ClinicalTrials.gov Study Document Cover Page

Official Study Title:
Milrinone for Prevention of Post-Ligation Cardiac Syndrome (PCLS)

Short Title:
MIDAS Trial

Document Type:
Informed Consent Form

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166891

Informed Consent and Authorization Statement for:

Milrinone for Prevention of Post-Ligation Cardiac Syndrome (PLCS)

We are asking your permission to let your baby be in a research study about the use of milrinone, a medicine that makes it easier for the heart to pump, after the patent ductus arteriosus (PDA) is closed. Your baby is a possible participant because he or she was born at a gestational age less than 28 weeks, is ≤ 90 days old, is receiving breathing support, and has a diagnosis of PDA. The clinical team has decided to close the PDA either through surgery or by placing a device inside the PDA through a catheter in the vein.

Before you decide whether 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. We would encourage you to 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) and the National Heart, Lung and Blood Institute (NHLBI), which are part of the National Institutes of Health (NIH). The study is being conducted across 15 sites in the Neonatal Research Network (NRN) and 4 additional non-NRN sites. The lead investigator is Dr. Patrick McNamara, who is a Professor of Pediatrics at the University of Iowa.

Investigator: Dr Tarah Colaizy

Location: University of Iowa

Telephone: 319-356-3508

Protocol Title: Milrinone for Prevention of Post-Ligation Cardiac Syndrome (PLCS), the MIDAS Trial.

Keywords:
Patent Ductus Arteriosus (PDA)- blood vessels that directs too much blood to the lung and to little to the body

Milrinone - drug to help the heart pump better

Post Ligation Cardiac Syndrome (PLCS) - a condition in which the heart function worsens after PDA closure causing problems with blood pressure and breathing

Background:

- PDA closure (surgery or transcatheter device placement) is a life-saving intervention for some extremely preterm infants.

Some babies take time to adapt to the change in physiology after PDA closure. When this happens, babies may develop poor heart function leading to problems with their blood pressure and

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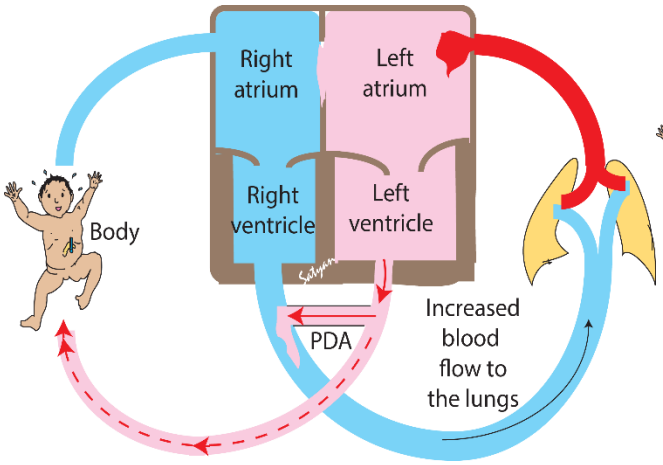
worsening of their breathing (see Figures below). This illness is called Post Ligation Cardiac Syndrome (PLCS).

Previous research has shown that smaller (<1 kg) and younger babies (≤ 90 days of age) are at greatest risk of PLCS. This may lead to long-term lung problems, changes in development, or sometimes death.

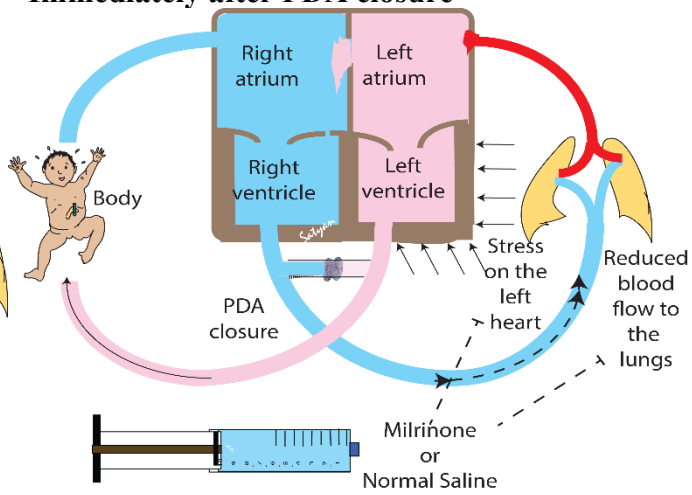
Currently, there is no clinical trial to determine what is the best way for doctors to prevent heart and lung problems after PDA closure (by surgery or transcatheter closure).

The picture on the left below shows how the blood flow to the lungs increases and blood flow to the body decreases when a baby has a large PDA. The picture on the right shows what happens after the PDA is closed. The blood flow to the lungs is reduced. This adds stress to the left side of the heart. After the PDA closure, babies in the study will be given a study medication which will be either milrinone or saline.

Before PDA closure

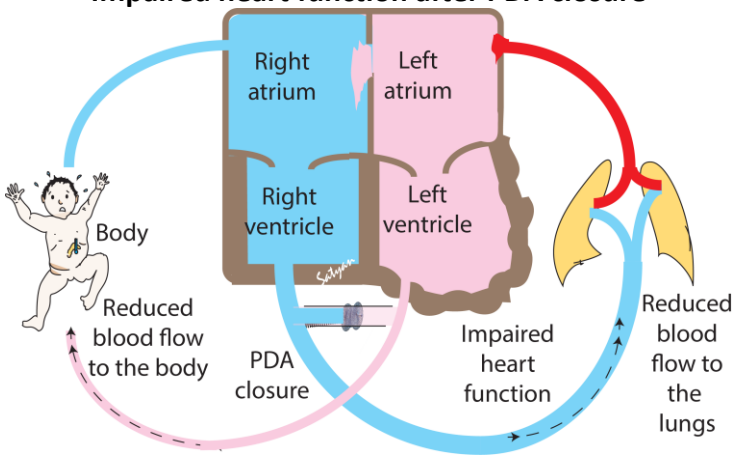


Immediately after PDA closure



This picture shows what happens if a baby develops PLCS after PDA closure.

Impaired heart function after PDA closure



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Why is this study being done?

- The purpose of this study is to find out whether a drug called milrinone, when given to infants after PDA closure, 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. Milrinone use in infants is considered investigational in this research study
- Milrinone works by helping the blood vessels relax, which makes it easier for the heart to work. Milrinone is used in certain critically ill babies and as a preventative medication after PDA closure.
- There are no clinical trials to investigate any benefit in preventing heart and lung instability and long-term safety.

The main purpose of this study is:

1. To determine if milrinone decreases the risk of death or PLCS within 7 days of the procedure, compared to standard treatment.
2. To determine the effects of milrinone on two-year survival and neurodevelopmental outcome at around 2 years of age.

How many people will be in this study?

About 316 babies in the United States will join this study. We expect 20 babies from this hospital will be part of the study.

What will happen if my baby is in this study?

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 saline (salt water) 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

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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 either a low dose (0.33 µg/kg/min) of milrinone in the treatment group, **OR** saline solution in the control group through an intravenous (IV) line.
  - The study drug will be started within 1 hour of the PDA closure procedure.
  - The study team will monitor very closely to see if there are any major side effects from the study drug.
  - If your baby develops high blood pressure, which places an added stress on the heart, the dose will go up to 0.66 µg/kg/min. One more increase will be allowed to 0.75 µg/kg/min. The study drug will then stay at this dose. No more changes will happen to the dose.
- If there are side effects, then the study drug will be stopped and will not be started again.
  - The study drug will be stopped after 24 hours if your baby only required the lowest dose and remains well. If your baby required higher doses of milrinone, it will take longer to wean them off the medication. Some babies may receive milrinone for up to 5 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 5 days.
  - Information will be collected from your baby's medical record including demographic information, gestational age, blood pressures, heart rates, respiratory rates, information about his or her breathing, medications, details of medical treatment for PDA, medical procedures including echocardiograms (ultrasound of the baby's heart), details of PDA closure (by surgery or transcatheter closure), head ultrasounds, and diagnoses.
  - We will also be collecting information from the maternal medical record including ultrasounds that may be relevant to the baby's course.
- Right after the study drug is stopped (which could be 5 days or less) your doctor may decide to give your baby the drug milrinone. This is a decision that will be made by your baby's doctor.

How long will my baby be in this study?

Your baby will be in this study for up to 2 years of age, which is when they will have a follow-up

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visit; however, the first 5-7 days after the study drug is given, is the period of most monitoring.

We will monitor for adverse effects until 7 days after PDA closure, or until 24 hours after the study drug is stopped if the treatment is continued to 7 days.

Sometimes important information can be learned from doing more follow-up when study participants are older. This study does not include follow-up beyond 2 years right now, but if that changes, we may contact you later about coming back to the follow-up clinic.

If your baby is transferred to another hospital before discharge, the study team will contact that hospital for information regarding your baby's treatments and outcomes.

This follow-up testing is a very important part of the study because it helps us understand how your baby is developing and to determine if there are any unexpected benefits or harms. It helps us learn more about the treatment being studied in this research.

Who has reviewed this study?

This study is sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI), which are part of the National Institutes of Health (NIH). We have taken several steps to make sure your baby's safety is ensured. As part of the approval process the study was reviewed by a panel of scientific experts who deemed the study feasible, important to conduct, and safe. The study has strict monitoring guidelines to quickly identify unanticipated safety concerns and limit the development of serious side effects. All adverse events are reported to a committee of experts whose primary role is to ensure the safety of all babies enrolled in this trial.

In addition, the study was reviewed and approved by the Neonatal Research Network Community Engagement Board. This board includes doctors, research coordinators, and former NICU parents from many diverse backgrounds.

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 medical team.

- Low blood pressure is common among babies after interventional PDA closure, and milrinone may or may not make this problem worse or more difficult to treat.
- If your baby develops low blood pressure in the first 4 hours after initiating milrinone treatment your doctors may look for another cause first.

If the blood pressure continues to stay low or reaches a level that is too low while your baby is getting study drug, the research team and your baby's doctor may decide to stop the study drug.

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Institutional Review Board
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Expires 3/10/2027
IRB_00185742

Studies have shown that most babies have high blood pressure immediately after PDA closure, and if the milrinone is administered early (less than 2 hours after PDA closure) then low blood pressure is rarely seen.

Other potential risks of milrinone treatment include low blood platelet count, low potassium levels, and heart rhythm disturbances. Although low blood platelet count and low potassium levels are occasionally seen in some patients, they can be treated.

Heart rhythm disturbances have not been reported in neonates. In adults who were given milrinone, there were some irregular heart rhythms called arrhythmias. We will monitor your baby for this.

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 better heart function leading to improved blood flow to their vital organs (including the brain) and less lung injury. 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 because they received the placebo (saline solution).

The period after PDA closure is a time of great vulnerability for the immature heart, with a high risk of complications. We hope that this study will help us learn how to take care of very sick babies after PDA closure in the future.

Follow-Up after Discharge:

- After your baby goes home from the hospital, they will be scheduled for follow-up exams in our clinic.
- The follow-up visit will be done when your baby is about 2 years old. The visit will take about two hours .
- During the follow-up visit we will test your baby's movement, behavior, and development. We will also check your baby to make sure they do not have high blood pressure or any evidence of kidney disease.
- The follow-up part of this study may help us find issues early so we may get the right developmental care for your baby. In addition, it will provide important information on the long-term safety of milrinone.

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

How may being part of the study be different from routine care at this hospital?

It is not routine in all hospitals to give milrinone to babies after their PDA has been closed surgically or with a percutaneous device. However at University of Iowa it is routinely given. If your baby is enrolled in the study, whether they receive milrinone will depend on which group your baby is in.

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. The information we will use and include in our research records are:

- Your baby's name, medical record number, date of birth, birth weight, sex, race, ethnicity and other general information.
- Information about your pregnancy and delivery, your age, years of education, marital status, race/ethnicity, type of insurance, and health issues during pregnancy.

This research study has a Confidentiality Certificate that protects your baby's privacy. If a legal matter happens, researchers may not use any information that might identify your baby unless you approve. You may share information about your baby or this study to others. If an insurer or employer learns that your baby is in a study and you agree to share study data with them, the researcher will do so. This means that you must also guard your baby's private information. The researcher may give information to authorities to prevent serious harm to you, your baby, or others.

A study number will be used to identify your and your baby's data. Only the study team will know your child's 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, RTI International, in Research Triangle Park, North Carolina. The Institutional Review Boards (IRBs) of the participating centers, the 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 RTI International and may be shared for future research in accordance with the NIH Data Sharing and Public Access Policy. Information released under this policy will not identify you or your baby or their participation in this research study. Because only de-identified data is being stored, we are not able to provide future results or findings back to you.

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

A description of this study will be available on ClinicalTrials.gov, ID number NCT06679855, 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 and read about the study.

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.

Will I be paid for being in this research study?

You will not be paid for your baby's participation in this study.

The cost of the neonatal follow-up clinic visit will be covered by the study. However, at the end of your follow-up visit you will be offered a $50 check. It is suggested that you use the gift card to purchase a developmentally appropriate toy or book and cover some of the travel expenses for your participation. This reimbursement is only offered if the baby attends the follow up visit.

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

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

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. Data collected up to withdrawal will be retained in the study.

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.

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

What happens if there is new research related to this study?

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 team will be notified and your baby's doctor will be responsible 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.

Can the research team withdraw my baby from the study?

The research team 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 local lead investigator (Dr. Tarah Colaizy) or other study team members via the University Paging Operator: [319-356-1616], the University NICU [319-356-1671],, 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.
Locally, if you have questions, concerns, or complaints about your rights as a research subject or about research-related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

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.

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Utah and University of Iowa Institutional Review Boards and support staff, the NICHD Neonatal Research Network's Data Coordinating Center, and RTI International in Research Triangle Park, North Carolina.

You cannot participate in this study unless you permit us to use your protected health information. If you choose not to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Yourpermission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:
Dr. Tarah Colaizy
8807 Pappajohn Pavilion (JPP)
200 Hawkins Drive
Iowa City, IA 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

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 and authorize you to use and disclose health information about my baby for this study as you have explained in this document.

_____
Baby's Name

_____
Parent/Guardian's Name

_____ _____
Parent/Guardian's Signature Date

_____
Relationship to Baby for Parent/Guardian

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

University of Utah
Institutional Review Board
Approved 3/11/2026
Expires 3/10/2027
IRB_00185742

WITNESS STATEMENT: (For Non-English-Speaking Participants Only)

Consent was obtained from the participant using a short form for non-English speakers. The short form is available in the participant's language and this (long) consent form was read to the participant using an interpreter.

As a witness, I confirm that I was present for the complete consent process for this study. I confirm that the participant named above was read the information in this consent document in a language he/she understands and that the participant has agreed to take part in the research study.

_____
Name of Witness

_____ _____
Signature of Witness Date

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Expires 3/10/2027
IRB_00185742