PLGF concentration < 5th centile for gestation age (Alere Triage® point-of-care platform) discriminates between IUGR of placental origin (confirmed histologically) and constitutionally small-for-gestational age (SGA) fetuses (normal placental histology), with a sensitivity of 94% [95% CI 71, 100] and specificity of 67% [46, 83]. In the 32 samples drawn <35 weeks gestation, the sensitivity becomes 93% [68, 100] and specificity 76% [50, 93]. This difference in design adds to the strength of the consortium, and will determine the place of PLGF screening in 'IUGR' pregnancies.

Figure 4: Maternal plasma placental growth factor in normal pregnancy, placental IUGR and constitutional SGA

Data from three sources: Evaluating Maternal Markers of Adverse placental outcomes (EMMA) Clinic



(prediction of disease), ongoing PLGF in Growth Restriction study (time of disease), and NORMALS study (including data from UBC) [32]. Normal range limits derived from combined data for three epochs, ≤19+6 wk (20pg/ml), 20+0-21+6 wk (75pg/ml), and 22+0-34+6 (100pg/ml).

GA, gestational age; **pIUGR**, placental intrauterine growth restriction; **PLGF**, placental growth factor; **SGA**, small-for-gestational age

Published normal ranges for PLGF using the Triage® platform exist to as low as 20 weeks gestation[32]. Using 200 samples from the Canadian Institute of Health Research (CIHR)-funded study in the EMMA (Evaluating Maternal Markers of Adverse placental outcomes) Clinic at BCW, drawn between 15 and 24 weeks in women who went on to have normal pregnancy outcomes, we have derived a normal range against which to identify eligible women for STRIDER Canada of 20 pg/ml up to 19^{+6} weeks, 75pg/ml (20^{+0} - 21^{+6} weeks), with 100 pg/ml being the manufacturer's cut-off between 22^{+0} and 34^{+6} (Figure 4).

Therefore, we believe that we have sufficient evidence to use PLGF as an eligibility criterion for STRIDER as it will identify an enriched cohort of those fetuses most likely to benefit from sildenafil.

1.3 Therapies for early-onset IUGR

There is no proven management strategy for women with severe, early-onset IUGR [4,5]. Women and their families have two standard of care options: (i) pregnancy termination when the perinatal mortality and morbidity risks are unacceptable to the parents; (ii) expectant care, either allowing for permissive stillbirth unless a goal gestational age and estimated fetal weight are achieved, or until maternal/fetal surveillance reveals non-reassuring results that mandate delivery and active resuscitation. There are no evidence-based therapies for early-onset severe IUGR. Relevant systematic reviews are summarised in Section 2.1[33]. For women receiving expectant care, the only therapy used in routine clinical practice is reduced physical activity (including bedrest), although this approach is unproven.

A recent RCT of a less-targetted NO-donor, L-arginine, for the treatment of severe IUGR did not find any beneficial effect on fetal growth velocity[34].

1.4 The rationale for sildenafil use in pregnancy

Sildenafil is a medication that inhibits phosphodiesterase-5 (PDE-5), thereby acting as an NO donor to the muscularis of small arteries. Doppler waveform analysis of pregnancies complicated by IUGR suggests compromised uteroplacental circulation and placental hypoperfusion.

Sildenafil has shown beneficial fetal effects in animal models of IUGR[35-37] (see appended papers). In ex vivo human experiments, sildenafil has shown beneficial direct vascular and immunological effects, including improved endothelial function from women whose pregnancies are complicated by IUGR (see appended papers)[38]. In human pregnancy in vivo, sildenafil improves conception rates in women undergoing IVF[39,40] and may alter NK activity to promote successful pregnancy in women with a history of recurrent miscarriage[41]. In addition to their ex vivo observations in arteries from women with pregnancies complicated by IUGR, Wareing et al examined the arteries of women whose pregnancies were complicated by pre-eclampsia (proteinuric gestational hypertension)[42], and found no vasodilatory effect.

Indications for sildenafil include maternal pulmonary artery hypertension in pregnancy (which has an untreated case-fatality risk of 25% [43]). Sildenafil use in such women has been associated with improved clinical status (New York Heart Association (NYHA) classification and echocardiographic) and delivery of healthy infants (Table 3). In Vancouver, we have an additional single (unpublished) case experience of sildenafil therapy for progressive systemic sclerosis-related pulmonary artery hypertension complicated by IUGR and increasing right heart pressures. Sildenafil effectively reduced pulmonary hypertension, improved NYHA status, and

was associated with improved fetal growth velocity. A healthy, live born infant was delivered by Caesarean section.

Table 3: Sildenafil for pulmonary arterial hypertension in pregnancy

Author	Year	Case report	Indications for therapy	Co-interventions	Outcomes
Lacassie, Germain, Valdés, Fernández, Allamand, López,	2004	Case report	Eisenmenger's syndrome	diltiazem, L-arginine	34 wk Caesarean BW 2.29 kg
Molelekwa, Akhter, McKenna, Bowen, Walsh	2005	Case report	Eisenmenger's syndrome	bosentan	30 wk Caesarean BW: 1.41 kg
Streit, Speich, Fischler, Ulrich	2009	Case report	SLE-related pulmonary hypertension	bosentan, prednisone, hydroxychloroquine, azathioprine, phenprocoumon, inhaled iloprost	37 wk Caesarean BW 2.76 kg

In addition, sildenafil is used safely to treat persistent pulmonary hypertension of the newborn (PPHN)[44]. Sildenafil selectively reduces pulmonary vascular resistance and is a useful therapeutic adjunct for critically ill neonates with PPHN[44]. As many of these infants were born remote from term, the effects of sildenafil exposure data are relevant to STRIDER.

Given the similar primary defect observed in women with IUGR and women with pre-eclampsia (Figure 3), the Manchester, UK, group undertook a study to determine whether or not sildenafil citrate might prolong pregnancy in women with pre-eclampsia (see appended papers)[45]. Thirty-five women with pre-eclampsia (gestational ages 24–34 weeks) were randomly assigned to sildenafil citrate or placebo. Medication was increased every 3 days from 20 mg three times daily (tid), to 40 mg, and 80 mg tid. The primary endpoint was prolongation of pregnancy from randomisation to delivery (days). Details of all adverse events were collected. Plasma samples were taken to establish pharmacokinetic information. Data were analysed on a modified intention-to-treat analysis. The study had a power of >95% to detect a difference of 5 days. Of the 35 women, 17 were allocated to sildenafil and 18 to placebo. There was no difference in time from randomisation to delivery in the two treatment groups, with a median time of 4 days (range 1–15) in the sildenafil group and 4.5 days (range 1–30) in the placebo group. Sildenafil achieved maximum drug concentrations of 48ng/ml, 88ng/ml, and 271ng/ml after 3 days of 20mg, 40mg and 80mg tid, respectively. The median (range) birth weights in the sildenafil- and placebo-treated groups were 1410g (553, 2480) and 1043g (519, 2510), respectively. Sildenafil, in the escalating dose regimen 20–80 mg tid, was well-tolerated, without increased maternal or fetal morbidity or mortality[45].

Within the Provincial Health Services Authority (PHSA), including BC Women's (BCW), we have a process for offering patients innovative therapy through a formal information sharing and consenting process. Through this mechanism, patients facing dire prognoses can be offered innovative therapeutic interventions. Under this rubric, we have included sildenafil in the management of a series of 12 women with severe early-onset IUGR ("Sildenafil-treated"), and, for analytical purposes have compared their outcomes with a series of 17 women who fulfilled

our treatment criteria but either declined or were not offered sildenafil ("Sildenafil-naïve"). We have summarised the demographics and outcomes for both groups in Table 2. The data related to the first 10 treated women and all 17 naïve women have been published (see appended papers)[1].

The women who received sildenafil treatment (25mg tid - the dose proposed for STRIDER Canada and consistent with all other STRIDER trials) tended to have poorer indices of fetal surveillance at baseline in terms of umbilical artery Doppler velocimetry and amniotic fluid indices. Other than one woman who suffered a stillbirth within 48h of commencing sildenafil treatment, all sildenafil-treated fetuses had increased fetal abdominal circumference growth velocity after treatment (odds ratio 12.9 [95% CI 1.3, 126] (Figure 2), and was replicated in a single case from Ottawa where sildenafil was again used as innovative therapy [2]. Sildenafil-treated fetuses tended to be more often live born and to survive intact to primary hospital discharge[1].

Cumulatively, these data provide direct human evidence that sildenafil citrate may offer a potential therapeutic strategy to improve uteroplacental blood flow in IUGR pregnancies; one that may not be present in hypertensive pregnancies.

STRIDER Canada is designed to be the next step in addressing this issue; one that would then contribute to the STRIDER consortium's IPD meta-analysis. We will attempt to maintain contact with the children, and then to secure funding for neurodevelopmental follow-up at 5 years of age.

2. TRIAL RATIONALE AND RISK BENEFIT EVALUATION

Currently, we have no evidence-based therapy to offer these women[4,5]. Our Canadian data have led to an international consortium that has formed to address this therapeutic gap. However, we are aware that sildenafil is being prescribed for this indication in the USA (https://www.inspire.com/groups/preemie/discussion/a-question-for-all-women-who-have-had-iugr-babies/; accessed 28 Aug 2013), an outcome against which we expressly counselled in the BC Women's case series paper[1]. We need an RCT.

In addition, there is an opportunity to join the international STRIDER consortium, and to contribute data to the planned IPD meta-analysis. This activity will be a proof of principle exercise for the Global Obstetric Network (GONet), headed by Dr Ben Willem Mol (lately principle investigator of the Dutch Obstetric Consortium, now in Brisbane, Australia)[46]. GONet, of which Dr Peter von Dadelszen is a steering committee member, is lobbying for a co-funding model for international perinatal trials - through the co-ordinated parallel funding approach taken by the STRIDER consortium, we hope to prove the principle that a single adequately powered trial (as we will achieve through the IPD meta-analysis) will be cost-effective for funding agencies. We do not need to repeat the time, effort and vast expense of the vitamin C and E for pre-eclampsia prevention saga[47-56].

Furthermore, we have real concerns about the prescription of sildenafil for this indication in the USA outside the confines of a clinical trial on the basis of our small case series but without adequate safety and efficacy data.

2.1 Relevant systematic review(s)

There are no reviews of trials of high quality and/or sufficient size to provide evidence-based

guidance for women with severe early-onset IUGR. All relevant Cochrane reviews have been considered.

For relevant maternal interventions and surveillance of placental function and/or fetal well-being that may be useful in pregnancies complicated by severe early-onset IUGR, most published trials have enrolled women with high risk pregnancy of various types, ranging from an increased risk of having a low birth weight baby, pre-eclampsia, to evidence of fetal compromise according to growth or other criteria. Most trials were small, of poor quality, and/or underpowered to comment on substantive perinatal outcomes.

2.2 Maternal interventions

Despite its widespread use among women with IUGR, there is insufficient evidence that bed rest improves perinatal outcome in the setting of IUGR. A single trial (107 women) of low quality for women with suspected IUGR, found that bed rest in hospital vs. ambulatory management did not improve fetal growth parameters or perinatal outcome[57].

There is no good evidence for other non-pharamcological interventions. Abdominal decompression (application of negative pressure to the maternal abdomen) for women in varied clinical circumstances (including fetal compromise) was associated with some improvement in maternal pre-eclampsia, fetal distress in labour, low birth weight, perinatal mortality and low Apgar scores (3 trials of low quality, 367 women)[33]. Abdominal decompression is an intervention of historical interest given the feasibility, of potential interest only in women hospitalised with IUGR. There are no trials of social support for women with early-onset (or any) IUGR, but 18 trials (12,658 women) of good-to-excellent quality found that among women at increased risk of having a low birth weight baby, additional social support did not improve perinatal outcome[58].

There is no pharmacological therapy that has been proven effective. Maternal calcium channel blocker administration has been administered in the hope of vasodilating the abnormally formed uteroplacental circulation; in a single trial (100 women), flunarizine was associated with higher birth weight, but all women were smokers[59]. Maternal nutritional supplementation is without proven benefit in IUGR; maternal oral or intra-amniotic administration (4 trials, 165 women) has shown conflicting results with regards to perinatal outcome[60].

2.3 Placental surveillance

Oestriol assessment in high risk pregnancies was not associated with a reduction in adverse perinatal outcome (1 trial of poor quality, 622 women)[61].

2.4 Fetal surveillance

There is no proven method of fetal surveillance in IUGR, with policies and protocols varying widely and consisting of numerous combinations of difference methods. The evidence does not support use of the biophysical profile (BPP), based on 5 trials (2974 women) of moderate quality in which perinatal outcome was not improved[62]. Non-randomised data suggest that use of BPP may be associated with false re-assurance (i.e., false negatives) in high risk pregnancies, particularly IUGR[63-67].

One trial (167 women) compared two different regimens of fetal surveillance for suspected IUGR but the study was underpowered to find a difference in substantive perinatal outcomes[68].

2.5 How will the results of this trial be used?

STRIDER Canada will answer the question about the relative benefits and risks of sildenafil therapy on the likelihood of improved fetal growth velocity in the setting of severe early-onset IUGR. However, the measurement of AC growth velocity is a surrogate for later pregnancy, perinatal, and neurodevelopmental outcomes. The results of STRIDER Canada will contribute to the planned IPD meta-analysis of data from the Canadian, Australasian, British, Irish and Dutch trials (Table 1). The primary outcome for the IPD meta-analysis will be intact survival at the expected date of delivery (EDD) (see Section 14 & appended paper). STRIDER Canada will add unique data to the IPD meta-analysis by having the lowest gestational age eligibility criterion and by requiring low PLGF as an eligibility criterion.

Ultimately, we aim to determine the short-and intermediate-term perinatal and maternal outcomes following sildenafil therapy in severe early-onset IUGR, and to be in the position to provide evidence-based guidance to women, their families, and their maternity care providers.

3. TRIAL HYPOTHESIS AND OUTCOMES

For STRIDER Canada, the trial-specific hypothesis is that sildenafil therapy will increase the likelihood of increased birth weight for fetuses of pregnancies complicated by severe early-onset IUGR. We will increase the certainty that the severe, early-onset IUGR is placentally-mediated by requiring randomised women to have significantly reduced serum PLGF concentrations using the Alere Triage® platform[3].

3.1 Primary outcome

The primary outcome will compare the gestational age at delivery (d) between sildenafil- and placebo-treated groups. The outcome is clear-cut and adjudication will not be necessary. The unit of analysis will be the fetus; in the unlikely event that a woman with an unknown multiple gestation is enrolled in STRIDER Canada, all babies of that pregnancy will be included in the analyses, correcting and weighting for multiple babies.

3.2 Secondary outcome

Will sildenafil (vs. placebo) increase (or decrease) the likelihood of

1. Live birth
2. Survival to hospital discharge
3. Intact survival (defined as survival to EDD without evidence of severe central nervous system [CNS] injury [by ultrasound and/or magnetic resonance imaging (MRI)])
4. Combined non-CNS severe morbidity (one/more of bronchopulmonary dysplasia requiring supplemental oxygen on hospital discharge, ≥grade 3 retinopathy of prematurity, or necrotising enterocolitis)?

3.3 Other outcomes

3.3.1 Maternal

Symptomatic hypotension, uterine artery Doppler indices; headaches; flushing; pre-eclampsia; mode of delivery; and haemorrhage requiring transfusion.

In addition, we will measure baseline, day 2 post-randomisation and then weekly maternal plasma PLGF. We anticipate higher PLGF (more favourable) concentrations in women in the sildenafil arm of the trial compared with those in the placebo arm.

3.3.2 Perinatal

Fetal growth velocity, fetal Doppler, amniotic fluid and fetal heart indices.

4. TRIAL & DRUG SAFETY

4.1 Risks to the safety of participants involved in the trial

It is anticipated that sildenafil for early-onset IUGR will be well-tolerated by the mother and the fetus/neonate (who may still have the drug in their circulation at birth). When given to mothers for primary pulmonary hypertension in pregnancy, sildenafil was well tolerated by mothers and babies (3 case reports, 1 additional unpublished, Table 3). None of the women treated with sildenafil for severe early onset IUGR at BC Women's complained of side effects. When given to (usually) preterm babies with persistent pulmonary hypertension, sildenafil was well tolerated[44]. Although sildenafil is associated with minor side effects (i.e., headache, visual symptoms, flushing, dyspepsia and nasal congestion) when administered to men with erectile dysfunction[69], pregnant women are already systemically vasodilated and the dose of sildenafil proposed in STRIDER (25mg/dose) is smaller than that used for erectile dysfunction (50-100mg/dose).

Nevertheless, eligibility for sildenafil is based on dismal fetal prognosis, and it is anticipated that despite best efforts, with or without sildenafil, stillbirth will occur and preterm growth-restricted newborns will suffer short- and long-term complications. Whether or not sildenafil can reduce perinatal mortality and morbidity is the question being addressed in STRIDER.

In all participating centres, and women will be approached to give informed consent to participate. All women will receive enhanced antenatal surveillance integral to local protocols. Although no interim analysis is planned in STRIDER Canada, an independent Data Safety Monitoring Board (DSMB) has been set up to review any safety concerns that may arise (Section 12.7).

4.2 Potential risks of sildenafil treatment

The primary risk of sildenafil treatment is that it will work and, therefore, that more babies will survive to face significant, life-altering, complications of prematurity. Such complications are severe intracranial haemorrhage (and consequent neurodevelopmental delay), hypoxic-ischaemic encephalopathy, severe retinopathy of prematurity, chronic lung disease/bronchopulmonary dysplasia requiring home oxygen therapy, and necrotising enterocolitis resulting in short bowel and failure-to-thrive. These complications alter the life trajectory of, and financial burden for, the affected child, any siblings, and their nuclear and wider family. Without sildenafil treatment, these complications occur anyway.

The early stillbirth (<48h after commencing sildenafil) within our institutional cohort occurred in the only fetus to have reversed umbilical arterial end diastolic flow (REDF) at the time of commencing sildenafil treatment. It is plausible that sildenafil may have so altered fetal blood distribution to accelerate fetal death.

The primary risk to the mother in severe early-onset IUGR is the development of secondary pre-eclampsia. The maternal risks due to pre-eclampsia can be mitigated through systematic assessment and surveillance[70].

4.3 Summary of safety information for sildenafil

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor developed for use in erectile dysfunction. It is cleared primarily by hepatic microsomal enzymes (i.e., cytochrome P450 (CYP) 3A4 and to a less extent, CYP 2C9). The parent compound and its active metabolites are excreted mainly in feces, with only 13% excreted renally. The half-life is about 4 hours[71].

4.3.2 Safety for mother and baby

For the mother, most safety information comes from studies of erectile dysfunction, the condition for which sildenafil was developed. Of all of the PDE-5 inhibitors, sildenafil has the longest safety record and has been documented to be well tolerated. Side effects are more common at higher doses. A low dose (25mg TID) is being used in STRIDER.

The most common side effects were **headache** (~15%), **flushing** (~10%), and **dyspepsia** (~5%)[72].

- **Visual changes**, consisting of a change in colour perception, blurring and/or sensitivity to light, occurred in a small number of patients (up to ~10%)[72]. These were mild, transient (lasting for up to 2-3 hours), and did not preclude future use of sildenafil.
- Healthy volunteers given 100mg of sildenafil experienced a transient decrease in blood pressure (BP), of about 8.4/5.5mmHg[69]; this was of no clinical importance. Sildenafil does not appear to increase the risk of myocardial infarction in those with no history of (or stable) cardiovascular disease.

There are two rare side effects that have been reported in association with sildenafil, but causal relationships have not been established.

- Nonarteritic anterior ischemic optic neuropathy (NAION)[69] has occurred in men with risk factors for both NAION and the erectile dysfunction that prompted sildenafil use (e.g., diabetes mellitus). Vision is not monitored in patients taking sildenafil and diabetic retinopathy is not a contraindication to use of sildenafil.
- Hearing loss has been rarely reported in sildenafil users. This loss has usually occurred within first 24hr of starting the drug. It is usually unilateral, and is temporary in about one third of patients. Hearing is not monitored in patients taking sildenafil.

Thirty women with either severe early-onset IUGR or late-onset pre-eclampsia, and three women with primary pulmonary hypertension, have been administered sildenafil in pregnancy. It is important to note that:

- No woman discontinued the drug due to maternal side effects, and no morbidity in the baby was attributed to sildenafil.
- Growth measured by abdominal circumference (AC) may increase before growth measured by femur length
- Sildenafil is administered routinely to premature babies themselves when they have persistent pulmonary hypertension of the newborn

Although it is hoped that sildenafil will improve survival and intact-survival in these babies with early-onset IUGR, these babies are usually born small and often very premature, so morbidity is expected. Reversed end-diastolic flow in the umbilical artery is not a contraindication to sildenafil therapy in pregnancy because of the grave prognosis of these babies at <28+0 weeks; however, in the BC Women's Hospital cohort, the only stillbirth that occurred within 48hr of commencing sildenafil occurred in a baby with such reversed end-diastolic flow.

Women with an undiagnosed coronary artery disease (CAD) may experience an adverse event to sildenafil. If a concern were to arise about coronary artery disease (CAD) in a woman in STRIDER Canada, the medication would be stopped pending an assessment by internal medicine, as per good clinical care. However, any women with an overt CAD will not be recruited in the trial.

As part of routine clinical care pregnancy complication(s) may be detected. The decision to continue with pregnancy will be discussed with your care giver.

Women will also be requested to record any symptoms that they may experience in a participant symptom diary (PSD). The PSD will be reviewed with participant during assessment visits.

4.4 Contraindications to sildenafil are:

- Conditions for which a decrease in BP may be detrimental, including known cardiovascular disease, certain types of cardiac disease (e.g., aortic stenosis), or a baseline BP that is very low (<90/50mmHg)
- Known cocaine use (an exclusion criterion in STRIDER) due to the risk of cardiac adverse events
- Very high BP (>170/110mmHg) until this is brought under control
- Co-morbidities or medication that may increase sildenafil concentrations and effect, including: cirrhosis or hepatic dysfunction, nitrates in any form, or certain antiretrovirals[69]. (HIV is an exclusion criterion for STRIDER.)
- Hereditary retinal disorders or a history of NAION

4.4.4 Women prescribed sildenafil should be advised to do the following:

- Not drive after their first dose to confirm that they will tolerate the medication
- Report any increase in postural hypotension, a common symptom in pregnancy
- Report any sudden loss of vision in one/both eyes and discontinue sildenafil
- Report any sudden loss of hearing in one/both ears and discontinue sildenafil

Clinicians prescribing sildenafil should

- Continue sildenafil if BP falls to <90/50mmHg and the woman is asymptomatic. However, the site investigator should be notified.
- **Notify Anaesthesia when these patients are admitted to delivery suite**:
- **Not prescribe nitrates in any form within 24hr of the last dose of sildenafil**, as these drugs potentiate the effects of sildenafil on BP. Nitrates used rarely in pregnancy include glyceryl trinitrate (sprays or tablets) for chest pain, hypertension, or preterm labour; and sodium nitroprusside for severe

hypertension. Other nitrates that are contraindicated for use with sildenafil include isosorbide salts; amyl nitrite; nicorandil; and organic nitrates in any form.

- **Preferentially choose nifedipine (or another calcium channel blocker) for treatment of hypertension**
  - Reduce the dose of existing, stable labetalol (a non-selective beta- and alpha -1-receptor blocker) or methyldopa (a central alpha-2 antagonist) therapy when prescribing sildenafil until the effect of sildenafil on a woman's BP can be ascertained.
  - Use smaller doses of labetalol or methyldopa when prescribing them to women already on sildenafil until the effect on a woman's BP can be ascertained. Ensure that women are asked to report postural hypotension which may be either more likely to occur or more severe if women are also taking sildenafil.
  - Do not prescribe a peripheral alpha-1 blocker (e.g., prazosin) within 24hr of the last dose of sildenafil, as these drugs may potentiate the effects of sildenafil on BP.
- **Exercise caution when prescribing drugs that can inhibit CYP 3A4** (the hepatic microsomal enzyme that is responsible for the majority of sildenafil metabolism) and increase sildenafil effect and side effects. Such drugs include: **erythromycin** and **fluconazole**[71]. If a clinically important effect on BP is noted, the clinician should contact the site study investigator about decreasing the dose of sildenafil (e.g., to 25mg orally BID).**Protease inhibitors (e.g., ritonavir)** can also inhibit CYP 3A4, but women with HIV in pregnancy are excluded from STRIDER.

5. TRIAL DESIGN

The STRIDER study is designed as randomised double blind, placebo-controlled clinical trial with an intention-to-treat analysis to quantify the effects of administration of sildenafil on pregnancy outcome in severe early-onset IUGR. 90 women with affected pregnancies will be recruited and randomised to receive either sildenafil or placebo (Figure 1). If additional funding is obtained and if feasible, we will increase our sample size to 126 and change primary outcome to birthweight (g).

Randomisation should equally distribute any error between the two arms of the trial and remove bias. We recognise that there is inherent error in the ultrasound measurement of fetal AC. As the trial will be double-blinded, the ultrasound staff, reporting sonologist, treating physician, site principal investigator (PI) and research staff, and the patient will remain blinded to the treatment being received. The primary outcome is the fetal outcome, irrespective of the way the policies are administered.

5.1 Participating centres

Subjects will be recruited from centres across Canada. Each centre will nominate local investigators to oversee local recruitment.

The PRE-eclampsia & Eclampsia Monitoring, Prevention & Treatment Clinical Trials Unit (PRE-EMPT CTU) team will assist in day-today coordination of the STRIDER Canada trial.

In advance of the trial starting at a site, the Principal Investigator must agree to adhere to the Good Clinical Practice (GCP) Guidelines and all relevant regulations. In addition, all relevant regulatory and ethics approvals will need to be in place.

We anticipate that most women will be outpatients at that time. After case identification and the verbal granting of permission by the patient to discuss the trial, the site co-ordinator will be contacted by the clinical team to go through the process of informed consent.

5.2 Protocol compliance

For the STRIDER Canada, compliance will be determined by performing pill counts at each visit (we will aim at least as frequently as every 14±2d). Adequate compliance will be defined as ≥80% pill usage. The PRE-EMPT CTU team will check compliance quarterly for the trial overall, and by centre. If poor protocol compliance is noted generally within a centre, the PRE-EMPT CTU team will work with that centre to identify and resolve compliance issues.

5.3 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.

6. TRIAL POPULATION

Women reviewed in the participating fetal medicine with a diagnosis of a pregnancy affected by severe early-onset IUGR between 18^{+0} and 27^{+6} weeks of gestation and Serum PLGF levels less than 5th percentile for gestational age will be considered for randomisation.

6.1 Inclusion criteria

- Maternal age of 18 years or older
- Singleton pregnancy
- Gestational age from 18^{+0} - 27^{+6} weeks
- ultrasound (U/S) estimate of fetal weight (EFW) <700g
- EO IUGR, defined as at least ONE of following:
    - U/S measurement of the fetal abdominal circumference (AC) <10th percentile for gestational age
    - reduced fetal growth velocity (AC interval growth less than 50% of expected) & abnormal uterine artery waveform
    - reduced fetal growth velocity (AC interval growth less than 50% of expected) & a prior pregnancy with early-onset IUGR with adverse perinatal outcome
- Serum PLGF < 5th percentile for gestational age (Figure 4)

Adverse perinatal outcome will be defined as either a perinatal or infant death related to IUGR or a life-altering complication of either prematurity or IUGR (e.g., hypoxic-ischaemic encephalopathy, cerebral palsy, or chronic lung disease). The Triage® PLGF meter is a point-of-care unit that will be available within the site at all times.

6.2 Exclusion criteria

- Decision made to terminate pregnancy
- Prior participation in a STRIDER trial
- Maternal
    - Pre-eclampsia or gestational hypertension (current pregnancy)
    - Known HIV positive status (due drug-drug interaction between sildenafil and antiretrovirals)
    - Known significant maternal heart disease
    - Current prescription or illicit drug therapy
        - Receiving Prazosin or other peripheral alpha-blockers
        - Treatment with nitrates
        - Current cocaine, crystal meth or vasoconstrictor use (risk of acute cardiac events)[73,74]
        - Allergy to sildenafil or another contraindication not listed above
- Fetal
    - Known aneuploidy
    - Anomaly, syndrome or congenital infection confirmed at enrolment

6.3 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 wherever possible must be documented in the CRF. All subjects will receive ongoing medical care according to clinical need.

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
- Early discontinuation of study drug, continued collection of data from clinical records and follow up contact to 6-12 weeks after delivery.

- All relevant adverse events identified will be reported as required to all relevant authorities

7. SUBJECT SELECTION & RECRUITMENT PROCESS

Due to the very high risk nature of these pregnancies, women who are eligible for the STRIDER Canada study are expected to be under the care of the Maternal Fetal Medicine high risk teams in each recruiting centre including participating centres from Canadian Perinatal Network (CPN)[75-79]. All hospitals participating in STRIDER are tertiary perinatal units with well-established resources and extensive experience with these women and their families.

Once women have been identified as eligible by meeting the inclusion criteria (and have no exclusion criteria), they will be provided with information regarding the trial. This will be done verbally and with a written information sheet and consent form provided by the study investigators or delegated staff.

All women will be given time for full consideration and consultation as required. Contact telephone numbers will be provided. Study investigators or the research personnel will then meet with the potential recruit again and if women wish to join the study the consent process, randomisation and first visit will be completed. Signed, written consent must be obtained by the subject.

For women who decline to take part in this drug trial antenatal care will continue to the same standard as for all women with this condition. Sildenafil will not be available as part of this standard of care.

8. RANDOMISATION

8.1 Randomisation process

In STRIDER Canada, randomisation will be centrally controlled using a web-based computerised randomisation platform at the CIHR Canadian HIV Trials Network/ CHÉOS, UBC (Centre for Health Evaluation and Outcome Sciences) at St. Pauls' hospital to which centres can gain access 24hr/day. CHÉOS will provide the randomisation platform, and web-linked drug supply management system. Randomisation will be stratified by centre (to prevent any imbalance between groups in aspects of maternal or neonatal care that may differ between centres; with random blocks of 2 or 4).

Women will be randomised on a 1:1 ratio to sildenafil:placebo. The randomisation process will assign each subject with a unique study ID number. This study ID number will be required when allocating study drug bottle and for recording data on the case report form (CRF). The drug bottle number will be dispensed by pharmacy directly to the patient or responsible health care professional. Site should sign and file the randomisation and drug bottle allocation confirmation page.

If a woman is found not to be eligible for the trial when her details are entered into the randomisation system, the program will return a screen failure notification. Potential subjects

who have screen failed can be re-screened for eligibility and included in the trial at a later date if appropriate.

8.2 System failure

In the event of a failure with the randomisation and drug allocation system, site should follow offline randomisation plan.

9. TREATMENT GROUPS & STUDY DRUG

9.1 Treatment groups

Women will be randomised to one of two groups:
1. **Sildenafil**
Oral sildenafil citrate 25mg three times daily (tds).

OR

2. **Placebo**

Matching placebo containing no active ingredient three times daily (tds).

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

In Canadian STRIDER, the treatment with either sildenafil or placebo will be applied from the time of randomisation until delivery, or up to 31^{+6} weeks of gestation whichever comes first (maximum 14 weeks).

9.2 Care common to women in BOTH drug and placebo groups

There is no standard of care for many obstetric interventions. As such, the Canadian STRIDER trial protocol allows centres to provide their usual form of care. This may involve differential monitoring which will reflect the way the treatments would be applied in normal clinical practice[80]. However, data are collected on potential co-interventions (e.g., bed rest, hospitalisation, and antihypertensives [other than sildenafil]) and their impact on outcome will be examined by secondary analyses (Section 14). Portions of the per-case funding may be used by individual sites to strengthen their ultrasound surveillance beyond their current standard of care.

All women will receive enhanced fetal and maternal surveillance based SOGC guideline on the Intrauterine Growth Restriction: Screening, Diagnosis, and Management, 295 - Published August 2013[4,5].

Fetal assessment will include biometry biparietal diameter (BPD), head circumference (HC), AC, femur length (FL), amniotic fluid index (AFI), Doppler (uterine artery, umbilical artery, middle cerebral artery, ductus venosus), Cardiotocography (CTG) (if available at sites). Fetal surveillance will occur as a minimum at least as frequently as every 7±2d and/or as clinically indicated.

Maternal surveillance will include, the measurement of PLGF, blood pressure, proteinuria (dipstick and random protein:creatinine ratio), complete blood count, creatinine, uric acid,

aspartate transaminase, bilirubin, and albumin[70,81,82]. Tests will be repeated at least every 14 ± 2d and/or as clinically indicated. As such, the STRIDER Canada trial protocol allows centres to provide their usual form of care. This may involve differential monitoring which will reflect the way the treatments would be applied in normal clinical practice. Thus, STRIDER Canada trial protocol allows centres to provide their usual 'real-world' care. However, randomisation is stratified by centre and data are collected on potential co-interventions (e.g., bed rest, hospitalisation, and antihypertensives [other than Sildenafil]) and their impact on outcome will be examined by secondary analyses. No special restrictions will apply with regards to diet, activities or other lifestyle items, unless so indicated by the treating physician.

If women require antihypertensive medications, we suggest that clinicians treat non-severe pregnancy hypertension with either labetalol, methyldopa, or nifedipine, as reflected in national and international guidelines[83-86]. Women must not use: atenolol (impairs intrauterine fetal growth), or angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor antagonists, or direct renin inhibitors (fetotoxic)[85,87]. Sildenafil, itself an effective antihypertensive agent in pregnancy[45], is not a contraindication for other antihypertensive use.

9.3 Drug supply and Storage

Each study drug bottle will contain 30 over-encapsulated capsules, equivalent to a 10-day supply. Sildenafil tablets will be sourced from Teva (DIN 02308738). For placebo, Bay Area Health Trust, ON will make placebo through process of over-encapsulation. The content of the placebo capsule (containing no sildenafil citrate) will be 1:1 ratio of Lactose and Methylcellulose enough to fill the capsule. Exact weights are not done and similar filler is used within the active capsule plus the addition of the active tablet inside the capsule. The packaging will be done by Bay Area Health Trust, ON. The distribution of bottles to each study site according to requirement will be done either through Bay Area Health Trust or directly through coordinating centre.

Once a site has been activated, the first shipment of study drug will be sent to site. Medication will be delivered to each study centre labelled to regulatory requirements and MUST be stored under appropriate conditions. The study drug must be stored in a limited access area or locked cabinet. Medication will be issued as 10-day supply (total 30 capsules) in a bottle to participants for self-administration if managed as an out-patient, or dispensed directly from pharmacy. The study drug is for oral use only and capsules must not be halved.

The Investigator at each site is responsible for study drug inventory and accountability throughout the trial. Under no circumstances will an investigator or pharmacist will use the study drug other than directed by the protocol. Partially used study drug (sildenafil/placebo) should not be redispensed to another patient after it has been returned. At the end of trial, unused drugs should either be returned to the sponsor or disposed as per local procedures.

9.4 Drug issue and assessment of compliance

At the time of randomisation the study drug allocation program (web based) will assign the first study drug bottle. Study drug will be re-issued as required thereafter by the study investigators and/or delegated study staff. Subjects will be asked to return used and unused medication containers for regular 'pill count' to assess compliance.

All other medications taken by a participant can be continued as normal, with the exception of nitrates, other medications mentioned in the exclusion criteria, and listed in product monograph or as deemed appropriate by the site investigator.

9.5 Overdose

STRIDER Canada trial 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. STRIDER Canada does not require rescue medications to be given. For any medical emergency, participant should immediately call 9-11. For any accidental overdose and if stable, participant should contact Principal Investigators or designated MD on call for immediate assessment and follow-up.

9.6 Emergency unblinding

Randomisation codes will be generated by the PRE-EMPT CTU at the University of British Columbia (UBC). In the event that there is an immediate need for the treating doctor to know a subject's treatment allocation in order to ensure patient safety it will be possible to break the randomisation code. The facility to perform emergency unblinding will be available 24 hours per day. It is recommended that the Investigator contact the Principal Investigator of the study to discuss the particular situation before breaking the subject's randomisation code, if possible.

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.

10. TREATMENT DURATION/INDICATIONS TO STOP TREATMENT

10.1 Treatment duration

Study drug treatment will commence as soon as possible following randomisation and continue three times a day until delivery or up to 31^{+6} weeks gestation (or intrauterine demise). Due to the nature of this condition and the inclusion criteria set it is unlikely that pregnancies will proceed beyond 32^{+0} weeks i.e. fetal compromise will determine that earlier delivery is necessary. In the event that a woman remains pregnant at 32^{+0} weeks, treatment will be stopped as neonatal outcomes beyond this gestation are generally very good and so it will no longer be appropriate to continue to use the study drug.

10.2 Additional indications to stop treatment

1. Severe maternal hypotension causing maternal and/or fetal compromise in the absence of other anti-hypertensive drug use (i.e. stop other antihypertensives first).

2. If the Investigator believes that it is in the best interests of the subject for safety or tolerability reasons (e.g. due an adverse or serious adverse event).

3. Subject request to discontinue study drug.

11. TRIAL PROCEDURES

The STRIDER Canada study procedures should be carried out as outlined in this section and Table: 4 and will involve consent, measurement of PLGF, 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 site's/hospital's standard protocol.

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 PRE-EMPT CTU 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 Sheet.

11.1 Individual Participant Trial Flow Chart

Identification of eligibility

↓

Information and education regarding trial

↓

Agreement and consent to participate
Baseline data collection, examination and investigations
(Ultra sound scan (USS), PLGF, Blood tests, Urinalysis prior to randomisation)

↓

Randomisation

↓

Commence study drug treatment regimen

↓

High risk antenatal care determined by clinician – may be in-patient or out-patient

↓

Regular study review incl: record concomitant clinical management, maternal & fetal surveillance

Maternal surveillance **– PLGF, BP, urinanalysis, blood tests**

Fetal Surveillance

USS as per Content of a Complete Routine Second Trimester Obstetrical Ultrasound Examination and Report No. 223, March 2009 SOGC guideline: Measurement of AC, BPD, HC, and FL; AFI, deepest vertical pocket (DVP); clinical indices of the following vessels of UtAD, UmAD, DV, and MCA.

Computerised CTG for assessment of FHR short term variability (if available).

↓

Provision of study drug and regular review of participant symptom diary and adverse events

↓

Decision for delivery determined by clinician according to fetal/maternal status as per clinical practice

↓

Collection of delivery details, birth outcomes, maternal outcomes and neonatal outcomes to discharge from hospital/EDD

↓

Postpartum questionnaire 6 - 12 weeks after delivery including request for agreement to follow-up paediatric outcomes

11.2 STRIDER Canada: Trial assessments and procedures

Table 4: Visit schedule

Trial Procedure	Screening	Randomisation (Day 0)	48 hours assessment after 1st dose	Weekly assessment[1] (Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, etc.)	48 hours after treatment discontinued (if not delivered)[2]	Delivery	Postnatal (discharge / neonatal EDD)	Follow Up 6-12 weeks postpartum
Informed consent	X							
Recruitment screening	X							
Demographics	X							
Baseline questionnaire		X						
Medical history		X						
Fetal assessment –								
Biometry (BPD, HC, AC,FL)	**Day – 4 to Day 0** (as close to Day 0 as possible)			X	X			
Standard clinical resistance indices	**Day -1 to Day 0** (as close to Day 0 as possible)		X	**At least weekly**	X			
cCTG (if feasible and available at sites)	**Day -1 to Day 0**			X	X			
Maternal assessment -								
PLGF testing	**Day -1 to Day 0 (except over holidays/weekends Day -4 to Day 0)**		X	X	X			

All procedures in a RED cell are in addition to the standard care patients will receive. Procedures in a CLEAR cell are procedures that are routinely performed as part of standard clinical care.

[1] To be conducted every week (weekly from recruitment to delivery)

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

Trial Procedure	Screening	Randomisation (Day 0)	48 hours assessment after 1st dose	Weekly assessment[1] (Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, etc.)	48 hours after treatment discontinued (if not delivered)[2]	Delivery	Postnatal (discharge / neonatal EDD)	Follow Up 6-12 weeks postpartum
Urinalysis (Proteinuria)	**Day -1 to Day 0**			**X**				
BP (and/or Vital signs)	**Day -1 to Day 0**		**X**	**X**	**X**			
Blood sample[3] (haematology/biochemistry)	**Day -1 to Day 0**			**X**[4]	**X**			
Dispensing of sildenafil/placebo[5]		**X**		**X**				
Review of complianceand symptom diary				**X**	**X**	**X**		
Return of empty bottles to pharmacy				**X**	**X**[6]	**X**		
Adverse Events/Serious Adverse Events Assessment[7]		**X**	**X**	**X**	**X**	**X**	**X**	
Review of Antenatal Management				**X**		**X**		
Labour & delivery details						**X**		
Maternal & Neonatal outcomes to hospital discharge						**X**	**X**	
Postpartum questionnaire								**X**

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

[4] If clinically indicated

[5] Study drug to commence as soon as possible after randomisation and to continue until physician decision for delivery, Intrauterine death, participant request for withdrawal, physician decision to stop study drug or until 31^{+6} weeks' gestation. Study participant should not drive within 4 hours after first dose.

[6] If treatment discontinued, return the bottle to the research staff and/or pharmacy

[7] AE/SAEs to be collected from the time of randomisation through to maternal hospital discharge after delivery; fetal/neonatal death occurring prior to discharge or EDD; neonatal hospital discharge or EDD, whichever is later.

11.3 Study Drug Treatment Phase

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

The study protocol time points are 48 hours, 7 days, 14 days and weekly thereafter post-randomisation. With the exception of the first post-treatment study assessment which must be conducted as close as possible to 48 hours after withdrawal or discontinuation of therapy , routine clinical assessment and scan data can be used and the assessment results closest to the protocol time points should be collected (recommended to be within +/- 2 days).

11.4 Baseline data collection

11.4.1 Medical history and demographics

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

11.4.2 Previous Ultrasound Scan (USS) data

We will collect the data from the 1st USS greater than or equal to 7 weeks for dating purposes. As well, we will collect biometry, and amniotic fluid data from all USS greater than or equal to 14 weeks in the current pregnancy.

11.5 Randomisation

11.5.1 USS

An USS must be performed prior to randomisation anytime within four days before enrolment (i.e. Day -4 to Day 0 (as close to Day 0 as possible)) and should include the following:

- Fetal growth measurements: abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL).
- Standard clinical resistance indices of the following vessels: uterine artery (UtAD), umbilical artery (UmAD), middle cerebral artery (MCA), and ductus venosus (DV).
- Cardiotocography (*CTG*) performed, if feasible and available at sites.

11.5.2 Maternal assessments

Prior to randomisation (i.e. Day -1 to Day 0), following assessments will be performed:

- PLGF(except over holidays/weekends Day -4 to Day 0) blood test results performed prior to randomisation including complete blood count, renal (creatinine, urea) and liver function (AST, ALT, albumin).
- Urinalysis results performed.
- The blood pressure recording.

11.6 Fetal assessment

11.6.1 Ultrasound Scan

Following randomisation an USS should be performed at 48 hours post-randomisation, days 7, 14 and then continued on a weekly basis and should include the following:

- Fetal growth measurements: AC, BPD, HC and FL (not performed at 48 hours post-randomisation).
- Standard clinical resistance indices of the following vessels: uterine artery (UtAD), umbilical artery (UmAD), middle cerebral artery (MCA), and ductus venosus (DV).
- Standard amniotic fluid measurement

11.6.2 Computerised CTG (if feasible and available at sites)

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

11.7 Maternal assessment

The following assessments will be completed at days 7, 14, 21 and then weekly following randomisation:

- Blood pressure measurement.
- Dipstick urinalysis (proteinuria), Protein/Creatinine ratio.
- Blood tests including: complete blood count, renal (creatinine, urea) and liver (AST, ALT, albumin) function.
- Concomitant medication review.
- Review of study drug compliance and PSD.
- Adverse Event (AE)/Serious Adverse Event (SAE) assessment.

The following assessments will be completed at 48 hours post 1st dose:

- Standard clinical resistance indices of the following vessels: uterine artery (UtAD), umbilical artery (UmAD), middle cerebral artery (MCA), and ductus venosus (DV).
- PLGF, BP and/or vital signs
- Adverse Event (AE)/Serious Adverse Event (SAE) assessment.

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

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

At the end of the study, participant will receive a postpartum questionnaire about their experience in participating in trial and general wellbeing.

If unintended findings are discovered in the course of the study assessments, all informative data will be shared with the clinical team to aid in decision making.

11.8 Bio-banking

Any leftover blood samples will be stored for future biomarker testing studies. Participant will be given an option to consent for this optional study. The purpose is to store any leftover blood samples for future biomarker (proteins found in the blood) testing. It is difficult to anticipate future advances in science. As such, new biomarkers may be identified for naturally small fetuses. Participation in this optional study does not require any additional involvement for participants and will not need to provide with any additional blood samples. Only leftover blood samples will be used for future biomarker testing.

11.9 Concomitant clinical management and co-interventions

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

All women with severe early onset IUGR, regardless of co-existing preeclampsia, will require intense fetal surveillance, possible in-patient stay, and early delivery. Once the fetus has reached an appropriate gestational age and size (and is deemed viable), corticosteroids may be administered to improve fetal lung maturity, and once delivery is planned, magnesium sulphate therapy may be considered for perinatal neuroprotection[4,5,88]. These additional therapies and management will be provided at the discretion of the clinician/study centre caring for each woman. It is recommended that data regarding these co-interventions are collected by study investigators.

Sildenafil is an antihypertensive agent and may be sufficient treatment for women with hypertension. In the event that further antihypertensive treatment is required, the recommended agents are; labetalol and methyldopa.

12. SAFETY ASSESSMENT & MONITORING

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

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

In this high-risk population, a large number of complications are anticipated in the absence of trial participation. Investigators should take the underlying condition into account in their assessment of potential adverse and serious adverse events. In general, the following expected events do not need to be reported as AEs/SAEs unless the investigator deems there to be a

causal relationship to the study procedures including potential exposure to sildenafil; these events will be documented in the CRF as part of maternal, delivery and neonatal outcomes:

- Maternal prolonged hospital stay antenatal or post-natal related to the diagnosis of IUGR
- Termination of pregnancy in maternal interest
- Admission for:
  - any of the expected Adverse Events
  - 'rest'
  - maternal discomfort
- Gestational 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
- Major antepartum haemorrhage (that requires transfusion[1])
- Postpartum haemorrhage (standard definition)
- Admission to neonatal intensive care
- Neonatal complications of prematurity
- Fetal death
- Neonatal death

12.1 Serious Adverse Events

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

- Maternal death
- Maternal life threatening event
- Maternal persistent or significant disability or incapacity
- Maternal hospitalisation/prolonged hospitalisation not related to preeclampsia, IUGR or standard postnatal recovery
- Unexpected congenital anomaly/birth defect

Other medically important event considered to be an SAE by Investigator

Important medical events that may not result in death, threat to life, or not require hospitalisation may be also considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. The term life threatening here refers to an event in which the participant 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.

[1] As per SOGC guideline - Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage No. 235 Ocotber 2009

12.2 Investigator review of AEs/SAEs

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

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

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

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

- Relationship to study medication: The investigator will determine if the study medication contributed to the AE/SAE. Factors to consider:
  Exposure: Was subject exposed to the study drug?

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

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

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

- Details of any treatment given.

12.3 Expectedness of SAEs

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

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

12.4 Expected events:

- **Expected Unrelated Event**: the SAE is expected based on the known information about the study drug or the underlying condition and is not considered to be related to the study drug. This is referred to as an **Expected SAE**.

- **Expected Related Event**: an SAE which the Investigator considers possibly, probably or definitely related to the study drug. This is referred to as a **SAR – Serious Adverse Reaction**.

12.5 Unexpected events:

- **Unexpected Unrelated Event**: the SAE is unexpected based on the known information about the drug or the underlying condition and is not considered related to the study drug. This is referred to as an **Unexpected SAE**.

- **Unexpected Related Event**: the SAE is unexpected based on the known information about the drug or the underlying condition and is considered possibly, probably or definitely related to the study drug. This is referred to as a **SUSAR – Suspected Unexpected Serious Adverse Reaction**.

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

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

12.6 Procedure for AE and SAE reporting

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

Actions for SAEs:

1. Report immediately, within 24 hours of becoming aware of the event:

   - SAR – suspected adverse reaction.
   - Unexpected SAE.
   - SUSAR – Suspected Unexpected Serious Adverse Reaction.

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

   - Expected SAE.

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

12.7 Data Safety Monitoring Board (DSMB)

The STRIDER Canada has established a local DSMB chaired by Dr. Gideon Koren, Professor of Pediatrics, Pharmacology, Pharmacy and Medical Genetics, The University of Toronto. The other DSMB members include Dr. Howard Berger, St. Michael's Hospital; Dr. Shabih U. Hasan, Alberta Health Services; Dr. William A Grobman, Northwestern University Feinberg School of Medicine; and Dr. Joan Crane, Eastern health.

12.8 Stopping rule

Study will be stopped if two other STRIDER trials (from consortium of STRIDER trials), determines any potential benefit or harm before the STRIDER Canada trial is complete.

If the study was stopped early all subjects currently on the study drug would be contacted as soon as possible by an Investigator and instructed to stop taking the study drug. A clinic visit/review would take place with the subject at their earliest convenience.

Any subjects who had completed the treatment phase already would be contacted by an Investigator as soon as possible and informed of the reasons for stopping the trial. Depending on the reason the study was stopped, additional safety information could be collected at this point from the subjects as required and as permitted by local regulations.

13. DATA COLLECTION AND MANAGEMENT

13.1 Data capture methods

Trial data will be captured using the platform called 'Randomization and Study Drug Allocation Website' (RAW) for conducting randomisation and drug allocation, and the Research Electronic Data Capture (REDCap) website for entering electronic Case Record Forms online directly. The RAW system is hosted by the CTN HIV group on the UBC network, and the REDCap system is hosted by the Child and Family Research Institute (CFRI) on the UBC/CFRI network. All data will be entered directly into the electronic case report form (eCRF) by the designated research staff at participating centres.

Initial information including baseline demographic data will be transferred from the hospital records to eCRFs. Full eCRFs can 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 RAW system. Subsequent data will be transmitted electronically to the PRE-EMPT CTU by entering the data into the REDCap trial database. Each participating centre will also be provided with hard copies of paper CRFs (pCRF) in case of the downtime of the systems. The data at each participating centre will be handled in accordance with local regulatory legislation and Ethics Committee approval.

Each randomised woman and fetus or baby will be followed-up until discharge from the randomising hospital or death (whichever occurs first). Some patients may be transferred out to another hospital and, therefore, neonatal outcome should be assessed at term age (as close to the 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.

13.2 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.

In order to resolve possible discrepancies between information appearing in the eCRF 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 eCRF should be consistent and verifiable with source data in source documents (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 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, the CRF will be considered as the source document**,** unless otherwise indicated by the investigator.

13.3 Data handling and record keeping

This trial will be coordinated by the PRE-EMPT CTU at UBC and conducted at the hospitals in Canada. Data will be collected at each site by local investigators or designated research staff and securely transmitted electronically or via fax to the PRE-EMPT CTU at UBC in British Colombia, Canada.

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

13.3.1 Site level

Any trial related documents including paper CRF, SAE forms, copies of histology, and autopsy reports should be kept in locked filing cabinets only accessible by authorised personnel. Site Master Files (SMF) should be stored in lockable filing cabinets.

Any documents that must be transferred to the CTU for data entry or data reporting such as AE/SAE forms, they should not contain any personal identifiers. Patient should be identified by trial subject number and initials and/or date of birth (DOB) only. If any data/documents/ information is requested by either PRE-EMPT CTU should be faxed directly to the PRE-EMPT CTU. A log of documents sent should be maintained at the Site. Copies of faxed documents must be retained in the SMF 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.

13.3.2 Clinical trials unit level

The eCRFs entered by sites will be stored on the UBC/CFRI 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 servers will be backed up daily by IT system administrators 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 CTU will also have access to the database to monitor the data collection for all sites in Canada.

13.4 Data recording and sharing

Records will be securely stored and will be kept for 25 years. The Principal Investigators will be responsible for their safekeeping. Only the Principal and Co-investigators, investigators and research staff will have access to the raw data and clinical information relating to the study, and they will hold and maintain the confidentiality of the code linking participant identifiers to the study IDs at their local sites only. The 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. De-identified data collected during the study will combined/transferred with other STRIDER Trials for the purpose of analysis within the international STRIDER research consortium.

Identifying 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.

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.

14. STATISTICAL ANALYSES

Assuming 16 days increase in mean GA at delivery (189days [sd 27days] in placebo-treated pregnancies [from BC Women's case series paper[1]] vs 205days in sildenafil-treated pregnancies), and with alpha of 0.05, we will have 80% power to detect this difference if we randomise 45 women per group. Analysis will be by intention-to-treat.

Randomisation will be stratified by centre, using random blocks of 2 or 4. This approach minimises imbalance between treatment groups in aspects of maternal or neonatal care.

Using an intention-to-treat approach, all randomised women will be included in the analysis. If women are lost to follow-up, they will be included for all outcomes for which we have information. Descriptive statistics will be computed to compare the baseline demographics between treatment groups.

The unit of analysis will be infant. While we intend to only enrol singleton pregnancies, in the rare case that a pregnancy with an unknown multiple gestation was included, all infants will be analyzed and correlation will be accounted for. The analysis will also be adjusted for any imbalance in multiples between groups.

In STRIDER Canada, there will be one analysis in year 5, after the last surviving infant has achieved 28 postnatal days. No interim analyses are planned.

The primary outcome is gestational age at delivery (days), and the study hypothesis is that sildenafil therapy will prolong the time to delivery. The non-parametric Mann-Whitney test will be used to test the distribution between treatment groups. Subgroup analyses by linear regression methods will be performed, and variables adjusted for will include centre (stratification factor), gestational age at randomisation, maternal age, and PlGF percentile at randomisation. Other baseline characteristics may be added to this list if felt to be clinically relevant.

For variables that were collected at multiple time points during the trial, such as PlGF or biometry, a repeated measures analysis may be carried out to compare changes between groups. While trial assessments are recommended at pre-specified intervals post randomisation (i.e., Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, etc.), it is anticipated that women will visit and deliver at different time points, such that assessments will not be completed equally for all women. Additional analysis may be carried out to account for any imbalance in the repeated measurements of important variables.

We will participate in the IPD meta-analysis of the five international STRIDER trials (see appended paper). This will be based on the checked and updated individual participant data from all available trials. All randomised participants with outcome data available will be included in the analyses, which will be performed on an intention to treat basis, according to the treatment allocation at randomisation.

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