Improving Right Ventricular Function in Young Adults Born Preterm: A Pilot Study

NCT03696758

08/30/2018

Protocol Title:
Improving Right Ventricular Function in Young Adults Born Preterm: A Pilot Study

Protocol Number:
2018-0796

National Clinical Trial Identified Number:
NCT03696758

Principal Investigator:
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Sponsor:
Kara Goss, MD

Funded by:
UW Institute for Clinical and Translational Research

Version Number:
V1, Aug 30 2018

Statement of Compliance:

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Sponsor Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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1. Protocol Summary

1.1 Synopsis

Title: Improving Right Ventricular Function in Young Adults Born Preterm: A Pilot Study

Study description: Adults born premature have smaller, less efficient hearts as demonstrated by recent cardiac magnetic resonance (CMR) imaging. The goal of this proposal is to assess the impact of pharmacologic reduction of right ventricular (RV) afterload and resting heart rate on RV energetic inefficiency in young adults born premature using novel 4D flow CMR imaging.

Objectives:

Aim 1: Evaluate the effect of acute right ventricular (RV) afterload reduction with sildenafil on RV function and energetic efficiency in young adults born premature. In addition to being a potent pulmonary vasodilator, several studies suggest that sildenafil may have direct inotropic and/or lusitropic effects on the RV. We hypothesize that sildenafil will reduce afterload and improve RV diastolic function, thereby improving RV function and energetic efficiency, as assessed by cardiac MRI (CMR) with 4D flow.

Aim 2: Assess the effect of acute beta blockade with metoprolol on RV function and energetic efficiency in young adults born premature. We have recently identified that adolescents and adults born premature have increased resting heart rates and autonomic dysfunction. We hypothesize that beta blockade with metoprolol will improve RV filling time and therefore improve function and energetic efficiency, as assessed by CMR and 4D flow.

Endpoints:

Primary endpoint: RV energetic efficiency. Energetic efficiency is defined as the kinetic energy (work) required for a given stroke volume in the heart, expressed as mL/mJ. Kinetic energy is measured using novel 4D flow imaging to assess flow velocities through the heart, which are then summed across the cardiac cycle. Stroke volume is calculated based on the end diastolic volume minus the end systolic volume.

Secondary endpoints: LV energetic efficiency, RV ejection fraction, stroke volume, and end systolic/diastolic volumes, LV ejection fraction, stroke volume, and end systolic/diastolic volumes.

The same endpoints will be used in both therapeutic interventions above, with comparison of efficacy of each intervention.

Study population:

Preterm subjects will be recruited from the Newborn Lung Project or the local population. Those identified from the Newborn Lung Project (NLP) cohort were born preterm from 1988-1991, birth weight <1500g, average gestational age 28 weeks, and have been prospectively followed since enrollment. Preterm subjects recruited outside the NLP will be aged 18-35, with a birth weight <1500 g OR gestational age of 32 weeks or less. Birth history for non-NLP subjects will be confirmed from health records.

Recruitment will include both male and female subjects of any race/ethnicity. Subjects must not be pregnant or lactating and may not be prescribed any other cardiac medications that would interact with the proposed therapeutic interventions (i.e. nitrates contraindicated with sildenafil, nodal-blocking agents contraindicated with metoprolol). Proposed sample size for pilot study is 10 subjects.

Phase: 2

Description of sites/facilities: University of Wisconsin

Description of study intervention:

Subjects will present for two imaging visits, with a single drug administered during each study day. Subjects will undergo CMR scanning with acquisition of standard measures of cardiac function sequences as well as 4D flow before and after therapeutic dosing, as described below (see **Figure 1** for overall study design). Order of drug dosing may be reversed.

During study visit #1, young adults born preterm will complete two CMR with 4D flow scans. Subjects will be monitored with continuous EKG and pulse oximetry during scanning, with blood pressure measures taken at least every 10 minutes. After completion of the first resting scan with image acquisition as described above, subjects will be administered metoprolol IV. Dosing will be titrated (1-5 mg Q2 min) to achieve a resting heart rate of 55-65. For subjects with a resting heart rate already within range, a 10-15% reduction in heart rate will be targeted. Subjects will then undergo a second CMR with 4D flow. Subjects will be monitored for side effects from metoprolol, including bradycardia, dizziness, and hypotension.

During study visit #2, young adults born preterm will complete two CMR with 4D flow scans. Subjects will be monitored with continuous EKG and pulse oximetry during scanning, with blood pressure measures taken at least every 10 minutes. After completion of the first resting scan with image acquisition as described above, subjects will be administered sildenafil 50 mg orally. Prior studies demonstrate that sildenafil reaches peak hemodynamic effect in approximately 50 minutes after oral intake, and its biological effects last for at least 3 hours.[1,2] One hour after oral administration of sildenafil, subjects will complete a second CMR with 4D flow. Subjects will be monitored for side effects from sildenafil, including flushing, headache, and hypotension. Sildenafil has been safely used even in advanced heart failure patients, and thus we expect this medication to be well tolerated.

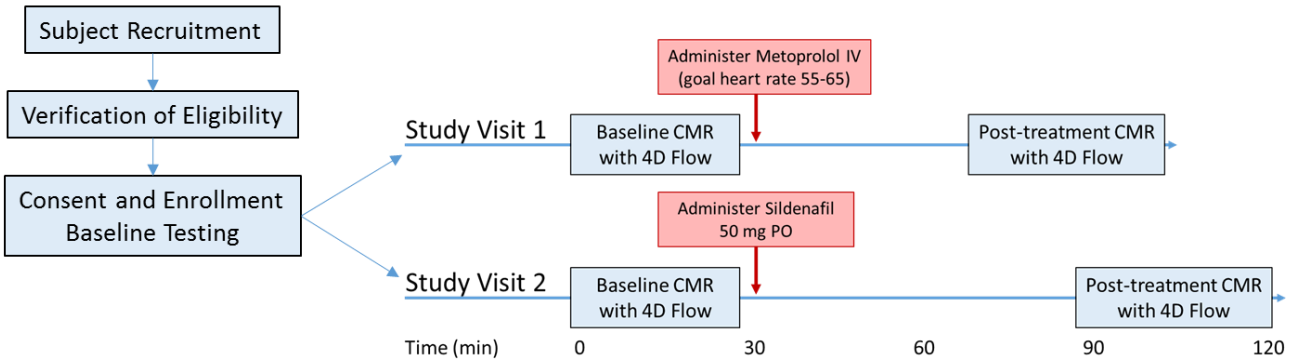
Blood and urine will be obtained during the initial visit for biobanking. The blood sample will be less than 80 mL. Biobanking is not optional for the study. Samples will be coded so that they can be linked back to data obtained in the study, including MRI data, pulmonary function data, and birth records. Samples will be stored in a locked laboratory and used exclusively for research purposes to learn more about the effects of premature birth on heart and lung function. Samples will be used primarily by the study investigators but may be shared with researchers outside of the University of Wisconsin. The identify codes not be shared beyond the investigators in this study. Participants will not receive results of any research tests using banked samples.

Study duration: 18 months

Participant duration: Each visit is estimated to take 2-3 hours.

1.2 Schema

Figure 1: Overall study design. Note study drugs may be administered in either order.



1.3 Schedule of activities

Procedures	Phone Screening	Enrollment/Baseline^ (may be combined with study visit 1 procedures)	Study Visit 1^ (administration of metoprolol or sildenafil)	Study Visit 2 (administration of metoprolol or sildenafil)
Review study requirements and eligibility	X			
Informed consent		X		
Demographics		X		
Medical history		X		
Vitals		X		AN
Height		X		AN
Weight		X		AN
EKG		X		
Pulmonary function		X		
Pregnancy test (*women only)		X		
Urine collection for biobanking		X		
Blood for biobanking (*obtained at time of IV placement)			X*	X*
Baseline cardiac MRI with 4D flow			X	X
Medication administration			X	X
Post-intervention cardiac MRI with 4D flow			X	X

[AN] Vitals, Height, and Weight will be repeated if Visit 2 occurs >7 days after Visit 1
* Blood for biobanking will be obtained either at Visit 1 or Visit 2, but not both.
^ Enrollment/Baseline and Visit 1 will most likely occur on the same day/visit. However, subjects can choose to complete these visits on separate days.

2. Introduction

2.1 Study Rationale:

Moderate to extreme preterm birth is associated with a 3-5 fold increased risk for development of pulmonary hypertension and up to a 17 fold increased risk for heart failure. We have identified early cardiac energetic inefficiency using cardiac 4D flow measures. The goal of this proposal is to assess the impact of pharmacologic reduction of right ventricular (RV) afterload and resting heart rate on RV energetic inefficiency in young adults born premature using novel 4D flow cardiac magnetic resonance imaging.

2.2 Background:

Preterm birth, defined as less than 37 weeks completed gestation, affects one in 10 live births in the United States.[3] In 2017, the NIH recommended that premature birth be considered a chronic medical disease due to its long-lasting multi-system effects.[4,5] While lung disease is the most frequently recognized complication of prematurity, adults born moderately to extremely preterm have a 3-fold increased risk for the development of pulmonary and systemic hypertension, and a 17-fold increased risk for heart failure.[6-8] Young adults born premature have biventricular hypertrophy, though the right ventricle (RV) is disproportionately affected, with functional impairments in RV but not left ventricular (LV) ejection fraction in early adulthood.[9-12] This relationship has significant clinical relevance since RV dysfunction and failure are associated with increased mortality regardless of the etiology.[13-15] However, the mechanisms of RV dysfunction in this population are poorly understood, and may have unique implications for treatment considerations.

The University of Wisconsin has recruited a rare cohort of approximately 265 young adults born premature between 1988-1991, prospectively followed as part of the Newborn Lung Project (NLP).[16-18] Our recent work in this cohort demonstrates that young adults born premature have lower exercise tolerance,[19] early pulmonary vascular disease, and impaired cardiac reserve. Novel 4D cardiac flow imaging demonstrates a higher kinetic work for a given stroke volume in young adults born premature, representing a decreased cardiac energetic efficiency that may predispose to heart failure. Intriguingly, using a rodent model of premature birth, we have also demonstrated early pulmonary vascular disease yet 'out-of-proportion' RV dysfunction that emerges when animals are aged to 1 year, despite no further deterioration in afterload or elevations of pulmonary pressures.[20-22] When applied to our human cohort, this paradox suggests that development of overt pulmonary hypertension may not be required for the RV to fail, and is in stark contrast to current RV failure paradigms. Therefore, there is a critical need to understand the direct RV effects of cardiac therapeutics in high-risk young adults born premature, as currently there are no RV-specific therapeutics for the treatment of pulmonary hypertension or RV failure. The goal of this proposal is to assess the impact of pharmacologic reduction of RV afterload and resting heart rate on RV energetic inefficiency in young adults born premature using novel 4D flow cardiac magnetic resonance (CMR) imaging.

2.3 Risk/benefit Assessment:

2.3.1 Known Potential Risks:

MRI: The standard risks associated MRI involve persons with certain metallic implants and devices (eg. pacemakers), and claustrophobia. Those patients eligible for study participation

will be screened for contraindicated metallic foreign bodies and claustrophobia using standard clinical exclusionary procedures on our MRI safety screening form. No gadolinium will be administered, which eliminates the concern of contrast induced reactions.

Electronic implants, such as cardiac pacemakers, may be susceptible to interference from the magnetic and RF fields produced by the MR system. This interference may destroy or negatively affect operation of these devices. The magnetic field of the MR system exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as an aneurysm clip, surgical clip, or prosthesis, to move or be displaced and cause injury or death. If the implant is large, sufficient currents can be induced in the metal by the magnetic field (eddy currents are induced by pulsed gradient fields) to cause heating of the implant. It is possible that subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR system. To date, however, no harmful biological effects have been demonstrated at the magnetic field strengths and exposure times utilized by the MR system. At the present time, the likelihood of any significant biomagnetic effect is considered to be very low. The magnetic field near the MR system is strong enough to attract ferromagnetic objects with great force. Near the magnet this force can be strong enough to pull objects in and cause them to fly down the axis of the magnet. Such objects become projectiles that can cause injury or death.

Pulmonary function testing: Risks associated with the pulmonary function testing include shortness of breath, dizziness, and cough. If they occur, they are expected to resolve after completion of testing.

EKG: Risks associated with EKG include discomfort or contact dermatitis from the adhesive used to adhere the leads.

Venipuncture: Risks associated with venipuncture are limited to slight pain, bleeding, bruising, and swelling at the puncture site. Some subjects may feel lightheaded during the procedure. IV catheter placement: may cause pain, bruising, fainting or infection. Topical anesthetic creams may be used to lessen the pain. With placement of the IV catheter, there is a rare risk (less than 1 out of 100 people) of bleeding, or infection associated with placement of the plastic tube in the vein.

Fasting: Risks associated with an overnight fast (minimum 8 hour) fast are minimal. Subjects may feel weak, lightheaded, or lethargic. Individuals accustomed to drinking caffeinated beverages may experience headaches. Subjects will be encouraged to drink plenty of water during this time and to notify a study team member if they need to stop the fast.

Metoprolol: Reported adverse reactions include (2-15% in chronic dosing): bradycardia, hypotension, heart block, heart failure, hypertension, angina, fatigue, dizziness, shortness of breath, bronchospasm, hypersensitivity reactions, diarrhea. Effects of acute one-time dosing are expected to be limited to hemodynamic effects. Subjects will be monitored with continuous EKG, continuous pulse oximetry, and cycled blood pressure (every 10 minutes) to minimize potential for adverse reaction. Furthermore, dose of metoprolol will be titrated to desired effect (goal heart rate 55-65 or 10-15% reduction in heart rate). Full prescribing information from package insert can be found at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017963s062,018704s021lbl.pdf.

Sildenafil: Reported adverse reactions include (2-46% in chronic dosing): headache, flushing, upset stomach, diarrhea, shortness of breath, runny nose/sinus congestion. Rare adverse events (<2% in chronic dosing) include visual disturbances and prolonged erection in

males. Effects of acute one-time dosing are expected to be minimal. Subjects will be monitored with continuous EKG, continuous pulse oximetry, and cycled blood pressure (every 10 minutes) to minimize potential for adverse reaction. Full prescribing information from package insert can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020895s033lbl.pdf.

Risk of Embarrassment: Persistent erection is a potential side effect of sildenafil, although occurring in <2% of males. If a male subject experiences this side effect, it's possible they could feel uncomfortable or embarrassed.

Questionnaires: Risks associated with questionnaires include subject fatigue and feeling uncomfortable.

Breach of confidentiality: There is a risk of breach of confidentiality. In order to protect against this risk, all data will be stored on a secure, password protected network. All data will be identified using unique identification numbers, not names, date of birth, or other identifiable information. In files where identifiable information is linked to the unique ID number, only staff members who specifically use this information for contacting participants, etc. will have access. All CMR scans performed for research purposes only will be given a unique study number that cannot be linked to the patients' hospital medical records in any way. CMR research images will be stored on PACS (Picture Archiving and Communication System) under this study number only. Study data will be managed by the PI and co-investigators.

Recruitment database: Participants may opt-in or opt-out for participation in a recruitment database. Study data will be included as part of this database, and participants may be recontacted for future studies based on data retained within the database. This data may include information from the phone screen, study visits & procedures, and NLP or neonatal records. Only research staff will have access to the information. There is a very small chance or breach of confidentiality (see above). This database will be maintained by the PI, and stored using the same confidentiality protections described throughout the study.

Biobanking**:** Blood and urine will be obtained during the initial visit for biobanking. TSamples will be coded so that they can be linked back to data obtained in the study, including MRI data, pulmonary function data, and birth records. Samples will be stored in a locked laboratory and used exclusively for research purposes to learn more about the effects of premature birth on heart and lung function. Samples will be used primarily by the study investigators but may be shared with researchers outside of the University of Wisconsin. The identify codes not be shared beyond the investigators in this study. Participants will not receive results of any research tests using banked samples.

Possible future genetic research: Future work with biobanked samples may include genetic research. Subjects may opt-in or opt-out of future genetic research, though biobanking is not optional. Future research involving large-scale genomic data may be subject to the NIH Genomic Data Sharing policy, and will comply with all applicable current regulatory requirements. This will be addressed as (1) part of any future protocols that involved large-scale genomic research using specimens collected on this study, or (2) a change of protocol under the current study to address GDS policy requirements on behalf of the researchers who conduct genetic analysis.

2.3.2 Known Potential Benefits:

Subjects are not expected to receive any immediate benefit from the study procedures. However, improving our long-term understanding of prematurity associated cardiomyopathy may have a direct impact on our understanding of treatment needs for both individual participants as well as individuals with a history of premature birth at large.

2.3.3 Assessment of Potential Risks and Benefits:

Overall, the study procedures are noninvasive aside from placement of an intravenous catheter. The study medications have a long history of tolerability in both healthy subjects as well as patients with even advanced heart failure and are expected to be well tolerated for acute dosing in this population. Subjects will be monitored closely for development of treatment-associated adverse events.

3. Objectives and Endpoints

Objectives	Endpoints	Justification
Primary		
Improve RV function	RV kinetic energy efficiency*	RV energy efficiency is reduced in preterm-born subjects, and is suspected to be an early marker of heart failure; improvement in RV energy efficiency may decrease heart failure risk
Secondary		
Improve LV function	LV kinetic energy efficiency*	To be most effective, a therapeutic intervention needs to improve both RV and LV efficiency/function
Assess standard measures of RV function	RV ejection fraction, stroke volume, and end systolic/diastolic volumes	These are standard measures of cardiac function, but change later than energy efficiency measures
Assess standard measures of LV function	LV ejection fraction, stroke volume, and end systolic/diastolic volumes	These are standard measures of cardiac function, but change later than energy efficiency measures

* Energetic efficiency is defined as the kinetic energy (work) required for a given stroke volume in the heart, expressed as mL/mJ. Kinetic energy is measured using novel 4D flow imaging to assess flow velocities through the heart, which are then summed across the cardiac cycle. Stroke volume is calculated based on the end diastolic volume minus the end systolic volume.

4. Study Design

4.1 Overall Design

Hypothesis:

1. Sildenafil will reduce afterload and improve RV diastolic function, thereby improving RV function and energetic efficiency, as assessed by CMR with 4D flow

2. Beta blockade with metoprolol will improve RV filling time and therefore improve function and energetic efficiency, as assessed by CMR and 4D flow

Phase: 2

Type of trial: Cross-over design pilot study

Methods to minimize bias: To minimize bias, we will utilize clearly defined outcomes (i.e. RV energy efficiency as primary). Eligibility, including history of preterm birth, will be confirmed in all subjects. The study will be registered at clinicaltrials.gov.

Study groups: All subjects will be adults born premature. Subjects will participate in a cross-over design study, where their responses to two therapeutic interventions are compared.

Site(s): University of Wisconsin

Study Interventions: sildenafil, metoprolol

4.2 Scientific Rationale for Study Design

This study will utilize a cross-over design to study the acute effects of two different classes of cardiac medications on cardiac performance. Prematurity associated cardiomyopathy is a newly described cardiomyopathy characterized by biventricular right greater than left hypertrophy found in neonates, children, and adults born premature. Our preliminary work demonstrates a biventricular impairment in cardiac energy efficiency, as well as elevations in pulmonary pressures. The biventricular dysfunction mandates added therapeutic considerations given that drugs targeting LV dysfunction may be harmful to the RV and vice versa. Here, we will utilize two treatment strategies – pulmonary vasodilation to reduce RV afterload and beta-blockade to improve filling time to assess the effects on biventricular function using 4D flow CMR imaging protocols.

4.3 Justification for Dose

Sildenafil is a pulmonary vasodilator. Subjects will be administered sildenafil 50 mg orally. Prior studies demonstrate that sildenafil reaches peak hemodynamic effect in approximately 50 minutes after oral intake, and its biological effects last for at least 3 hours.[1,2] This dose has previously been well tolerated in both healthy subjects and in patients with heart failure.

Metoprolol is a beta-blocker, with primary cardiac effect of slowed heart rate. Subjects will be administered metoprolol IV. Dosing will be titrated (1-5 mg Q2 min) to achieve a resting heart rate of 55-65. For subjects with a resting heart rate already within range, a 10-15% reduction in heart rate will be targeted, with the goal of improving cardiac filling time which may lead to improved cardiac filling time and cardiac energy efficiency.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study including the final scheduled visit/procedure shown in the Schedule of Activities. The end of the study is defined as completion of the last visit or procedure shown in the Schedule of Activities in the trial globally.

5. Study Population

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Male or female aged 18-35
3. History of preterm birth:
    a. Participant in the Newborn Lung Project (birth year 1988-1991, birth weight <1500 g)
    b. Non-NLP participant, with birth weight <1500 g and gestational age 32 weeks or less, verified by medical records

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the study:

1. Pregnant or lactating
2. Use of prescribed medications that would interfere with study medications
    a. Sildenafil: Use of phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil), nitrates, soluble guanylate cyclase inhibitor (riociguat) within 48 hours of study visit
    b. Metoprolol: Use of nodal blocking agents including beta blockers, non-dihydropyridine calcium channel blockers (i.e. diltiazem), and anti-arrhythmics (i.e. amiodarone)
3. Presence of known comorbidities for which these therapeutic interventions would be contraindicated:
    a. Moderate to severe heart failure
    b. Severe bradycardia (heart rate <45), or second or third-degree heart block
    c. Systolic blood pressure <90 mmHg or >190 mmHg
    d. Angina
    e. Severe peripheral arterial circulatory disorders
4. History of severe bronchospasmPresence of any implanted device incompatible with CMR imaging
5. Known allergic or hypersensitivity reaction to components of the study medications
6. Any other reason for which the investigator deems a subject unsafe or inappropriate for study participation.

5.3 Lifestyle Considerations

During this study, participants are asked to:

- Abstain from caffeine and alcohol for 24 hours prior to each imaging study.
- Avoid grapefruit consumption for 48 hours prior to imaging study

- Fast for a minimum of 8 hours prior to the study visit involving lab draw for biobanking.
- Fast for a minimum of 4 hours prior to the study visit involving oral sildenafil administration.

Subjects unable to meet these restrictions may be excluded from the study or may have their visits rescheduled for a different time when they can better meet the restrictions (investigator discretion).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Individuals who do not meet the criteria for participation in this trial (screen failure) because of a specific modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

Pilot study target sample size: 10 completed subjects (not including screen failures)

Anticipated accrual rate: 1 subject per month

Number of sites: 1

Source of participants:

- Newborn Lung Project.
- General public with verified history of premature birth.

Subject identification and recruitment:

Preterm subjects who have previously participated in research conducted in the Eldridge laboratory or by Dr. Kara Goss (IRB 2009-0212, 2013-1523, and 2017-0238) and who have previously given consent for contact will be recruited for participation. We have mailing addresses, email addresses, and phone numbers for these members of the NLP cohort. Using contact information provided by the subjects for re-contact, potential subjects from the NLP cohort will receive a recruitment email, letter, or phone call, asking if they would like to be part of the study. Subjects will not be contacted more than 3 times total by any single method if we don't receive a response. Messages left on phones will not include health information. If the subject is not reached, the message will give our contact information for them to call back.

Recruitment of non-NLP preterm subjects from the general public will be done via:

- Mass mailing (ie through UW email)
- Posting local flyers (ie UW Hospitals and Clinics approved message boards) or via paid newspaper advertisements

- Through internet posting (ie posting on social media sites, UW Facebook Research pages, Jobcenter board, or Craiglist Madison).

Interested individuals will contact the study coordinator. Women and minorities will be recruited, with a goal to have equal distribution of sexes. Given the small initial study size, minority ethnic groups will not be directly targeted but will be welcomed.

Compensation:

$450 for completion of all study visits. Parking validation and travel expenses (ie mileage) will be provided for research subjects. Compensation may be prorated at $50/hr if a subject is unable to complete the visit.

6. Study Intervention

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Both study drugs (sildenafil and metoprolol) are commercially available and will be used in accordance with approved labeling.
Metoprolol:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017963s062,018704s021lbl.pdf.
Sildenafil:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020895s033lbl.pdf.

6.1.2 Dosing and Administration

Metoprolol: IV, dose titrated 1-5 mg every 2 minutes to achieve goal heart rate of 55-65 beats per minute, or for subjects with a resting heart rate already at goal, titrated to achieve a 10-15% reduction in heart rate.

Sildenafil: 50 mg oral once

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Study medications will be acquired from the University of Wisconsin Pharmaceutical Research Center (PRC). All unused medications will be returned to the PRC.

6.2.2 Formulation, Appearance, Packaging and Labeling

Medications will be packaged in standard clinical packaging, concentration of 5 mg/5ml.

6.2.3 Product Storage and Stability

Medications will be retained in original packaging/carton until time of use, and protected from light.

6.2.4 Preparation

Metoprolol will be drawn into a syringe for administration by an appropriately credentialed team member (RN or MD) by IV push. Saline flush will be administered after each dose.

No special preparation concerns for sildenafil.

6.3 Measures to Minimize Bias

Study interventions are not blinded. There will be a minimum period of 12 hours between drug interventions to ensure adequate drug wash-out.

6.4 Study Intervention Compliance

All study medications will be administered in a clinical setting to ensure compliance.

6.5 Concomitant Therapy

Use of concomitant medications will be assessed at the baseline visit. Medications to be reported in the Case Report Form are concomitant prescription medications, over-the-counter medications, and supplements.

6.5.1 Rescue Medicine: not applicable

7. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. The UW IRB approved consent form will state that subjects may withdraw from this study at any time without any change in the quality of their medical care or loss of benefits.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive the study intervention

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent

form, and are enrolled and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for 1 visit and is unable to be contacted by the study site staff. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

• The site will attempt to contact the participant and reschedule the missed visit and ascertain if the participant wishes to and/or should continue in the study.

• Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

• Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. Study Assessments and Procedures

8.1 Efficacy Assessments

Cardiac Imaging: CMR will be performed on a 3T scanner (GE Healthcare, Waukesha, WI). The CMR protocol, including sequences and analyses, is summarized in **Table 1**. Multiplanar, cardiac gated, cine balanced steady-state free precession (bSSFP) series will be acquired through the heart for assessment of heart size and function. Flow through the tricuspid and mitral valves will be assessed with cardiac gated, cine two-dimensional (2D) flow-sensitive sequences. Four-dimensional flow sensitive magnetic resonance imaging (4D flow MRI) will be performed with a radial undersampled acquisition, Phase Contrast with Vastly undersampled Isotropic Projection Reconstruction (PC VIPR).[32-34] CMR sequence parameters will be individually adapted to each participant's anatomy to optimize scan time and temporal resolution as recommended by the Society of Cardiovascular Magnetic Resonance.[35]

Cardiac MRI Analysis: Standard CMR images will be analyzed per published recommendations.[36] Analysis will be conducted by the University of Wisconsin Medical Imaging Research Support-Image Analysis Core. Outcomes determined will include measures of RV and LV cardiac systolic and diastolic function (Table 1). Assessment of systolic function will include quantification of RV and LV end-diastolic volume index, end systolic volume index, stroke volume index, ejection fraction, cardiac output, and cardiac index. Peak filling rate and time to peak filling rate, indices of diastolic function, will be determined by segmentation of the RV and LV throughout the cardiac cycle. Diastolic function will also be evaluated by quantifying the peak transtricuspid and transmitral valve velocities during ventricular relaxation (E-wave velocity) and atrial contraction (A-wave velocity), as well as their ratio (E/A).

4D Flow Analysis: Ventricular kinetic energy (KE), main pulmonary artery (MPA) flow and ascending aorta flow will be quantified from the 4D flow MRI data using previously published algorithms developed at our institution.[33,34] Briefly, the heart and thoracic vasculature will be segmented from the complex difference angiographic images using commercial image processing software (Mimics, Materialise, Leuven, Belgium) and exported as a mask to be combined with the time-resolved three-directional velocity data within a visualization software package (Ensight, CEI Inc., Apex, NC). Flow in the MPA and ascending aorta will be measured

from planes 2 cm from the annulus. RV and LV KE is determined by independently segmenting each of the ventricles from time-averaged PC VIPR magnitude images in Mimics. A mask is applied to the time-resolved velocity images, and the kinetic energy across the cardiac cycle is computed using the formula: $KE_{total}=^{frame}{}^{voxel}\sum_{1}$ ½ mv^2, where m=mass and v=velocity. To characterize energy efficiency, the total KE across the cardiac cycle is normalized to the flow through the MPA (Q_P) and aorta (Q_S).

Table 1. CMR protocol for assessment of RV and LV systolic and diastolic function, efficiency and fibrosis.

Ventricle	Assessment	MRI sequence(s)	Measurements
RV	Systolic function	Axial cine bSSFP	EDVi, ESVi, SVi, EF, CO, CI
	Diastolic function	Axial cine bSSFP 2D flow (tricuspid valve)	PFR, TTPFR E, A, E/A
	Efficiency	4D flow MRI	KE, MPA flow
LV	Systolic function	Short axis cine bSSFP	EDVi, ESVi, SVi, EF, CO, CI
	Diastolic function	Short axis cine bSSFP 2D flow (mitral valve)	IVRT E, A, E/A
	Efficiency	4D flow MRI	KE, aorta flow

Abbreviations – bSSFP, balanced steady state free precession; 2D, two-dimensional; 4D, four-dimensional; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; SVi; stroke volume index; EF, ejection fraction; CO, cardiac output; CI, cardiac index; PFR, peak filling rate; TTPFR, time to peak filling rate; E, peak flow velocity during ventricular relaxation; A, peak flow velocity during atrial contraction; KE, kinetic energy; MPA, main pulmonary artery.

8.2 Safety and Other Assessments

Screening: Study coordinators will conduct a phone screen to determine eligibility.

Verification of medical records: General information regarding birth history will be asked of all subjects (i.e. gestational age, birth weight). This history will be verified and additional birth history will be collected from Newborn Lung Project medical records, records from previous studies that collected NLP data (IRB 2009-0212, 2013-1523, and/or 2017-0238), or birth hospitals, where available. This information will include prenatal characteristics (including but not limited to: maternal age, demographics, gravidity, comorbidities such as diabetes, hypertension, asthma, tobacco use, alcohol use, antenatal steroid use), birth and postnatal characteristics (including but not limited to: gestational age, anthropometric data, delivery type, and data regarding neonatal comorbidities such as bronchopulmonary dysplasia, intracardiac shunts, sepsis, respiratory failure, nutrition), and childhood characteristics (including but not limited to: anthropometric data, history of early wheezing, cigarette exposure, treatment for respiratory illnesses such as bronchopulmonary dysplasia and asthma, and serial pulmonary function testing).

Baseline measures: Study coordinators will verify demographic and medical history data with subjects. An MRI metal screening sheet will be completed in accordance with standard clinical practice. Anthropometric measures (height, weight) and vital signs (heart rate, respiratory rate, pulse ox, blood pressure) will be obtained in accordance with standard clinical practice. If the CMR imaging visits are separated by >7 days, anthropometric and vital sign measures will be repeated.

Pregnancy testing: All female participants will complete a urine pregnancy test. If the CMR imaging visits are separated by >7 days, a repeat pregnancy test will be required.

EKG: All subjects will undergo a resting EKG for screening purposes to verify absence of severe bradycardia or heart block prior to proceeding to imaging. EKGs will be reviewed by a qualified study personnel at the time they are completed. Abnormal findings that would exclude participation will be discussed with the study participant immediately. Devices are non-investigational.

Pulmonary function testing: Subjects will undergo non-invasive pulmonary function testing including spirometry, plethysmography (for lung volumes) and diffusion capacity, according to standard clinical testing. All procedures are performed according to standard clinical practice and all devices are non-investigational.

Venous cannulation: One intravenous (IV) line will be placed by qualified study personnel. Lidocaine or topical anesthetic may be administered as a local anesthetic.

Biospecimens for biobanking: Blood for biobanking will be collected at the time of IV placement. Blood volume sampled will be less than 80 ml total. Urine samples will be collected for biobanking at the baseline visit.

Health questionnaires: The subjects will answers health questionnaires, a Pre-Session Questionnaire and Symptom Questionnaire.

Monitoring during CMR: Subjects will be monitored with continuous EKG and pulse oximetry during scanning, with blood pressure measures taken at least every 10 minutes. Subjects will be assessed for adverse events during and after therapeutic intervention.

Incidental Findings: Testing that excludes a subject from study participation (i.e. positive pregnancy test, second or third-degree heart block) will be disclosed immediately. EKG and pulmonary function testing will be reviewed by the study team, and any potentially clinically significant abnormal findings will be discussed with subjects by a qualified RN or MD on the study team. Clinically significant non-investigational CMR findings will be discussed with subjects by a qualified MD on the study team.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening do not need to be considered an adverse event, unless they:

1. fulfill the definition of a serious adverse event, or
2. have worsened and are clinically significant requiring medical intervention other than the use of the rescue medication, or
3. result in discontinuation of subject from the study.

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the PI, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 Expectedness

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

A study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 Adverse Event Reporting

All non-serious and unexpected adverse events will be kept in an adverse event log and reported annually. Other adverse events that are both not serious and expected will not be reported. These are the expected adverse events listed in the protocol and consent as possible results from a study procedure. The investigator will meet all local reporting requirements as dictated by the UW IRB.

8.3.6 Serious Adverse Event Reporting

The PI will be immediately notified of any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

The PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. In addition, the PI must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

8.3.7 Reporting Events to Participants

Participants will be informed about AEs and SAEs on an aggregate level as needed.

8.3.8 Events of Special Interest

Not applicable.

8.3.9 Reporting of Pregnancy

A positive pregnancy test will immediately be reported to the subject.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

• Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

• Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

• Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

• Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

• A detailed description of the event, incident, experience, or outcome;

• An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

• A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

• UPs that are serious adverse events (SAEs) will be reported to the IRB within 72 hours of the investigator becoming aware of the event.

• Any other UP will be reported to the IRB 7 days of the investigator becoming aware of the problem.

• All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the

Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems to Participants

Participants will be informed about UPs on an aggregate level as needed.

9. Statistical Considerations

9.1 Statistical Hypothesis

Sildenafil: We expect sildenafil will improve RV energetic efficiency, systolic, and diastolic function. LV measures will be included in all subjects to ensure absence of worsening LV function (energy efficiency, systolic, and diastolic function) with RV afterload reduction. We expect that LV function will improve with sildenafil as well.

Metoprolol: We expect metoprolol to improve cardiac filling times, resulting in an improved RV and LV energetic efficiency.

9.2 Sample Size Determination

As a pilot study, we propose enrolling and completing 10 subjects. Our prior study (n=9) demonstrates an RV energy efficiency of 1.09±0.26 mL/mJ, and thus we estimate that 10 subjects will allow us to detect a 30% improvement in RV energy efficiency (alpha 0.05, beta 0.8) for either drug intervention.

9.3 Populations for Analyses

Participants who received at least one dose of the study intervention will be analyzed in a modified intention to treat analysis. Safety analysis will be completed in all subjects who received at least one dose of the study intervention.

9.4 Statistical Analyses

9.4.1 General Approach

RV kinetic energy efficiency serves at the primary endpoint for both therapeutics. Secondary endpoints are LV kinetic energy efficiency and standard biventricular measures of RV and LV function (Table 1). All measures will be assessed by individuals blinded to the intervention, and results will be summarized as means +/- standard error. Data analysis will be quantitative, with differences among means compared using Wilcoxon Rank Sum tests for each therapeutic intervention. Comparisons between interventions will be with ANOVA. All p values will be two-sided, with $p<0.05$ used to define statistical significance.

9.4.2 Analysis of the Primary Efficacy Endpoint

To determine RV kinetic energy, a mask is applied to the time-resolved velocity images, and the kinetic energy across the cardiac cycle is computed using the formula: $KE_{total}=^{\text{frame voxel}}\sum_{1}$ ½ mv^2, where m=mass and v=velocity. To characterize energy efficiency, the total KE across the cardiac cycle is normalized to the flow through the MPA (Q_P) and aorta (Q_S). Analysis will be completed in blinded fashion. RV energy efficiency measures will be compared using Wilcoxon

Rank Sum tests for each individual after each intervention. All p values will be two-sided, with $p<0.05$ used to define statistical significance. Comparison between intervention will be with ANOVA.

9.4.3 Analysis of the Secondary Endpoint(s)

LV kinetic energy efficiency will be determined similar to RV kinetic energy efficiency, and may not be dependent of the primary endpoint. Measures will be compared using Wilcoxon Rank Sum tests for each individual after each intervention. All p values will be two-sided, with $p<0.05$ used to define statistical significance. Comparison between interventions will be with ANOVA. Standard morphometric analysis (ventricular volumes, ejection fractions) will be compared similarly.

9.4.4 Safety Analyses

LV kinetic energy efficiency will be determined as a primary safety endpoint, and could worsen despite improvement in RV kinetic energy efficiency.

9.4.5 Baseline Descriptive Statistics

Baseline descriptive characteristics will not be compared, as each subject will serve as his/her pre-post comparison for each intervention.

9.4.6 Planned Interim Analysis

Not applicable.

9.4.7 Sub-group Analysis

Not applicable.

9.4.8 Tabulation of Individual Participant Data

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. See consent materials.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or delegate will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Prior to providing written informed consent, subjects will provide oral consent to fast and abstain from caffeine, alcohol, and consuming grapefruit prior to their study visits (part of the phone eligibility screen). Subjects will also provide oral permission to receive a copy of the consent form via email or post-mail. Subjects born premature that are not part of the NLP Cohort will provide oral consent for the release of their neonatal records, which will be used to confirm eligibility. If a Non-NLP subject incorrectly reports meeting the study inclusion/exclusion criteria (based on their neonatal records), they will be contacted by a member of the study team and any scheduled study visits will be cancelled. Additionally, their neonatal information/records will be destroyed.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and PI will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the PI, IRB and/or Food and Drug Administration (FDA).

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and future genetic tests (from biobanked samples) in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the PI. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the PI, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or PI requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on secure servers or in locked file cabinets. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the University of Wisconsin. After the study is completed, the de-identified, archived data may be be transmitted to and stored at the University of Wisconsin, for use by other researchers including those outside of the study. Permission to transmit data to future Data Repositories will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored in a biobank (in the PI's lab) at the University of Wisconsin. These samples could be used to research the causes of prematurity associated cardiomyopathy, its complications and other conditions for which individuals with a history of premature birth are at increased risk, and to improve treatment.

During informed consent, subjects will be informed that biobank storage of their blood and urine samples for future research is not optional.. However, subjects can choose if they want their samples to be used in future genetics research. Subjects can withdrawal consent by written request to the PI.

When the study is completed, access to study data and/or samples will be provided through the NLP Repository.

10.1.5 Key Roles and Study Governance

Principal Investigator:
Kara Goss, MD
Assistant Professor of Medicine and Pediatrics

University of Wisconsin
600 Highland Ave CSC H4/616
Madison, WI 53792

10.1.6 Safety Oversight

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Safety oversight will be under the direction of the PI, who will conduct safety assessments annually at a minimum. The investigator will use her clinical expertise to evaluate the effect of the study procedures on the proposed primary and secondary outcomes, noting a direction of improvement, stagnation, or exacerbation. Any adverse and serious adverse events will be reviewed both cumulatively and individually to assess the continuing safety of the trial. The investigator will compare/contrast AEs/SAEs occurring after Sildenafil administration with those of Metoprolol. Findings from these assessments/evaluations will be used collectively to determine the continuing risk/benefit ratio of the study. Based on the risk/benefit ratio, the investigator may choose to continue the study under the current protocol specifications, continue the study with an altered design, or terminate the study.

10.1.7 Clinical Monitoring - Not applicable: internal safety and data oversight

10.1.8 Quality Assurance and Quality Control

Annually at minimum, designated members of the study team will perform quality management of study conduct, data and biological specimen collection, documentation and completion. Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to PI for clarification/resolution.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a 21 CFR Part 11-compliant data capture system provided by the University of Wisconsin Department of Medicine. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 Study Records Retention

Study records will be retained for a minimum of three years after study completion (including the completion of data analyses) and funding expiration. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the PI, if applicable.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations meeting the following criteria will be reported to the IRB within 7 days of the PI's awareness of the event unless more immediate reporting is required:

- The deviation affected or had the potential to affect the subject's rights, safety or welfare*;
- The deviation resulted in a change to the participant's clinical or emotional condition or status;
- The deviation affected the integrity, accuracy and/or reliability of the research data; and
- The deviation resulted from willful or knowing misconduct on the part of the study team.

*The IRB considers all study drug dosing errors (under- or over-dosing) to meet this criteria; therefore, all dosing errors require reporting to the IRB.

10.1.11 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting Kara Goss.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

None.

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