STUDY TITLE: Patent Ductus Arteriosus (PDA) Prediction Study **Version 4**

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE:
Early Prediction of Spontaneous Patent Ductus Arteriosus (PDA) Closure and PDA-Associated Outcomes (The PDA Prediction Study)

PRINCIPAL INVESTIGATOR: Carl Backes, Jr., MD and Jonathan Slaughter, MD

CONTACT TELEPHONE NUMBER: Dr. Backes, 614-264-6374 (24 hours a day, 7 days a week)

STUDY SPONSOR Nationwide Children's Hospital (NCH) / National Institutes of Health (NIH)

BABY'S NAME: _____ **DATE OF BIRTH:** _____

Key Information About This Study
The following is a short summary of this study to help you decide whether or not to participate. More detailed information follows later in this form.

The purpose of this study is to develop a way to predict the timing of PDA closure. This will enable health care providers to potentially decrease unnecessary treatment of the PDA in infants with the highest chances for the PDA closing on its own, as well as help guide treatment for infants with PDA.

Study participation: Participating babies will have several echocardiograms along with blood and urine collected at specific intervals throughout the study. All blood will be collected with a clinical lab draw. No separate "needle sticks" will be performed. Study staff will examine study babies to look for signs of an open PDA at intervals throughout the study, and there will be a movement assessment done near 36-weeks corrected age (approximately 4-weeks prior to your original pregnancy due-date). Study babies will have a final developmental appointment at 2 years of age, which is standard for premature infants. Parents will complete brief surveys at the beginning of the study and at the end. Study staff will collect information from your medical record and the medical record of your baby.

Study visits: Most study activities will be completed while your baby is in the NICU. Echocardiograms, blood and urine collection are completed once a week for the first 4 weeks of life. If there is still an open PDA at 4-weeks, the echocardiograms will then be completed every other week until the PDA is closed. An echocardiogram is done at 36-weeks corrected age, as well as a movement assessment. Some infants will need to complete visits in the Cardiology clinic after NICU discharge, depending on the results of the echocardiograms. All study participants will complete a standard follow-up appointment at 2-years of age in the Early Development clinic. This visit will last 1-2 hours. See a more detailed discussion later in this form.

The main risk(s) of the study are possible stress from the stimulation of the echocardiogram, as well as pain, bleeding, bruising or infection at the site where the blood is drawn. Because the blood is being drawn with other bloodwork, these risks are not increased because of this study. . . Other risks are listed later in this form.
The benefit(s) of the study are potentially better diagnosis of any undiscovered heart problems your baby may have. The movement assessment may help alert you to a higher risk of later

developmental problems where early intervention may be helpful. We hope that the information learned will help others.

If you are interested in learning more about this study, please continue reading below.

1) INTRODUCTION

We invite you to be in this research study because there is the possibility that you will have a preterm birth, or you have given birth to a preterm infant, and this study will look at one aspect of care for some babies more premature.

Participation is voluntary. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. Once you understand this study, we will ask you to decide whether you would like to participate or not. By signing this form, you agree to be in this study. If you do not want to be involved with this study, all regular and standard medical care will still be available to you here or at another institution. You also have the right to leave this study at any time, even if you agree to join now.

You will be given a signed and dated copy of the consent.

2) WHY ARE WE DOING THIS RESEARCH STUDY?

The ductus arteriosus (DA) is a blood vessel connecting the lungs and the body. In older infants, the DA normally closes after birth. In premature infants, the DA either: 1) closes on its own; 2) remains open or "patent." If the DA remains patent it is referred to as a patent ductus arteriosus or PDA. Currently, there is no way to tell which PDAs will close and which will remain open. The goal of this study is to develop a prediction model on the timing of PDA closure. This will enable health care providers to potentially decrease unnecessary treatment of the PDA in infants with the highest chances for the PDA closing on its own, as well as help guide treatment for infants with PDA.

3) WHERE WILL THE STUDY BE DONE AND HOW MANY SUBJECTS WILL TAKE PART?

This study will be done at several Nationwide Children's Hospital NICU sites, including The Ohio State University, OhioHealth Riverside Methodist Hospital, Mt. Carmel St. Ann's Hospital, Grant Medical Center, and Nationwide Children's Hospital Main Campus. Overall, we hope to enroll 700 participants from the Nationwide Children's Hospital participating NICU's.

4) WHAT WILL HAPPEN DURING THE STUDY AND HOW LONG WILL IT LAST?

1. Screening Echocardiography (ECHO) Study: If you consent to this study, your baby will receive a screening ECHO study within 72 hours of birth to determine if he/she has a patent ductus arteriosus (PDA). If when your baby is 72 hours old falls on a weekend day, the screening ECHO may be done the following Monday. ECHO is an ultrasound of the heart. If the PDA has already closed, then your baby will be able to participate in the non-PDA control group of the study. If other forms of heart disease sometimes found in premature infants are also found, your baby may also no longer be eligible to participate and we will refer your baby to our cardiology team for immediate evaluation.

ECHO uses sound waves to take pictures of the heart. It will not hurt your baby since the instrument is only placed on the skin and there is no radiation used. The ECHO will be performed at your baby's bedside. Your baby will not be sedated during the echocardiogram. For an ECHO scan, your baby will be placed on their back. Pre-warmed coupling gel will be placed on the chest, and the scanning wand will gently be placed in contact with the skin. The wand will be moved around in order to obtain the best "views" of your baby's heart. The ECHO scan is expected to take approximately 10-20 minutes, and will be performed by a specially-trained technician.

2.Echocardiography (ECHO) exams until confirmed PDA closure: After the screening ECHO has confirmed the presence of PDA, weekly ECHOs will be performed for the next 3 weeks, and then every other week thereafter until PDA closure, or discharge. If your baby has a closed ductus arteriosus on the screening ECHO, no further ECHO's will be done. These scans are expected to take approximately 10 minutes. Routine information collected from this study will not be shared with your child's physician since it is only for research purposes. The ECHO exams may provide information that we were not specifically looking for in this study. This information is called "incidental findings". We will discuss these results with you and your baby's doctor if we believe that they may have a significant impact on your child's health. If heart disease is found, this information will be shared with your baby's treatment team. Treatment and follow-up visits related to such findings will not be part of this study. Therefore, you and your insurance company would be responsible for any fees and costs related to them.

3.Urine sample collection: Prior to 72 hours of life, and then once a week for 3 weeks, we will collect a sample of urine for research purposes. Clean cotton balls/pads will be placed in the diaper of your infant to collect the urine sample. ***The urine used for this study would typically be discarded by the medical team***. These samples will be used to examine biomarkers indicating stress on the kidneys. The sample collection procedure is only expected to take 1 – 2 minutes to collect the cotton balls/pads with sample. Infants in the non-PDA control group will not have additional urine collected after the screening sample.

4.Blood sample collection: Once prior to 72 hours of life, and then once a week for 3 weeks, we will collect approximately 5 drops of blood, or 1/8 of a teaspoon (0.5ml) of blood for research purposes. During the first weeks of life, many infants will have an umbilical arterial line, and this will be used to obtain the sample. For those without a line, blood samples will be obtained by heel stick, at the time of routine blood collection. **No separate "needle sticks" will be performed for the purposes of this study**. The blood samples will be used to examine markers of stress on the heart. The sample collection procedure is only expected to extend the time of routine blood collection by no more than 1 – 2 minutes. Infants in the non-PDA control group will not have additional blood collected after the screening sample.

5.Data Collection and Exams: If you allow your baby to take part in this study, research staff will collect information about your health and pregnancy. They will also collect information about your baby's health and care while in the NICU. Information will be collected by reviewing you and your baby's medical records and by questionnaires you may be asked to complete while your baby is in the NICU and at the follow-up visit. All study information is coded and personal identifiers are kept in a safe place. Study information is entered by study staff into a secure study database called REDCap. A study physician or study staff member will complete a clinical cardiac examination of your infant up to twice a week for the first 4 weeks of life, and at other times while your baby is in the NICU. This examination is not painful and consists of observing your infant and listening to his/her heart with a recording stethoscope.

The examination should take about 2 minutes. If you would like, we will provide you with a digital copy of a recording of your infant's heartbeat.

6. 36 Week Corrected age assessment: An Echocardiogram will be performed once your child reaches 36-weeks PMA (approximately 4-weeks prior to your original pregnancy due-date), or before hospital discharge, whichever comes first. We will be performing a general movement assessment (GMA) neurodevelopmental surveillance test also. This test is performed routinely on preterm infants by infant developmental follow-up examiners at the Nationwide Children's Hospital as standard of care. However, since these examiners are not present in all of the NICUs where the study is being conducted, we will make a short video of your baby's movements for the neurodevelopmental examiners to review. If any abnormalities are noted which indicate a potentially higher than normal risk of neurodevelopmental delay, and your baby does not already qualify for high risk follow-up, we will refer your baby to the Nationwide Children's Neurodevelopmental Follow-up Physicians for evaluation and any early therapies that could be beneficial for development. The video of your baby is only for scoring the assessment and will be discarded once it has been reviewed by a trained examiner. Infants in the non-PDA control group will not participate in the 36-week assessment.

7. Cardiology Follow-up: Per standard of care at our hospital, all infants with an "open" PDA at time of discharge will receive follow-up in the outpatient Cardiology Clinic in the Heart Center at Nationwide Children's Hospital. At this visit, it is likely for your infant to receive an additional echocardiogram (ultrasound of the heart) and possibly other tests, as determined by the doctor. Further follow-up visits will be at the discretion of the treating physician.

*8. Two-Year Neurodevelopmental Testing: Per standard of care at our hospital, a*t approximately 2 years of age, follow-up testing will be scheduled for your child to examine motor (movement), speech and behavior. There will be one additional questionnaire at this follow-up visit to assess your child's behavior. Scores on these tests will compared with the length of time your infant was exposed to a PDA, and other data collected during their hospital stay. There will be no additional ECHOs, blood draws, or urine specimens during this part of the test, which is expected to take 1 - 2 hours. Infants in the non-PDA control group will complete the standard visit, but will not be asked to complete any additional questionnaires.

It is very important for this study that we keep in contact with you. As part of this study we may contact you via telephone, email or text. In order to make sure that your privacy is maintained we will provide you with a study specific password. Please make sure that only you use this study specific password. Please inform the study team promptly of any changes in contact information. If you have an urgent issue, please call us at the number provided on page 1 of this form.

5) WHAT ARE THE RISKS OF BEING IN THIS STUDY?

We believe that there is very little chance that bad things will happen as a result of being in this study. Great care will be taken during the ECHO procedures to minimize the amount of discomfort or stress that your infant will experience due to a premature infants' sensitivity to touch. For this reason, the gel on the ultrasound wand will be warmed. The wand will very gently be placed in contact with the skin. Movement of the wand and the pressure applied to obtain the necessary views will be minimized as much as possible. Rarely, very sick infants may have brief decreased oxygen levels during the ECHO. If this happens, the ECHO will be stopped, and the infant will be given time to recover. If you have concerns about anything while in the study, please call the study doctor at the telephone number on page 1.

Drawing blood by heel stick may cause pain, bleeding, bruising, or swelling at the puncture site. Infection is a rare possibility. In infants for whom blood is drawn from a catheter, the primary concern would be infection, which is rare. Because the blood is taken only with a clinical lab draw this poses no additional risks to your baby. We will obtain the minimum amount of blood required to obtain the test result. Collection of urine in the manner planned will cause no additional risks.

The privacy policies of telephone communication, e-mail, and text messages are not as strong as those for medical or research records. Thus, there is the risk that someone else may be able to view communications related to this study. Also, it is possible that the actual transmission can be intercepted and looked at by people not associated with this study. In order to make sure that your privacy is maintained, we will provide you with a study specific password. If you have either lost your password or think that someone is viewing your communications, please let the study team know immediately.

Although we will take every precaution, there is a small chance of loss of confidentiality of your study information.

There may be other risks of being in this research study that are not known at this time.

6) WHAT ARE THE COSTS AND REIMBURSEMENTS?

All costs related to the research parts of this study will be covered by the research team. You will not be billed for the ECHO's done for the research study or the labs that are part of the study. However, the parts of the study that would be done for routine clinical care will be billed to you and to your insurance company or third party payer. There will likely be additional costs related to travel and meals during this study while your infant is in the hospital. We do not provide money to help with these costs, as they would be incurred regardless of study participation. Cardiology follow-up visits are standard care for baby's who have an open PDA at hospital discharge, so these visits and any echocardiograms at these visits will be billed to your insurance. Neurodevelopmental testing is done for premature infants at 22-26 months of age as routine medical care and is billed as such. You may have to pay any costs that the insurance company or third party payer does not pay. The study team will discuss these costs with you. For your time and inconvenience, you (study participant) will receive $40 at your 22-26 month follow up study visit and a parking pass. You will be issued a debit card specially designed for clinical research. When the study visit is completed, funds will be approved and automatically loaded onto your card. This does not apply to non-PDA control group participants, as they will no longer be enrolled in the study after discharge home.

7) WHAT HAPPENS IF BEING IN THIS STUDY CAUSES INJURIES?

We believe there is very little chance that injuries will happen as a result of being in this study. If you believe your baby is hurt by the procedures that are part of this study, you should seek medical treatment for the injuries and call the study team as soon as possible at the number on page 1 of this form. If it is an emergency, call 911 or go to the nearest emergency department.

In most cases, this care will be billed to your health insurance company or whoever usually pays for your health care at the usual charges, but some insurance companies will not pay for care related to a study. If the care is provided at Nationwide Children's Hospital, we make no commitment to pay for the medical care provided to you. No funds have been set aside to compensate you in the event of injury.

If no one else pays for your care, you may have to pay for the cost of this care. This does not mean that you give up any of your legal rights to seek compensation for your injuries.

8) WHAT HAPPENS IF I DO NOT FINISH THIS STUDY?

It is your choice for your baby to be in this study. You may decide to withdraw him/her from this study at any time. If you decide withdraw him/her from this study, call the study team at the number on page 1 of this form to see if there are any medical issues about stopping. If you choose to withdraw your infant, there will be no penalty or loss of benefits to which they are otherwise entitled.

If at any time the Principal Investigator believes that this study is not good for your baby, the study team will contact you about stopping. If unexpected medical problems come up, the Principal Investigator may decide to stop your participation in the study.

Removal of your infant from the study will not have any effect upon the approach to treatment of your baby for a PDA. Further procedures and tests will be at the discretion of the care team. In addition, Cardiology follow-up for babies with an open PDA at hospital discharge, and neurodevelopmental testing at 2 years of age for former premature infants is routine at Nationwide Children's Hospital.

9) OTHER IMPORTANT INFORMATION

If there have been any prenatal tests or diagnoses by your obstetrician, we ask that you provide this information to the study team. This may impact your infant's eligibility for study participation.

Being in more than one research study at the same time may cause confusion or injury. Please tell us if your infant is in any other research studies. We may need to notify the other study team to see if your infant can participate in both studies.

If you are an employee of Nationwide Children's Hospital or the Research Institute at Nationwide Children's Hospital, your job or performance appraisal will not be affected in any way if you decline to participate or withdraw your consent for your infant to participate in this study.

If you are interested, the final study results will be shared with you once they are available. Please provide us with an email or address where we can send these results.

I would like the final study results to be sent to me via email: (initial)

_____YES _____ NO EMAIL (if yes):_____

If you are interested, we will give you a recording of your infant's heartbeat. Please provide us with an email address where we can send the digital file.

I would like a digital copy of my baby's heartbeat recording:

_____YES _____ NO EMAIL (if yes):_____

The Principal Investigator and members of the research team are being paid, at least in part, using funding obtained through a research grant provided by the National Institutes of Health.

Nationwide Children's Hospital is a teaching hospital and we are committed to doing research. Doing research will enable us to learn and provide the best care for patients and families. You may be asked to participate in other research studies in the future. You have the right to decide to participate or decline to participate in any future studies. We will not share your contact information with researchers outside Nationwide Children's Hospital.

10) HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?

Information collected for this study includes information that can identify you. This is called "protected health information" or PHI. By agreeing to be in this study, you are giving permission to this study team to collect, use, and disclose your PHI for this research study. Information collected is the property of Nationwide Children's Hospital, its affiliated entities, and/or the sponsor.

The collection of information regarding the delivery of your baby (for example, gestational age, birth weight, etc.) will require access to medical records from the birth hospital.

- PHI that may be used or disclosed will include**:** Names (infant, parents) ; Address (including city, state, zip code and county); Telephone Numbers; Dates; Birth Date; Admission Date; Discharge Date; Treatment Dates; Date of Death (if applicable); E-mail Addresses; Medical Record Numbers; Biometric Identifiers (video of infant movement for scoring purposes only- will be de-identified and will be destroyed immediately following assessment)

People or Companies authorized to use, disclose, and receive PHI collected or created by this research study:

- PI and study staff
- The Nationwide Children's Hospital Institutional Review Board (the committee that reviews all human subject research)
- Nationwide Children's Hospital internal auditors
- Research sites (whenever applicable): The Ohio State University Wexner Medical Center; Riverside Methodist Hospital; Mt. Carmel – St. Ann's Hospital; Grant Medical Center
- The Office for Human Research Protections (OHRP) (the federal government office that oversees human subject research)
- Registries or Research Databases: REDCap. This is so that they can make sure that the data submitted to them is complete and valid. This only applies to the registries or research databases described in the earlier parts of this consent form.
- Your insurance company

Because of the need to give information to these parties or obtain additional information from these parties, absolute confidentiality cannot be guaranteed. Information given to these people may be further disclosed by them and no longer be protected by federal privacy rules.

Reason(s) why the use or disclosure is being made:

Your PHI, and PHI of your baby will be necessary for a number of reasons. As noted previously, we will need access to the records from the birth hospital detailing demographics and information collected during your baby's delivery as well as your baby's health and care while in the NICU. We will also need to maintain up-to-date contact information (telephone numbers, mailing addresses, e-mail addresses) in order to communicate with you regarding follow-up visits for your child, particularly the 2-year neurodevelopmental evaluation that is part of this study.

You may decide not to authorize the use and disclosure of your PHI. However, if it is needed for this study, you will not be able to be in this study. If you agree to be in this study and later decide to withdraw your participation, you may withdraw your authorization to use your PHI. This request must be made in writing to the Principal Investigator at Carl Backes, Jr., MD, 700 Children's Drive, Columbus, OH, 43205. If you withdraw your authorization, no new PHI may be collected and the PHI already collected may not be used unless it has already been used or is needed to complete the study analysis and reports.

PHI will only be shared with the groups listed above, but if you have a bad outcome or adverse event from being in this study, the study team or other health care providers may need to look at your entire medical records.

The results from this study may be published but your identity will not be revealed.

The PHI collected or created under this research study will be used or disclosed as needed until the end of the study. The records of this study will be kept for an indefinite period of time and your authorization to use or disclose your PHI will not expire.

Certificate of Confidentiality:

To help us protect your privacy, the National Institutes of Health has issued a Certificate of Confidentiality for this study. This Certificate will be used to resist attempts to force us to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

The Certificate cannot be used to resist a demand for information that is used for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then we will release the information even though we have the Certificate of Confidentiality.

The Certificate of Confidentiality also does not prevent us from disclosing voluntarily, without your consent, information that would identify you as a participant in the research if required by state and/or federal law. In Ohio, if we have reasonable knowledge that a felony has been or is being committed we are required to notify state officials.

The Certificate does not protect study information that is placed into your medical records.

Storage of PHI

With your permission, we would like to store your PHI for future research purposes, and as part of such future research purposes, your PHI may be disclosed to people or entities not listed above, such as researchers not involved with this study, government agencies, research foundations, or pharmaceutical or device companies sponsoring future research. This future research may or may not

be related to your medical problem. This future research may include sensitive information. Any future research projects will be reviewed and approved by an Institutional Review Board which protects the rights, welfare, and safety of human research subjects. If your PHI is used or disclosed in future research studies, absolute confidentiality cannot be guaranteed. Information shared for future research may be shared further with others and no longer be protected by federal privacy rules.

If you decide at any time that you do not want your PHI stored for future research, you must make this request in writing to the Principal Investigator at Carl Backes, Jr., MD, 700 Children's Drive, Columbus, OH, 43205. Once we receive your written request, we will destroy your PHI. However, if we have already shared your PHI with another individual or entity, we will not be able to destroy any of the PHI that are no longer in our possession.

Nationwide Children's Hospital retains the right to cease storage and destroy the PHI at any time without sending notice to you or obtaining your consent.

You do not have to agree to use of your PHI for future research in order to be in this study, and your decision will not affect the care you receive from the study doctors or Nationwide Children's Hospital.

I agree to allow my PHI to be stored and used for future research as described above: (initial your choice)

_____ YES _____ NO Signature_____ Date:_____

11) WHOM SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns, or complaints about anything while on this study or you have been injured by the research, you have 24-hour access to talk to the Principal Investigator at *614-264-6374 24 hours per day, 7 days per week.*

If you have questions, concerns, or complaints about the research; if you have questions about your rights as a research volunteer; if you cannot reach the Principal Investigator; or if you want to call someone else, call (614) 722-2708, Nationwide Children's Hospital Institutional Review Board, (the committee that reviews all research involving human subjects at Nationwide Children's Hospital).

STUDY TITLE: Patent Ductus Arteriosus (PDA) Prediction Study **Version 4**

Your signature documents your permission for the named child to take part in this research.

_____
Printed name of child

_____ _____
Signature of parent or individual legally authorized to consent to the child's general medical care Date & Time AM/PM

_____
Printed name of parent or individual legally authorized to consent to the child's general medical care

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact Legal Services if any questions arise.

_____ _____
Signature of second parent or individual legally authorized to consent to the child's general medical care Date & Time AM/PM

_____
Printed name of second parent or individual legally authorized to consent to the child's general medical care

If signature of second parent not obtained, indicate why: (select one)

- ❑ Not required by IRB
- ❑ Second parent is deceased
- ❑ Second parent is unknown
- ❑ Second parent is incompetent
- ❑ Second parent is not reasonably available
- ❑ Only one parent has legal responsibility for the care and custody of the child

_____ _____
Signature of person obtaining consent Date & Time AM/PM

_____
Printed name of person obtaining consent

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

_____ _____
Signature of witness to consent process (For Telephone Consent or Interpreter) Date & Time AM/PM

_____
Printed name of person witnessing consent process