Official Title: "Targeng Normoxia in Neonates With Cyanotic Congenital Heart Disease in the Intra-operative and Immediate Post-operative
Period (T-NOX)"

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UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:

Targeting Normoxia in Neonates with Cyanotic Congenital Heart Disease in the Intra-operative and Immediate Post-Operative Period (T-NOX)

Names, degrees, and affiliations of the principal investigator and study coordinator:

Principal Investigator: Nathaniel Sznycer-Taub, MD, Assistant Professor of Pediatrics and Communicable Diseases

Study Coordinator: Adriana Batazzi, ScM, CCRP

1.1 Key Study Information

Your child may be eligible to take part in a research study. Parents or legal guardians who are giving permission for a child's participation in the research, note that in the sections that follow the word 'you' refers to 'your child'.

This form contains information that will help you decide whether to join the study. All of the information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the use of different levels of oxygen exposure during and after cardiopulmonary bypass in small numbers of infants to learn about its safety during heart surgery. Researchers want to understand how different levels of oxygen work in your body and how your body will react to it. This study will aim to demonstrate that a normal amount of oxygen (compared to very high levels) is feasible and safe. Your health-related information, blood samples, head ultrasound and brain wave patterns will be collected for this research study.

This study involves a process called randomization. This means that the levels of oxygen you receive during surgery in the study is not chosen by you or the researcher. The study design divides study participants into separate groups, based on chance (like the flip of a coin), to compare different treatments or procedures. We will inform you of the outcome of randomization prior to surgery.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. There are no known risks to using normal and high levels of oxygen during surgery. More detailed information will be provided later in this document.

While there may be no benefit to the subject, pediatric clinical and pre-clinical experimental studies suggest that there is a likely benefit to using normal amounts of oxygen compared to high doses. Future subjects may also benefit from the information gained from this clinical study. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be one year.

You can decide not to be in this study. Alternatives to joining this study include the standard of care, which is the use of high levels of oxygen during and after cardiopulmonary bypass.

Even if you decide to join the study now, you are free to leave at any time if you change your mind. Even after you sign the consent, at the time of the surgery, the surgeon may decide it is in your best interest to receive the standard of care. They will determine what best fits your needs.

More information about this study continues below.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The purpose of this Pilot Study is to look at the safety and feasibility of using normoxia (normal levels of oxygen) in infants undergoing cardiac surgery and cardiopulmonary bypass.

During the surgery, the levels of oxygen circulating in the blood will be monitored and kept at near-normal level based on what is expected for your heart disease. Physicians have used normal levels of oxygen during cardiopulmonary bypass previously, but this is the first formalized clinical study of its use in infants to better understand the possible benefits and risks.

The results of this study may support the use of normoxia during cardiopulmonary bypass in a larger study.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

You are being asked to participate in this study because your child is less than 30 days of age and needs surgery requiring cardiopulmonary bypass.

3.2 How many people are expected to take part in this study?

This research study will enroll a total of 42 subjects at the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

Pre-Operative:

You must meet all of the guidelines for the study before being asked to participate.

Prior to the procedure the research coordinator or study doctor will review your child's medical history including demographic information (age, gender, race), medication and treatment history to determine your child's eligibility for the study.

A physical examination will be performed (including weight, height, blood pressure, heart rate). A routine blood study will be performed to check your child's overall health status, including a renal function and liver function panel on the morning of surgery. Your child will also have a head ultrasound before the surgery as part of the study.

The above-mentioned procedures will be scheduled on the same day with your standard of care pre-operative visit.

Study Procedure:

Your child will be prepared in the standard fashion for surgery, and placed under anesthesia as directed by the surgeon. Labs will be drawn before, during, and after the procedure and arterial blood gases will be recorded. Other blood tests for biomarkers (normal body substances in the blood which measure body function) drawn before, during and after surgery will be included in these labs. Urine collected as part of standard of care will also be used for research purposes. All patients will be connected to a cardiopulmonary bypass machine via standard procedures.

There are two arms for this study:

- Arm A: Normoxia (normal levels of oxygen) group
- Arm B: Standard of Care (high levels of oxygen).

During the heart surgery, the level of oxygenation will depend on which arm of the study your child is in:

- If your child is in the Normoxia group, then oxygen levels in child's blood while on the bypass machine will be controlled and will be similar to the level of oxygen in his or her blood during normal breathing.
- If your child is in the Standard of Care group, then oxygen levels in your child's blood while on the bypass machine will be higher than the level of oxygen in his or her blood during normal breathing (this is what is normally done).

As your child is taken off the bypass machine, the anesthesia team will initiate mechanical ventilation.

- If your child is in the normoxia group, then oxygen levels in your child's blood during mechanical ventilation will be controlled for 24hours post-surgery and will be similar to the level of oxygen in his or her blood during normal breathing.
- If your child is in the standard of care group, then oxygen levels in your child's blood during mechanical ventilation will be higher than the level of oxygen in his or her blood during normal breathing and will be adjusted per standard goals set by the clinical team (this is what is normally done).

Post-Operative Period through Hospital Discharge

Regardless of which group your child is in, your child will be monitored for the duration of your stay in the hospital. Prior to discharge, the following procedures will occur:

- Assessment of any adverse experiences
- Assessment of any changes in medical status
- Assessment of medications
- Blood laboratory tests (about 2 teaspoons of blood will be drawn) at 2, 6, 24, 48 and 72 hours post-surgery
- A head ultrasound will be performed at 24 hours and 72 hours after surgery
- EEG monitoring may be performed after your child arrives to the ICU as part of standard of care. Monitoring, if performed, will be reviewed to assess for seizures.

The combination of these tests will evaluate the safety and feasibility of using different levels of oxygen during cardiopulmonary bypass. This follow-up schedule may be different from the standard of care following surgery. Some of the blood tests may be performed more often.

4.2 How much of my time will be needed to take part in this study?

Your participation in this study will take roughly one year.

4.3 When will my participation in the study be over?

Your participation in this study will take one week (or until your hospital discharge). Additional data will be collected from your standard of care follow-up appointments could be collected for longer (about a year).

4.4 What will happen with my information and/or biospecimens used in this study?

With appropriate permissions, your collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information will be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Risks of the Surgical Heart Procedure

Your doctor will review the possible risks of the surgical heart procedure. These are risks your child would have even if he or she were not enrolled in this study. Parents will be asked to sign a surgical consent form to authorize your child's surgery.

Risks for the procedure may include anemia (low red blood cell counts); arrhythmias (irregular heart rhythm); bleeding; infection; low cardiac output syndrome (poor heart function); mediastinitis (inflammation in your sternum or surgical area) pericarditis (inflammation around the sac containing your heart); pneumonia; procedural delay; kidney failure; scarring from incision; tamponade (critical build-up of fluid around the heart); heart attack; stroke; transient ischemic attack ("miniature stroke"); and death as well as the standard risks associated with general anesthesia during or after the surgery.

Estimates of your risk of these complications depend on your specific health, whether or not you smoke, prior medical conditions and your heart function. Your doctor will discuss these with you.

Risks Associated with the Clinical Protocol Procedures Required during the study:

Blood Draws (rare: less than 1%)

Normal blood tests may cause minor discomfort. In this study, blood samples will be drawn from intravenous lines so the discomfort should be minimal.

Risks of being in the normoxia arm (Arm A):

Based on previous studies from other centers, there have been no reported additional risks associated with having normal oxygen levels in your blood during cardiopulmonary bypass. Potential risks are similar to what is listed above with regards to what can happen during and after cardiac surgery.

Current experience indicates that surgical outcome is not affected by hyperoxia (increased levels of oxygen) versus normoxia (normal levels of oxygen in the blood). On the other hand, there is some evidence that normoxia results in improved acute response to measures of several biomarkers (blood sample measures of body function) compared to hyperoxia (increased levels of oxygen in the blood). However, long term outcome of the heart surgery has not been related to levels of oxygen administered during surgery.

Risks of being in the standard of care arm (Arm B):

As this is what is currently done for patients undergoing cardiac surgery requiring cardiopulmonary bypass, the risks are no different than what can happen during and after cardiac surgery.

Unknown Risks

Your child might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to your child. Side effects may occur after your child is discharged from the hospital, so it is important that you notify your doctor right away if you suspect any side effects.

Inconveniences

You may be inconvenienced by the additional time required for baseline examinations/testing and follow-up examinations/testing that are required by the study but that are not generally required as standard of care.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. All tests and procedures will be performed by trained medical staff who are familiar with working with patients like you to make these procedures go smoothly. If you think your child has an injury, bad, or adverse (harmful) effect, or any other unusual health problem while you are in this research study, get medical help as soon as possible. For medical emergencies, contact your emergency service: Dial 911 in the United States.

It is also important that you telephone the Investigator at the number in section 10 as soon as possible to report your child's condition.

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to your child. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You do not need to take part in this research study. Your study doctor can discuss treatment alternatives and the risks and benefits of these alternatives with you. Alternative treatment options include the standard of care, which is to pump a lot of oxygen through the blood during and after cardiopulmonary bypass. Your surgeon may choose to modify the oxygen levels regardless of the research study during the surgery if they deem it best for treatment.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

As the success of this study depends on the information obtained from all enrolled patients until the end of the study. If you decide to withdraw from the study before the end of the study, the study team will ask to contact

you by phone to find out about your medical status. This is done to meet regulatory agency expectations for having complete safety follow-up information about the study.

If you want to withdraw from the study, please contact your study team. It is in your best interest to follow any instructions that the doctor or study staff may give you if you choose to withdraw. Consequences of stopping the study may include discontinuation of follow-up, testing, and monitoring, which may adversely affect your health. Your care may need to be transferred to another doctor or health care center. Your study doctor can provide assistance with this.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher's telephone number listed in Section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

Some insurance companies and Medicare may not cover the costs of care during the research study, even if it is a standard treatment for your condition. Your insurance company may not pay for any disease-related treatments if you are in a research study. You should contact your insurance company before agreeing to participate to find out what they will cover. If your insurance does not pay for these treatments, procedures, tests, or you do not have insurance, you will be billed for these costs.

8.2 Will I be paid or given anything for taking part in this study?

You will not be paid for being in this study.

8.3 Who could profit or financially benefit from the study results?

No person or organization has a financial interest in the outcome of the study.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my information?

The information collected about you during the study will be placed into a research record. The study data does not include your name, address, social security number or other information that directly identifies you. Instead, the researchers assign a code number to the study data.

This trial will be registered and may report results on www.ClinicalTrials.gov, a publicly available registry of clinical trials.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Demographic information
- Billing information
- Personal Identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
    - Learn more about future research to improve the device or to develop of new ways to treat conditions like yours
    - Discuss or present at medical meetings
    - Learn more information about the cost of treatment over the research study time

- Provide to Federal or State agencies as laws may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:

Dr. Nathaniel Sznycer-Taub
Mailing Address: 1540 E Medical Drive, Floor 11 rm. 661, Ann Arbor, MI 48109-5204
Telephone: 734-764-5176
Email: nsznycer@med.umich.edu

Study Coordinator:

Adriana Batazzi
Mailing Address: 1500 E Medical Drive, L2110 Women's hospital, Ann Arbor, MI 48109-5202

Telephone: 734-763-3140
Email: batazzia@med.umich.edu

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record).*

12. SIGNATURES

Parent Permission

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and the other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or participation, I may contact one of the people listed in Section 10. I understand that I will receive a copy of this form at the time I sign it and later upon request.

Subject Name: _____

Parent/Legally Authorized Representative:

Printed Legal Name: _____

Signature: _____

Address: _____

Date of Signature (mm/dd/yy): _____

Relationship to subject: Parent Sibling Legal guardian Other

If "Other," explain: _____

Reason subject is unable to consent: _____Neonate_____

If this consent is for a child who is a ward of the state (for example, a foster child), please tell the study team immediately. The researchers may need to contact IRBMED.

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____