STRIDER NZAus

THE UNIVERSITY OF AUCKLAND
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SCHOOL OF MEDICINE

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

Investigators

Auckland	**Local Centre**
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You are being invited to take part in this research study. Before you decide, it is important for you to understand why this research is being done and what it will involve. Please read through this leaflet and feel free to discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide if you would like to take part in the study. Your participation is entirely voluntary (your choice). You do not have to take part in this study and if you chose not to take part you will receive the standard care available. Thank you for your interest in the study and for taking the time to think about whether you wish to take part.

What is the purpose of the study?

Intrauterine growth restriction (IUGR) occurring very early in pregnancy is rare, affecting only 0.2% of pregnancies. Unfortunately due to the severity of disease and extreme prematurity the risks to the baby are very high. Babies may die in-utero before delivery without ever getting big enough to have a chance of survival and even if they do reach an age where they may survive they are susceptible to the effects of hypoxia (lack of oxygen) which may result in poor health in the neonatal period, as children and through to adulthood. There is currently no treatment to improve outcome once growth restriction has occurred and therefore the only treatment doctors are able to offer is timely delivery. Intense monitoring of mother and baby aims to predict when the fetus has maximised its time in-utero and the risk of hypoxia and death is so high that early delivery is indicated. However, this results in very early (premature) birth and its inherent risks including death, severe neonatal morbidity and again potential life-long health consequences.

The purpose of this study is to investigate a drug called sildenafil that may improve blood supply to babies with severe IUGR occurring early in pregnancy. It is possible that by improving the blood supply to the baby that it grows better and can remain in-utero for longer and so less susceptible to the risks of prematurity.

The STRIDER NZAus study will assess whether, in babies with severe early onset IUGR, sildenafil increases the growth rate of the baby's abdominal circumference whilst it is still in-utero. We will also use the results of the study in collaboration with similar studies being done across the world to find out if, by improving baby's growth in-utero, sildenafil reduces the number of babies that die or survive with major handicap as a consequence of being IUGR and premature i.e. do more babies survive free of major handicap?

The study is a randomised double-blind placebo controlled trial. This means that half the women in the study will be randomly assigned to sildenafil treatment and the other half will be randomly assigned to a placebo tablet that is identical to the sildenafil tablet and taken in the same way. Whilst the study is on-going neither the women taking part in the study or the doctors caring for the women will know who is on which treatment. At the end of the study we will find out if sildenafil affects fetal growth and ultimately improves outcomes for babies affected by severe IUGR.

Why is this study suitable for me?

You have been invited to take part in this study because you have a singleton pregnancy (one baby) with a baby that is very small for gestational age measured by:

1. At ≥22 weeks + 0 days and ≤ 27weeks + 6 days: fetal abdominal circumference ≤3rd percentile.
2. At ≥28 weeks + 0 days and ≤ 29 weeks + 6 days: an ultrasound estimate of fetal weight (EFW) <700g.

This means your baby is at very high risk of a poor outcome.

We intend to enrol 122 women at similar risk to take part in the study.

Women will be invited to take part in the study across New Zealand and Australia.

Are there any reasons why some women should not take part in the study?

Some women who meet the criteria listed above can not take part in the study. Reasons include:

1. Known major fetal anomaly/syndrome/congenital infection (such as Toxoplasmosis and Parvovirus) that is deemed to be the likely cause for the baby being small.
2. Known fetal aneuploidy e.g. Down syndrome.
3. Already made plan for termination of pregnancy due to the poor prognosis for their baby.
4. Your doctors expect that your baby will need to be delivered within the next 48 hours.
5. Treatment with sildenafil would not be suitable for you e.g. due to a known allergy.

Do I have to take part?

It is up to you to decide whether you take part in the study. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form that says that you agree to take part in the study. Even after deciding to take part you can withdraw from the study at any time and you don't have to give a reason. A decision at any time to withdraw from the study or a decision not to take part will not affect the standard of care you receive.

Women who do not wish to take part in the study will receive the same standard of care we provide for all with this condition. Sildenafil will not be available as part of this standard care.

What is standard treatment for women with this condition?

Once a baby is found to be much smaller than expected early in pregnancy, doctors will consider possible causes of IUGR (this includes aneuploidy such as Down syndrome, fetal structural abnormalities not related to chromosome problems and fetal infections such as Toxoplasmosis and Parvovirus). However, most cases of IUGR are related to problems with how the placenta (whenua/after-birth) plants into the wall of the uterus (womb) and in this situation unfortunately there is no current proven medicine or treatment.

The aim of management is to watch mother and baby closely to determine when the baby is at a high risk of dying in-utero or being severely affected by lack of oxygen. This is done by ultrasound scans and cardiotocograph (CTG) monitoring of baby's heart rate. Mothers also have regular review of blood pressure and urine to assess for possible development of preeclampsia. Once it has been decided that baby and/or mother are too sick to continue monitoring, and as long as the baby has reached an age and a size where it may have a chance of survival, delivery is arranged. As babies are so premature, treatments to mothers, such as corticosteroid injections to help the baby's lungs develop and a magnesium sulphate infusion to protect baby's brain are considered prior to these planned births (these treatments have been proven to be effective in randomised controlled trials). As the babies are

so small and at risk, delivery is almost always by caesarean section and usually before 30 weeks gestation.

In some cases babies are unable to grow to a size that may result in a live-birth or any chance of the baby surviving without major handicap, or the mother may develop the additional complication of preeclampsia (as can occur in 40% of these cases) when the baby is still too small to survive. In these situations termination of pregnancy on health safety grounds may be discussed with women and their families.

With early onset IUGR care is provided at the hospital by a 'high risk' care team including doctors specially trained in maternal and fetal medicine (MFM), specialised obstetricians, specialised midwives, senior sonographers and neonatologists. With such intense monitoring of mother and baby sometimes it is necessary to admit women to hospital for in-patient care.

What additional things will happen to me if I take part in this study?

If you agree to take part in the study we will ask you to complete the consent form. You will then be randomly assigned (selected by chance by a computer) to either sildenafil or an identical looking placebo (inactive 'dummy' tablet) treatment. You will have a 50:50 chance of sildenafil or placebo treatment. These will be taken as an oral tablet (by mouth) three times a day from when you start the trial until baby is born (or you reach 32 weeks gestation, whichever occurs first). Neither you nor the doctors caring for you will know which treatment you are receiving. We will ask you to complete a subject medication diary to record your medication use and any side effects that may be related to the treatment.

You will be cared for by the Maternal Fetal Medicine High Risk team. Blood tests and a urine sample will be taken when you join the study and around days 5, 10, 14 and then at least once a week while you are on the study treatment. In the majority of cases these tests are required as part of normal care given to women in these situations. Ultrasound monitoring of your baby will occur at the time you join the study and then at around 48 hours, 5 days, 10 days and 14 days after you join the study (and will continue at least weekly until the baby is born). It is likely these scans would be performed regardless of your involvement in the study (and may need to occur more frequently depending on the clinical situation). Once your baby is big enough we will do regular CTG monitoring of your baby's heart beat, this is also part of standard care for very small babies.

If you stop the study treatment (sildenafil or placebo) and you have not yet delivered your baby we would like to carry out a post-treatment assessment between 2 and 10 days after you take the last study drug tablet. This assessment will include an Ultrasound scan, blood and urine tests which may be part of your normal care even if you were not involved with the study.

All other care during the pregnancy will be similar to that given to women not taking part in the study who have comparable high-risk pregnancies and the doctors and midwives caring for you will advise you about this. We will collect information about any additional therapy (such as hospital stays and use of blood pressure tablets if you develop preeclampsia) as your pregnancy proceeds, details of your baby's birth and any complications that arise until you and your baby are discharged from hospital. This information will be collected from your and your baby's medical

notes. If your baby is discharged before their Estimated Delivery Date (EDD) a research midwife or one of the study Investigators will contact you by phone around the time of EDD to ask about your baby's progress.

We will ask you to complete a questionnaire after the birth of your baby telling us about how happy you were with the treatment. We would also like to make contact with you when your child is about two years old to find out how well he or she is developing.

For Auckland Study Centre Participants only (voluntary addition).

At the time of delivery we would like to take a sample from the placenta (whenua/after-birth), and if you deliver by caesarean section, a small sample from the myometrium (muscle) of your uterus (womb). If you would like to take your placenta (whenua/after-birth) home after delivery this will still be possible after the study sample has been taken.

Most of your sample will be studied on the day it is collected. A small amount will be frozen and stored within The University of Auckland for a period of up to five years to allow the final studies to be performed once enrolment to STRIDER NZAus is complete. Once these planned studies are complete your tissue sample will be will be destroyed following University approved guidelines for safe and appropriate disposal of tissue.

Myometrial sampling has been performed for many years for research purposes. It causes no extra risks, pain or increased operating time for the caesarean section and has no long term consequences.

Placenta (whenua/after-birth) and myometrial sampling is an optional part of this study, you may still take part in the study but decline these samples.

What is the drug being tested?

Sildenafil (also known by the trade name Viagra®) is a 'nitric oxide donor' drug. This means it acts on some blood vessels within the body to cause vasodilatation (relaxation of the blood vessel walls). Due to the inadequate changes in the uteroplacental vessels that occur with IUGR (and preeclampsia) we believe the blood vessels from the maternal side feeding the placenta and the placental vessels may still respond to nitric oxide beyond the second trimester and by dilating these vessels we may increase blood supply to the baby and improve fetal growth.

Sildenafil has been used in pregnancy in women with a severe lung condition called pulmonary hypertension. In these cases it has a positive effect on the mother's heart and lung function and does not appear to cause harm to babies. It has also been used across the world in a few women with preeclampsia and severe early onset IUGR with no suggestion of an adverse effect on babies and a possible effect improving fetal growth. We will be using the drug at similar doses to these reported cases.

What are the side effects of the drug?

The relatively commonly reported side effects of sildenafil include; headache, flushing, dyspepsia (indigestion), nasal congestion and impaired vision, including photophobia and blurred vision. However, none of these side effects were reported when used by pregnant women in the cases mentioned above.

You will be given a subject medication diary to record your medication use and report any side effects you may have. If you were to have any serious effects that may be related to the drug we are able to 'break the code' and find out what treatment you have been receiving before the trial is complete.

What are the alternatives for treatment?

If you choose not to take part in the study you will be offered the standard care provided for pregnancies at such high risk. This includes care provided by a 'high risk' team, very close surveillance of mother and baby with timely delivery (with antenatal corticosteroids and magnesium sulphate where appropriate). Sildenafil is not part of standard high-risk care and will not be offered to women not taking part in the study.

What are the blood and urine tests for?

The blood tests from you will measure your blood count, liver and kidney function. The urine sample will be collected to measure the amount of protein in your urine. These tests are done routinely in women with preeclampsia or at high risk of it (as occurs with severe early onset IUGR). The blood and urine tests required for study purposes may be carried out more frequently than is required for clinical reasons if you have IUGR only.

What are the ultrasound scans for?

The scans will include growth measurements of your baby, measurement of fluid surrounding your baby and Doppler blood flow measurements to and from the placenta, in the maternal vessels supplying the uterus (womb) and in the baby itself. These measurements are standard care for IUGR babies and will not cause harm to you or your baby. These scans are performed routinely with IUGR babies to decide when is the best time to deliver them. For the study we will also use this information to find out if sildenafil works to help improve blood flow and growth for these very small babies delivered so early and if it does how the exact mechanism of action might work.

What are the placental and myometrial studies for? (Auckland Study Centre only)

We will use these samples in the laboratory to compare the effects of sildenafil and placebo treatment on blood vessel development and function. This will help us work out the exact mechanism of action of drug and its influence on the uteroplacental circulation.

What are the possible benefits of taking part in the study?

The study is designed to find out whether the use of sildenafil will reduce the risk of babies dying or having major handicap as a consequence of IUGR and being born early. However, we do not know if it will make a difference. The information from this study will help us find out whether the drug improves fetal growth. By combining our results with similar studies taking place across the world we will find out if this leads to an improved outcome for these babies and so help us to plan care for women in the future with pregnancies affected by the same condition.

Women taking part in the study will not receive any financial remuneration but there is no cost to the women who take part in the study. If we find that sildenafil does improve outcome there may be some advantage to the women who have received the active drug.

What are the possible disadvantages of taking part in the study?

We will not know whether taking sildenafil will make a difference to the in-utero growth of babies until the study is completed. Possible side effects of the drug include headache, flushing, dyspepsia (indigestion), nasal congestion and impaired vision. There is also the possibility that if sildenafil is effective at improving growth a baby that would otherwise have died due to hypoxia in-utero, grows sufficiently to be born alive but then as a consequence of its small size and prematurity has significant handicap. (However, if this were the case then it is likely the drug will also reduce handicap in babies that are slightly older and/or larger that would otherwise have had major handicap).

What if I join the study but change my mind later?

Participation in this study is entirely voluntary. You can decide to stop taking the study drug (sildenafil or placebo) or withdraw from the study at any time. If you decide to stop taking the study drug your study Investigator may invite you to attend a post-treatment assessment if you have not yet delivered your baby, this may be part of or in addition to your normal care.

If you decide to stop taking the study drug or to withdraw your consent you may still wish to contribute to the study at a reduced level, for example you may still agree to some follow up contact and/or allow the Investigator and study staff to obtain information from your and your baby's medical records after this point (this decision will be your choice). If you decide to completely withdraw your consent from further trial participation no further information will be collected about you or your baby, however, any information that has been collected about you and your baby to that point will be retained and any publically available information about you or your baby may still be collected, such as information from the Birth Register.

A decision to withdraw from the study at any time will not affect the standard of your continued medical care.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

You are also advised to check whether participation in this study would affect any indemnity cover you have or are considering, such as medical insurance, life insurance and superannuation.

What if new information becomes available?

Sometimes in the course of a research project new information becomes available about the drug that is being studied. If we become aware of significant new information one of the study Investigators will tell you about it. If you are still in the treatment phase of the study the Investigator will discuss with you whether you want to continue taking the study medication. If you decide to withdraw from the study the investigators will arrange for your care to continue. If you decide to continue taking the study medication you will receive an updated information sheet and consent form to sign. Also, on receiving new information, the investigators may consider it best to withdraw you from the study or discontinue the study itself. In this situation the investigator will explain the reasons and arrange for your care to continue.

Will my GP be told I am in the study?

Yes, if you agree, we will tell your GP that you are taking part in the study.

If I need an interpreter, can one be provided?

Yes, if you require an interpreter we will provide one.

Will my taking part in the study be kept confidential?

If you consent to take part in this study your medical records will be reviewed by the research team and study investigators for the purposes of analysing the results. All information collected about you during the research will be kept strictly confidential. No material that could potentially identify you will be used in any reports of this study.

Data will be transmitted overseas and entered into an electronic data collection system managed by University of British Columbia, Vancouver, Canada. Data in this electronic system will be stored under your unique study ID number only. Identifying details such as your name, address and national hospital number will be stored separately to your study ID number and will only be known to the research staff at your hospital and at the Auckland coordinating centre, Department of Obstetrics and Gynaecology, University of Auckland, New Zealand. All hard copy data will be stored at your hospital and in the Department of Obstetrics and Gynaecology, University of Auckland, New Zealand. Records will be stored in a locked room and will be kept for a minimum of 10 years. The Principal Investigators will be responsible for their safe keeping. Access to your personally identifying information will be restricted to the research staff at your hospital, the Lead Principal and Co-investigators at the Auckland coordinating centre and research staff at the Auckland coordinating centre appointed by the Lead Principal Investigator.

Your data may also be accessed by an approved auditor appointed by an Ethics Committee or regulatory authority responsible for overseeing this research, or their approved representative, as required by law for the sole purpose of checking

the accuracy of the information recorded for this study or to ensure the rights and wellbeing of study participants are protected.

Can I find out the results of the study and what drug I received?

If you would like to know the results of the study and whether you received the active or placebo drug we will send you a summary of the study and your treatment allocation once the trial is complete (this is not expected to occur until 2016 or 2017).

Who is organising and funding the research?

The study is being organised by the Department of Obstetrics and Gynaecology, University of Auckland. The study is being funded by a Health Research Council (HRC) project grant (13/242). Each recruiting site will be provided with funding to support recruitment and data entry. Doctors conducting the research will not receive any money for recruiting women to the study or for looking after women in the study.

Where can I get more information about the study?

If you need more information about the study you can contact the Lead Principal Investigator Dr Katie Groom, your local study investigator and/or the local research midwife (contact details on page 1). You may wish to have a friend, family or whānau support person to help you ask questions and understand the study.

If you require Māori cultural support talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324.

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact and independent health and disability advocate:

Freephone: 0800 555 050

Freefax: 0800 2 SUPPORT (0800 2787 7678)

Email: advocacy@hdc.org.nz

Thank you for taking the time to read this and for thinking about being involved in the study. Please feel free to contact the researchers if you have any questions about this study.

YOU WILL BE PROVIDED WITH A COPY OF THIS FORM TO KEEP

This study has been reviewed and received ethical approval from the Northern A Health and Disability Ethics Committee (CEN/12/06/028).

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Consent form

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

Request for interpreter

English	I wish to have an interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

1. I have read and I understand the information sheet dated 5th July 2016 for volunteers taking part in the STRIDER NZAus study designed to compare the efficacy of sildenafil tablets to placebo tablets in improving fetal growth velocity in severe early onset intrauterine growth restriction (IUGR). I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
2. I have had the opportunity to use whānau/family support or a friend to help me ask questions and understand the study.

3. I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my continuing health care.

4. I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

5. I understand that the research staff will collect and process information about myself and my baby, including information about my health and the health of my baby.

6. I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.

7. I understand the compensation provisions for this study.

8. I have had time to consider whether to take part in the study.

9. I know who to contact if I have any side effects from the study.

10. I know who to contact if I have any questions about the medication used in this study or about the study in general.

I consent to blood tests to check my blood count, kidney and liver function. I understand these samples will not be stored for any further research purposes.	Yes	☐	No	☐
I consent to a placental biopsy being taken after the delivery of my baby. I understand that this sample will be stored for a period of up to 5 years. *(Auckland Study Centre only)*	Yes	☐	No	☐
I consent to a myometrial (uterine muscle wall) biopsy being taken at the time of delivery if I need a caesarean section. I understand that this sample will be stored for a period of up to 5 years. *(Auckland Study Centre only)*	Yes	☐	No	☐
I consent to the study investigators contacting me when my child is around two years old.	Yes	☐	No	☐
I wish to receive a copy of the results when they are available. *Please note that a significant delay may occur between data collection and publication of the results.*	Yes	☐	No	☐
I agree to my GP or other current provider being informed of my participation in this study.	Yes	☐	No	☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.
I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

Lead Principal Investigator:	**Local Hospital Investigators:**
Dr Katie Groom **Senior Lecturer in Obstetrics and Gynaecology** **Department of Obstetrics and Gynaecology** **University of Auckland, New Zealand** **Level 12, Support Building** **Auckland City Hospital** **Phone number: 09 3737599 ext 98923 or 021 245 9622**	Dr Katie Groom Mobile: 021 245 9622 Professor Peter Stone Mobile: 021 864726 Laura Mackay, Clinical Trial Manager Phone: 09 3737599 ext 81366 Research Midwife: 021 083 14824

Notes:

1. A copy of the consent form is to be provided to each participant and a copy is to be placed in the medical file.