Institutional Review Board
Informed Consent Document for Research

Study Title: STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS trial)
Version Date: 8/28/2019

Part 1 of 2: MASTER CONSENT

Name of participant:_____Age: _____

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

What is the purpose of this study?

You are being asked to take part in this research study because your child was born with a heart defect that requires surgery in his/her first year of life. Taking part in a research study is voluntary. Before you decide to let your child take part, you should know why the research is being done and what it involves. Please read this form carefully and take your time to decide. Ask the study doctor (or his or her staff) any questions you may have. You will be given an unsigned copy of this form to take home with you to read again. Take your time to think and talk about it with your family and friends before making your decision. Being in a research study is not part of your child's routine medical care. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to let your child to participate, your child's doctor for the study and will be in contact with your child's regular health care provider throughout the time that your child is in the study and afterwards, if needed.

Please tell the study doctor or study staff if your child is taking part in another research study.

In order to surgically repair congenital defects of the heart, surgeons have to use cardiopulmonary bypass. Cardiopulmonary bypass is a technique that temporarily takes over the function of the heart and lungs during surgery. Although cardiopulmonary bypass is absolutely necessary to repair most congenital heart defects, bypass causes an inflammatory response from the body. This inflammatory response can complicate the post-operative recovery period and can contribute to serious complications like liver, kidney, respiratory failure and even death. For decades some surgeons have given an anti- inflammatory steroid known as methylprednisolone to children before they perform congenital heart surgery because they believe that methylprednisolone reduces the severity of post-operative inflammation. However other surgeons do not administer methylprednisolone because they believe that its use might contribute to other potentially serious post-operative problems like infection. Although methylprednisolone is approved for use in children for treatment of other conditions like asthma, allergies and cancer, it has never been well studied in children undergoing heart surgery and we don't know if methylprednisolone is helpful in these children. It is important for us to do studies like this so we can better understand the best and safest ways to treat children with heart disease. Whenever we do research, we do everything possible to ensure that the studies maximize the potential benefits to the child and minimize any potential risks.

The main goal of this study is to determine if methylprednisolone is safe and effective in children with heart disease undergoing surgery with cardiopulmonary bypass in the first year of life. A secondary goal is to determine the optimal dosing of methylprednisolone in children undergoing congenital heart surgery. An independent committee of doctors and statisticians will review all information throughout the study to protect the safety of the children taking part. They may ask to make changes or even to stop the study if they have concerns.

This study is being funded by a grant from the National Institutes of Health (NIH) to Jennifer Li, MD of Duke University. Kevin Hill, MD of Duke University is the lead investigator and is the study sponsor- investigator. Duke University is paying your child's study doctor and his or her research staff to conduct the study.

What will happen and how long will you be in the study?

If you decide to allow your child to participate, you will be asked to sign and date this consent form. This will likely be at the time of your child's routine pre-operative evaluation. Your child will have a complete physical examination including blood pressure, heart rate, temperature, and breathing rate. We will take a full medical history, including any new problems and medicines. We will also record any recent laboratory values.

Children in this study will be randomly assigned (like flipping a coin) to receive one of two different drug regimens:

1. Methylprednisolone given at the time of surgery
2. Placebo given at the time of surgery.

Placebo is an inactive substance made to look like the study drug. You child will have a 50 percent chance of receiving methylprednisolone during his or her surgery. Neither you nor any of the doctors, nurses, or study team will know if your child is receiving methylprednisolone or placebo. However, this information will be available to the study doctor in case of emergency.

If you allow your child to be enrolled in this study, he or she will receive the methylprednisolone or placebo medication during the surgery. These medicines will be administered into the cardiopulmonary bypass circuit in the same way as they have always been administered by those surgeons who believe that methylprednisolone is helpful. Because your child already needs an IV for his or her care, there is no need for any additional needle sticks as part of this study. Your child's surgeon will then perform the surgery in the normal fashion. Enrolling your child in this study will not affect his or her surgery in any way. After the surgery is completed, your child will undergo routine post-operative care. This will not be any different than if he or she had not enrolled in this study. As your child recovers from his or her surgery, doctors and staff participating in the study will monitor his or her recovery. They will record information about his or her clinical course, including whether or not he or she has any complications, and how long he or she stays in the intensive care unit and in the hospital. After your child is discharged from the hospital, you will follow up with your child's doctors and surgeons just as you would if your child was not enrolled in a study.

Your child will be in the study for the duration of his/her hospitalization. The only aspect(s) of his or her care that will differ from routine care is the first day when he or she receives the dose of methylprednisolone or placebo, and the optional collection of blood samples during the first 48 hours after drug administration.

Side effects and risks that you can expect if you take part in this study:

The inflammatory response to heart surgery with cardiopulmonary bypass can complicate the post- operative recovery period and can contribute to serious complications like liver, kidney or respiratory failure and even death. It is not known whether methylprednisolone can help to alleviate this inflammatory response and improve outcomes or whether methylprednisolone might cause more harm than good (see below for further discussion of risks associated with methylprednisolone). If steroids do alleviate the inflammatory response, and your child is randomly assigned to the placebo group, then your child would not receive any of the benefits associated with methylprednisolone treatment.

Potential Discomforts, Side Effects, and Risks Associated with Methylprednisolone

Methylprednisolone has been used for many years to treat children and adults with asthma, severe allergic conditions, kidney diseases and certain types of cancer. Side effects are generally rare and are mostly associated with long term use. Methylprednisolone can sometimes cause:

- Elevation of blood pressure
- Salt or water retention
- High blood sugar
- Transient suppression of the immune system leading to increased susceptibility to infection
- Allergic reactions including anaphylaxis
- Cardiac rhythm abnormalities

There is also the risk of loss of confidentiality. We will do everything we can to keep your medical and research data private.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

Good effects that might result from this study:

a) The benefits to science and humankind that <u>might</u> result from this study: There is no guarantee that your child will personally benefit; however, the knowledge gained from your child's taking part in this study may help other patients undergoing heart surgery procedures in the future.

b) The benefits you might get from being in this study: Methylprednisolone is an anti- inflammatory steroid. It may help decrease post- operative inflammation and, in so doing, decrease your child's risk of serious complications including liver, kidney or respiratory failure. There is no guarantee, however, that your child will personally benefit.

Other treatments you could get if you decide not to be in this study:

Instead of taking part in this study, you may choose for your child to receive standard treatment. This may or may not involve receiving methylprednisolone depending on the practices of the surgeon at the center where your child is receiving his or her care. Methylprednisolone is sometimes used at the discretion of the surgeon, but all have agreed to participate in this trial because they do not know if its use is beneficial.

Reasons why the study doctor may take you out of this study:

If at any time your child's doctor, the study doctor or the study sponsor decide that the study is not in the best interests of your child's medical care, they will take your child out of the study. If this happens, the study team or the medical team will let you know. If the study doctor or Sponsor ends your child's participation, or if you decide not to continue, you will be asked to return to the study doctor or study site to have all of the final clinical evaluations and laboratory tests done.

What will happen if you decide to stop being in this study?

You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because your child has had an unexpected reaction, or because the entire study has been stopped.

If you withdraw your child, no new information will be collected but we will use data that has already been collected unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your child's entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

If you decide to stop participating in the study for any reason, please tell your child's study doctor immediately. We ask that you contact your child's study doctor in writing and let them know that you are withdrawing from the study. The study doctor's mailing address is listed on the Part 2 consent form.

Clinical Trials Registry

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:

Study records that identify your child will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law or for your child's care, your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier except date of birth in study records disclosed outside of the center where your child is receiving his or her care. For records

disclosed outside of the center where your child is receiving his or her care, your child will be assigned a unique code number.

The key to the code will be kept securely at the center where your child is receiving his or her care.

As part of the study, the study team will report the results of your child's post-operative course to the National Institutes of Health and the Food and Drug Administration.

In addition, your child's records may be reviewed for verification of study procedures and/or data in order to meet federal or state regulations. Reviewers may include representatives from the study coordinating center (the Duke Clinical Research Institute, Durham NC), the Food and Drug Administration, representatives of the National Institutes of Health, Office for Human Research Protections, and the Institutional Review Board at the center where you child is receiving his or her care. If any of these groups review your child's research record, they may also need to review your child's entire medical record.

Study results will be kept in your child's research record for at least 6 years after the study is completed. At that time either the research information not already in your child's medical record will be destroyed or information identifying your child will be removed from such study results. Any research information in your child's medical record will be kept indefinitely.

A copy of this consent form will go into your child's medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your child's identity will not be revealed.

Your information may be shared without identifiers, to others or use it for other research projects not listed in this form. We will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use

or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.