APPENDIX F. SAMPLE CONSENT

Informed Consent Statement for:

Milrinone in Congenital Diaphragmatic Hernia

Investigator

Location

Telephone

Protocol Title
<Full Title>

We are asking your permission to let your baby be in an initial pilot research study about using a drug called milrinone in babies with congenital diaphragmatic hernia. Your baby is a possible participant because he or she has a congenital diaphragmatic hernia (CDH) and needs a breathing machine (called a ventilator) to help him/her breathe.

Before you decide whether or not to let your baby be in the study, it is important for you to know why this research is being done and what it means to be in the study. Please take time to read the following information carefully, and talk about it with family, friends and others if you wish. It is very important that you ask us any questions you have about this research study.

This study is sponsored by the *Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The NICHD Neonatal Research Network* is conducting this study at 15 centers across the country including this hospital.

Background: What is congenital diaphragmatic hernia?

Congenital diaphragmatic hernia is a serious congenital condition managed in the neonatal intensive care unit (NICU). The diaphragm is a muscle that moves up and down in the chest when you breathe. Congenital diaphragmatic hernia is a hole in the diaphragm.

The diaphragm keeps the lungs in the chest and away from the stomach area. The hole in the diaphragm causes the stomach and other organs to move up into the chest closer to the lungs. When this happens, the lungs do not grow properly because there is now less room in the chest area. Lungs become smaller in size. Small lungs may lead to low blood flow to the lungs and high blood pressure in the lung vessels, also known as persistent pulmonary hypertension of the newborn (PPHN).

In the past 20 years, there have been new types of breathing machines, new drugs for PPHN, better surgical techniques and the use of heart-lung bypass also known as extracorporeal membrane oxygenation (ECMO). ECMO is a process where a baby is hooked up to a machine that takes over the work of the lungs and sometimes the heart; it is a way to allow your baby's lungs time to rest while making sure that he/she is getting the right amount of oxygen to all the organs in the body. Sadly, 30% of babies with CDH die because of the disease and low blood flow to the lungs.

Why is this study being done?

The purpose of this study is to find out whether a drug called milrinone, when given to infants with CDH, will help the heart work better by supplying oxygen to the lungs and tissues.

Milrinone is a medication that is currently approved by the Food and Drug Administration (FDA) for short-term use in adults with heart failure. In a large study involving 238 children, milrinone was shown to help the heart work better after heart surgery. From our past survey, we found out that about 17% of babies with CDH who are patients in some large hospitals are given milrinone as a treatment for CDH.

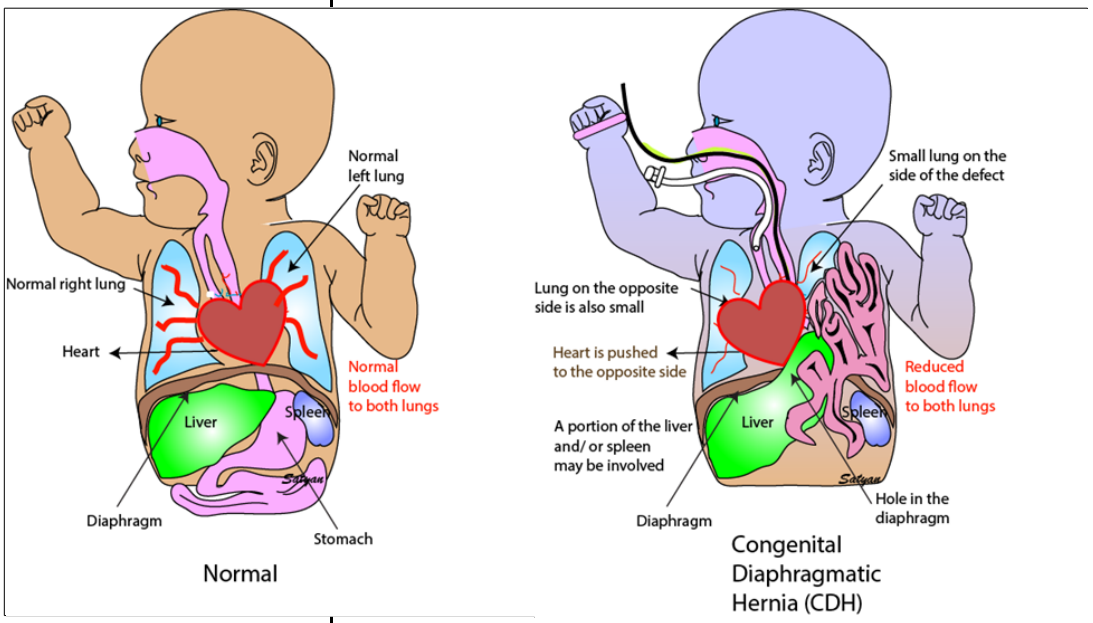
Some doctors use milrinone to help improve blood flow to the lungs in babies. Milrinone may help in CDH, by opening up the blood vessels in the lung which may help the heart and lungs give enough oxygen to tissues and other organs.

The main purpose of this study is:

This initial pilot study will help us to understand how milrinone works to help the heart and lungs give oxygen to the tissues and other organs in infants with CDH. We are hoping this pilot study will support and look at the possibility and safety of conducting a much larger study.

How many people will be in this study?

About 65-70 babies in the United States will join this study. We are expecting ## babies from this hospital will be part of the study.



What will happen if I refuse to have my baby participate in this research?

If you decide not to participate in the study, standard care will be provided to your baby. Your baby's doctor may or may not use milrinone to treat your baby.

What will happen if my baby is in this research?

If you decide to allow your child to take part in this research study, the following steps will explain what will happen in the study.

There are two groups in this study:

- **Control group** is the group of babies in the study who will get placebo, a sugar solution. This group will not get the study drug milrinone.
- **Treatment group** is the group of babies in the study who will get the study drug milrinone.
- Only the pharmacist will know which group your child is in. No one else will know the group, not your baby's doctor, nor you or the study team. This is called a masked study where very few people know which baby is in which group. This helps make sure that there is no bias when taking care of the baby.
- The research team will use a computer that decides which group your baby will be a part of. This is called randomization. Your baby will have an equal chance of being in either group. There is a 50% chance that your baby will receive the study drug, just like a flip of a coin.

After randomization the following will happen in both the **control** and **treatment groups**:

- Your baby will start receiving a low dose (0.33µg/kg/min) of milrinone in the treatment group or sugar solution in the control group through an intravenous (IV) line.
- For the first 2 to 4 hours, the study team will check to see if there are any major side effects from the study drug.
- If your baby has no major side effects, the dose will go up to 0.66 µg/kg/min. The study drug will then stay at this dose, no more changes will happen to the dosage.
- The study drug will continue to be given for up to 72 hours (3 days).
- If your baby's heart starts to work better by using less oxygen from the breathing machine (ventilator), the study drug may be stopped before 3 days.
- If there are side effects, then the study drug will be stopped and will not be started again.
- If your baby needs surgery or ECMO, it is up to your baby's doctor or surgeon if study drug will be continued.
- Once your baby's oxygen levels are better or 72 hours is reached, milrinone or placebo is lowered by 0.33 µg/kg/min every two hours and stopped.
- Your baby will have a head ultrasound done before study drug starts or shortly after and another one around 24 hours after study drug is stopped. These head ultrasounds will be paid for by the study.
- Information will be collected from your baby's medical record including demographic information, gestational age, blood pressures/heart rates/respiratory rates, information about his/her breathing, medications, medical procedures including echocardiograms (sonogram of the baby's heart), ECMO (placement on a heart-lung bypass machine), surgeries, head ultrasounds and diagnoses.
- We will also be collecting information from the maternal medical record including ultrasound and MRI (if performed during pregnancy).
- Right after the study drug is stopped (which could be 3 days or less) your doctor may decide to give your baby the drug milrinone. This is up to your baby's doctor.

Follow-up

We will continue to collect data on your baby while he/she is in the NICU until discharge. After discharge, we will contact you (or your baby's healthcare provider in the event that your baby is still hospitalized) to complete a

short questionnaire at 4, 8, and 12 months of age regarding your baby's health.

How long will my baby be in this study?

Your baby will be given the study drug (which is either milrinone or sugar solution) for up to 3 days only. We will be collecting data from your baby's hospital stay. We will also be calling you at 4, 8 and 12 months to ask you a few questions about your baby's health. After the 12 month phone call, the study is over for your baby. The overall study will continue until the last baby that joins the study has the one year phone call.

What are the possible risks and discomforts from being in this research study?

Treatment Group

The most common side effect of milrinone is having low blood pressure. Your baby's blood pressure will be closely watched by your baby's doctor. Low blood pressure is common among babies with CDH and milrinone may or may not make this problem worse or more difficult to treat. In infants with CDH, low blood pressure can worsen respiratory status. If the blood pressure continues to stay low while your baby is getting study drug, the investigator and your baby's doctor may decide to stop the study drug.

In adults who were given the drug, milrinone, there were some irregular heart rhythms called arrhythmias. We do not know if milrinone causes arrhythmias in babies.

In critically ill newborn infants who did not have CDH, there have been reports of bleeding in the brain that could be related to milrinone. This is rare and does not happen often. Your baby's doctor will closely watch for this by ordering a head ultrasound prior to starting study drug and repeating one after completion of study drug. A head ultrasound shows a picture of your baby's brain to check if there is any bleeding. If there is a sign that there is some bleeding in the brain, the study drug will be stopped.

Uncommon risks experienced in adults: In addition to the risks outlined above, adults receiving milrinone have rarely (< 1%) experienced low potassium levels, low platelet counts and allergic reactions. These side effects have not been reported in children at a frequency higher than that associated with placebo (sugar water). Your child will be monitored for these side effects as part of routine care in the NICU.

Milrinone does not alter urine output. However, the body gets rids of milrinone by excreting it in the urine. If urine output is very low, your baby's doctor may stop the study drug.

Control Group

Your baby's blood pressure and respiratory status will be closely watched by your baby's doctor. Low blood pressure is common among babies with CDH. If the blood pressure continues to stay low while your baby is getting study drug, the investigator and your baby's doctor may decide to stop the study drug.

Unknown Risks

There may be risks to being in this study that are not known to the researchers at this time. Some unknown risks may be learned during this study. If any new risks that might affect your baby are learned while your baby is in this study, we will let you know about them.

Confidentiality

If your baby is in this study there is a small risk of loss of confidentiality or privacy. Every effort will be made to keep your baby's information confidential.

What are the benefits of being in this study?

We cannot promise any benefits to your child from your taking part in this research. However, some babies may have improved blood flow to the lungs and higher oxygen in their blood. Milrinone may help the heart work better and give more oxygen to the tissues, and organs. There are some babies who may not benefit from taking part in this study either because milrinone will not have an effect or they received the placebo (sugar solution). Congenital diaphragmatic hernia is a disease that has a high risk of complications. We hope that this study will help us learn how to take care of very sick babies with CDH in the future.

Will my baby's medical information be kept private/confidential?

Any personal information about you or your baby that is collected during this study will be kept confidential under the law. A study number will be used to identify your baby. Only the study team will know your name. We will do everything we can to keep your and your baby's records confidential, but we cannot guarantee absolute confidentiality.

Your or your baby's personal information may be shared if required by law. Your and your baby's identity will not be shared in reports or publications about this study.

Coded study information will be sent to the NICHD Neonatal Research Network's Data Coordinating Center, Research Triangle Institute (RTI) International, in Research Triangle Park, North Carolina. The University Institutional Review Board (IRB), Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) may access these records.

Information from this research study will be kept by <Local Research Institution> and RTI International and may be shared for future research in accordance with the NIH Public Access Policy. Information released under this policy will not identify your baby or his/her participation in this research study.

A description of this study will be available on ClinicalTrials.gov, ID number NCT02951130, as required by U.S. Law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results of this study. You can search this website at any time.

<Insert Institution-specific HIPAA language.>

What are the costs of being in this research study?

There will be no cost to you or your insurance, for any test, treatment or visit that is done only for this study. The parts of your baby's care that would normally be done as standard treatment will be billed to you or your insurance company. The study will pay for all parts of your baby's care that are done only for the study including two head ultrasounds and the cost of the study medication.

Will I be paid for being in this research study?

If you agree to allow your baby to take part in this research study, we will pay you $25 in the form of a gift card after completion of the 4, 8, and 12 month follow-up questionnaires for your time and effort.

What happens if my baby is injured as a result of being in this research study?

If you have questions, concerns, or complaints, or think the research has caused harm to your baby, talk to the research team at (XXX) XXX-XXX. You may also contact the research participant advocate at XXX.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (XXX) XXX-XXXX or email XXX if:

- You have questions about your baby's rights as a participant in this research
- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You want to get information or provide input about this research.

Is being in this study voluntary?

Yes, being in this study is voluntary. If you decide to let your baby be in this study you are still free to withdraw him/her at any time. You do not have to give a reason for changing your mind. If you do not let your baby join or you decide to withdraw your baby from this study later, there will be no penalty or loss of benefits to which he/she is otherwise entitled.

If you do not let your baby be in the study, he/she will still receive all usual care that is available to him/her. Your choice will not affect the relationship you or your baby have with his/her doctor or other staff, or change the care that your baby receives.

There is a possibility that there may be changes in your baby's blood pressure and oxygen level in the body if the study drug is stopped too quickly. For this reason, the study team and the clinical team may choose to stop the drug slowly over a few hours if you decide to withdraw your baby from research.

If you decide to have your baby leave the research, contact the investigator so that the investigator can notify the study team.

If you decide to not have your baby receive any more study drug, we will ask for your permission to keep the data that has already been collected. You will be asked if the study team can continue to collect data from your child's routine medical care. There will be no other study related activity other than data collection. If you agree, this data will be handled in the same way as research data. If you decide to no longer have your baby be a part of the study while in the NICU, we will ask you for permission to contact you when your child is 4, 8, and 12-months old to complete the follow-up questionnaires.

New Information

Sometimes new information becomes available during a research study that may influence your decision to let your baby be in the study. If this happens, the study team will tell you about it and talk with you about whether you want your baby to stay in the study. If you decide to withdraw your baby at that time, the research doctor will make arrangements for your baby's ongoing medical care. If you decide to let your baby stay in the study, you will be asked to sign an updated consent form.

Right of Investigator to Withdraw Participants

The investigator can withdraw your baby from the study without your approval. Possible reasons for withdrawal include new information that shows the risks of the study are greater than the benefits, or if your baby develops a severe problem that requires the study procedures to be stopped.

Who should I contact if I have questions or concerns about this study?

If you have any questions about the study or complaints or concerns during the study, you should contact the investigator (Dr. ___), the co-investigators (Drs. ___ or ___) or other study team members via the University Paging Operator: (xxx) xxx-xxxx, the University NICU (xxx-xxx-xxxx or the ____ NICU (xxx) xxx-xxxx, 24 hours a day. If you

think your baby may have been injured from being in this study, you can contact the same people.

Institutional Review Board

Contact the Institutional Review Board (IRB) if you have questions regarding your baby's rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the study team. The University IRB may be reached by phone at (xxx) xxx-xxxx or by e-mail at irb@xxxxx.edu.

We are always available to answer your questions. If you have any questions that come up during this study, please be sure to ask us.

STATEMENT OF CONSENT

I confirm that I have read this parental Informed Consent document and have been able to ask questions. I will be given a signed copy of this form to keep.

I agree to allow my baby to be in this research study as you have explained in this document.

_____
Baby's Name

_____
1st Parent/Guardian's Name

_____ _____
1st Parent/Guardian's Signature Date

_____
Relationship to Baby for 1st Parent/Guardian

<Insert 2nd Parent/Guardian line if necessary.>

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date