The Children's Hospital *of* Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title:	**Pediatric REPlAcement of the PulmonaRy ValvE in Tetralogy of Fallot – The PREPARE-TOF study**
Version Date:	September 30, 2019
Consent Name:	TOF PVR Subjects

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You, or your child may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child, please note that the word "you" refers to your child.

Why are you being asked to take part in this study?

You are being asked to take part in this research study because you are between the ages of 13 and 21 and have Tetralogy of Fallot (TOF).

What is the purpose of this research study?

The purpose of this research study is to gather information on adolescents and young adults to help understand and improve the lives of patients with TOF.

Some patients diagnosed with TOF will have a procedure called pulmonary valve replacement (PVR) and some will not. PVR is done for valves that are too damaged to be repaired. This requires a surgeon or an expert in a procedure called cardiac catheterization to replace the damaged pulmonary valve with a valve made of tissue or amechanical valve. Multiple studies in adult TOF patients have suggested that PVR may lessen many clinical symptoms but no one is sure if it truly does. There is little information about PVR in adolescence but it is thought that lessening the amount of leakage of the pulmonary valve at a young age may avoid future complications such as right heart failure or abnormal beats of your heart. There is no agreement among cardiologists, surgeons or other healthcare providers as to whether PVR truly helps avoid

complications in the future and if it does, when PVR should be done. Using the information in this study, we hope to find out if PVR in adolescents is helpful in both the short and long term.

We believe the results of this study will help provide doctors with enough information to support a future large scale research study to further evaluate the outcomes PVR.

How many people will take part?

About 100 people will take part in the study, including approximately 20 participants from CHOP.

What is involved in the study?

If you agree to take part, you will be assigned to one of two treatment groups. One group will undergo PVR and the other group will continue to have medical management. You may be assigned to treatment you may have had anyway or one that you would not have had. Neither you nor your doctor will be able to choose which group you are in yet it is important to understand that whether you participate in this study or not, you will still fall into one of these 2 groups. Right now, doctors do not have evidence to determine the optimal timing for PVR or whether PVR truly improves lives of patients with TOF.

How long will you be in this study?

If you agree to take part, your participation will last 12-18 months and will involve 2 study visits.

What are the study procedures?

Some of the procedures in this study will be repeated several times. Tests that are part of your regular, routine medical care will continue to be performed. Additional tests may be performed if any of your initial test results are not normal. The study involves the following tests and procedures. If any of these tests are performed for your standard clinical care we will use those results whenever possible.

Randomization: You will be randomly assigned (like the flip of a coin or drawing lots) to one of two groups. One will undergo PVR with catheter or surgery (whichever is most appropriate for your situation). The other group will continue with medical management. You will have a 2 in 3 chance of being assigned to the PVR group.

Medical Record Review and Interview: A team member will review your medical record and will take your medical history, including any tests performed at the time of your diagnosis and afterwards, and medications you have taken or may be currently taking. We will collect information from any cardiac magnetic resonance (CMR) imaging, exercise test, holter monitor, echocardiograms, and other forms of monitoring are performed as standard of care.

Exercise Testing (if not part of your standard of care): This test looks at how your heart functions while exercising. You must be able to complete this test with maximal effort to participate in this study. Comfortable clothes and shoes should be worn. You will get on a stationary bike and pedal as the wheels become harder to turn over time. During the exercise test, we will monitor your breathing, heart rate, oxygen level and blood pressure. You will breathe in and out of snorkel-like tubes

before you start and during the exercise testing. The amount of air and pressure of air flowing will be measured.

The exercise testing takes up to one hour to complete, although you will only be pedaling on the bike for about 10-12 minutes. This test may be part of your standard of care as indicated by your cardiologist; if not it will be performed on a research basis.

Exercise CMR: This test looks at how your heart functions during exercise but while in the magnetic resonance imaging (MRI) scanner. You will get on an MRI compatible stationary bike and pedal hooked to the MRI table as the wheels become harder to turn over time. During the exercise test, we will monitor your heart rate and oxygen level. The exercise testing portion of the CMR examination takes up to one half hour to complete, although you will only be pedaling on the bike for about 10-15 minutes. This optional testing will only be done on 10 patients

During the Exercise CMR, we may use sequences (computer programs that control the MRI scanner) that are not currently approved for use by the US Food and Drug Administration (FDA) but that are in the testing phase. The data we obtain will help the FDA evaluate whether or not they can approve the sequences for clinical use as well as evaluating your heart function and flow in this study that could not be done with an FDA approved sequence.

Questionnaires: For both of your study visits, we will ask you and your parent/guardian, to answer some questions, verbally and/or on paper. The questionnaires will either be completed in person or sent to you via mail to complete and send back to the study team. These questionnaires will help us to know how you are doing, and how you feel about your heart condition.

Procedures for Subjects randomized to PVR

Before PVR surgery or cardiac catheterization, your doctor and treatment team will explain what to expect before, during and after the surgery or cardiac catheterization and the potential risks. PVR using cardiac catheterization may require a much shorter hospital stay than traditional heart surgery, however, you and your doctor will decide on an individual basis what is best for you. If by surgery, the doctor will open your chest and directly implant a pulmonary valve whereas by catheterization, this is implanted by a long tube called a catheter.

You will need general anesthesia in order to have PVR. This medicine is used to help pain prevention by making you fall asleep. You will need a breathing tube while under anesthesia You will also receive other pain medicines to help in your recovery.

Your doctor may give you instructions to follow during your recovery, such as watching for signs of infection in your incisions, properly caring for incisions, taking medications, and managing pain and other side effects after your surgery. You will come back to clinic for followup care.

Procedures for Subjects randomized to medical management (No-PVR)

If you are in the non PVR group you will continue with medical management determined by your doctor based on your child's age, overall health, and medical history, extent of

the condition, your tolerance for specific medications, procedures, or therapies, or your opinion or preference. You will come back to clinic for followup care and you will be monitored for signs of worsening of your condition.

Visit Schedule

Visit	Purpose	Main Procedures	Duration
Visit 1	Screening visit*	Consent	1 hours
Visit 2	Study Visit 1*	Exercise test (if applicable), exercise CMR, randomization to treatment group, those assigned to the PVR group will have PVR within 6 months and questionnaires	2 hours
Visit 3	Follow up visit-this will occur approximately 12-8 months after visit 1	Medical record review, exercise test (if applicable), exercise CMR, and questionnaires	2 hours
*Screening visit and study visit 1 can be completed on the same day			

What are the risks of this study?

Taking part in a research study involves inconveniences and risks. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

While in this study, you are at risk for the following side effects:

Risks associated PVR and No-PVR treatment assignment:

The risks presented by the two treatment groups are different.

- Those randomized to PVR are risk of immediate complications from the procedure, general anesthesia and post-procedure care.
- Those who are randomized to medical management (No-PVR) continue to be at risk from the medications and from disease progression.

Risks for Subjects assigned to have PVR

Risks associated with PVR procedure

Subjects having PVR will need to be hospitalized. The valve could fail and need to be replaced. Potential complications from inserting the valve include:

- Blood clots
- Bleeding
- Infection
- Pain
- Stroke
- Need for blood transfusion

- A scar on the chest (if PVR by surgery)
- Abnormal heart beats (skipped, missed beats, fast or slow beats)
- Death
- If you need a blood transfusion:
  - Blood products come from voluntary donors who are carefully selected and tested. There are still some risks to blood transfusion. These risks are uncommon and are usually mild, but may be severe or life threatening.
  - •Occasional risks include: fever and allergic reactions due to the formation of antibodies (formed by the body to fight infections).
  - •Less common risks include: infections with viruses, such as hepatitis and fluid overload
  - •Very rare but serious reactions include: reactions due to a mismatch between the donor's blood and the recipient's and serious infections including HIV (the virus that causes AIDS). The alternative to volunteer donor blood is directed donor blood donated by a family member or friend, if appropriate for your disease.

Risks associated with general anesthesia (GA)

You will need GA in order to have the PVR. There are very rare but serious side effects associated with general anesthesia including: irregular heartbeat, increases or decreases in blood pressure, rare reactions to medications used in the anesthesia, and blockage of breathing passages. Other rare complications include nerve injury, lung injury, heart attack and brain damage. An extremely rare but serious complication is rapid increase in body temperature. All of these complications are treatable but might lead to coma or even death. You will have an opportunity to discuss these risks with the anesthesiologist.

Risks for medical management (No-PVR Group)

- A start or increase in your symptoms
- Decrease in ability to exercise
- Poorer quality of life
- Abnormal heart beats (skipped, missed beats, fast or slow beats)
- A dilation of your right ventricle (the pumping chamber to the lungs) beyond the ability of the pumping chamber to come back to its normal shape
- Right ventricle heart failure - the pumping chamber to the lungs fails and may cause abnormal heart rhythms or death
- Hospitalization for heart failure, abnormal heart beats or increasing symptoms for example
- Need to undergo PVR
- Need for medication or additional medication

- Death

Risks for all Subjects

Risks associated with exercise stress test (if this not ordered by your doctor):

The risk of falling or injury is low. The doctor may stop the test if he/she feels it is not safe for you to continue. You may have some discomfort using the snorkel-like tube. You may stop the test at any time if you feel uncomfortable or unable to continue the test. During the study, your

- Heart rate will be monitored by an electrocardiogram and a pulse oximetry monitor
- Blood pressure will be monitored by a blood pressure cuff
- Oxygen level will be monitored by a pulse oximetry monitor

Risks associated with exercise CMR:

For a select group who agree, we may ask you to exercise in the MRI scanner with a bicycle lying down which would be in addition to your standard MRI scan. There are no known risks of physical harm associated with the additional MRI scanning time. However, MRI machines produce loud banging noises, which cause some people to become stressed or upset which you will hear as you would during your routine MRI scan. You may also feel uncomfortable inside the magnet if you do not like to be inside small places or have difficulty lying still, similar to your standard scan. You may feel tired after you exercise. During exercise, your heart rate will be monitored by an electrocardiogram and pulse oximetry monitor and your oxygen level will be measured by a pulse oximetry monitor as well.

The MRI magnet is always on and attracts certain metal objects. Any metal objects on or inside of your body may heat up, move, and/or not function properly within the scanning room. Metal objects in the room can fly through the air toward the magnet and hit those nearby. There are many safety measures in place to reduce these risks. The staff will screen all persons and materials entering the scanning room for metal. When the study begins, the door to the room will be closed to minimize the risk of someone accidentally bringing a metal object into the scanner room.

Risks associated with Questionnaires:

Answering the questionnaires may bring up certain emotional feelings and concerns about your condition. You do not have to answer any questions that make you feel too uncomfortable. If you become too upset or need to talk to someone, we will refer you to the Department of Social Work and Family Services.

Risks associated with breach of confidentiality:

As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure your personal information to ensure confidentiality. At the time of participation, each participant will be assigned a study identification number. This number will be used on study questionnaires, data collection forms, and in the database instead of names and other

private information. A separate list will be maintained that will link each participant's name to the study identification number for future reference.

Are there any benefits to taking part in this study?

It is not known whether or not PVR or medical management is the best approach to treatment. If PVR is effective, those who are in that group may benefit from better quality of life and ability to exercise as well as avoidance of the adverse effects of no-PVR. If PVR is not effective, those not assigned will avoid the risks and adverse effects of the PVR procedure. It is possible that you will be assigned to a treatment group that does better. However, there may be no direct benefit to you from taking part in this study.

The knowledge gained from this study may help doctors determine how to treat adolescent TOF patients in the future

Summary of the Benefits and Risks of the Two Treatments

The table below summarizes the major differences in possible benefits and risks with the two treatments. It is important to remember that it is not known whether PVR works or which group will do better. Since it is unknown whether or not PVR prevents disease progression, your symptoms may get worse regardless of which arm you are assigned to. It is also important to understand that whether you participate in this study or not, you will still fall into one of these 2 groups.

Treatment Arm	Possible Benefits	Possible Risks
PVR	• Improved exercise capacity • Improved quality of life • Avoidance of the complications of no-PVR	• Complications from PVR procedure including: pain, bleeding, clots, that could lead to death • Need to undergo valve replacement
No-PVR	• Avoidance of the complications of PVR	• Progression of symptoms due to right heart failure that could lead to death • Decreased ability to exercise • Decrease in quality of life • Need for additional medications

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record.

What are your responsibilities?

Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study.

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

Can the study doctor take you out of the study early?

The study doctor may take you off of the study if:

- Your condition worsens.
- The study is stopped.
- You cannot meet all the requirements of the study.
- New information suggests taking part in the study may not be in your best interests.

What choices do you have other than this study?

There are other options for you other than this study including:

- Receiving care for TOF outside this study.
- Not participation in this study.

You may discuss other options available to you with your doctor. It is also important to understand that whether you participate in this study or not, you will still fall into one of these 2 groups.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information from your medical records, procedures, interviews and tests. Information related to your medical care at CHOP will go in your medical record. This could include physical exams, imaging studies (x-rays or MRI scans) or tests done in the clinical lab. Medical records are available to CHOP staff. Staff will view your records only when required as part of their job. Staff are required to keep your information private. Information that could identify you will not be shared with anyone - unless you provide your written consent, or it is required or allowed by law. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your de-identified data may be shared with all participating centers.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized staff at CHOP
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections.
- Groups monitoring the safety of this study (e.g. DSMB);
- The National Institutes of Health who is sponsoring this research.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

Your permission to use and share the information and data from this study will continue until the research study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

A Certificate of Confidentiality (CoC) issued by the NIH covers this research. A CoC helps protect your identifiable information and biological samples.

A CoC protects your private information from all legal proceedings. Unless you consent, information from this research study that identifies you will not be shared outside this research.

- No one can be forced to share your identifiable information or biological samples for a lawsuit.
- Your information can't be used as evidence even if there is a court subpoena.

If you consent, your information or biological samples could be shared for:

- other scientific research.

The CoC does not prevent some disclosures.

- The researchers can't refuse requests for information from those funding this research. The NIH may need information to assess this project.
- You can still share information about yourself. You can also freely discuss your involvement in this research.

The researchers must disclose things required by law. This includes suspected child abuse and neglect, harm to self or others, or communicable diseases.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you inform the investigator in writing.

Dr. Mark Fogel
The Children's Hospital of Philadelphia
Division of Cardiology
34th Street and Civic Center Blvd.
Philadelphia, PA 19104

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Additional Information

A Data Safety and Monitoring Board, an independent group of experts organized by the National Institutes of Health, will be reviewing the data from this research throughout the study.

You will be informed if changes to the study are needed to protect your health. You will be told about any new information that could affect your willingness to stay in the study, such as new risks, benefits or alternative treatments.

Financial Information

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

Will there be any additional costs?

There will be no additional costs to you by taking part in this study

Will you be paid for taking part in this study?

Participants will be compensated $25 for their participation, upon the completion of the follow up study visit. If you receive payment using a bankcard, the bank will have access to identifiable information. The bank will not have access to any medical information.

Who is funding this research study?

The National Institutes of Health is providing funding for this study.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. Mark Fogel at: 215-590-3534. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

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

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research.

You and your insurance company will be billed for the costs of any care or injuries.

If you think you have been injured from taking part in this study, call Dr. Mark Fogel at 215-590-3534. He can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

Consent to participate in the optional exercise CMR

Please indicate whether you will participate in the exercise CMR portion of this study by putting your initials next to one of the following choices:

_____ (initials) I agree to participate in the optional exercise CMR

_____ (initials) I do not wish to take part in this optional part of the research.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date

By signing this form, you are indicating that you have had your questions answered, you agree to take part in this research study and if you are giving permission for a child to participate in this research study, you are legally authorized to consent to the child's participation. You are also agreeing to let CHOP use and share the health information that will be collected for this study, as explained above. If you don't agree to the collection, use and sharing of health information, you cannot participate in this study. **NOTE:** *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject	
Signature of Subject (18 years or older)	Date
Name of Authorized Representative (if different than subject)	Relation to subject: ☐ Parent ☐ Legal Guardian
Signature of Authorized Representative	Date

Child Assent to Take Part in this Research Study

For children capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

This study has been explained to me and I agree to take part.

_____ _____
Signature of Subject (optional) Date

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STUDY SUMMARY SIGNATURE PAGES

For Non-English Speaking Subjects

Consent to Take Part in this Research Study and Authorization to Disclose Health Information

Name of Subject

Name of Authorized Representative (if different than subject)

Relation to subject:
☐ Parent ☐ Legal Guardian

The research study and consent form have been explained to the subject or parent/legal guardian.

By signing this form, you are indicating that you have answered the subject's or parent's/legal guardian's questions, they have agreed to take part in this research study and they are legally authorized to consent to their or their child's participation. They have also agreed to let CHOP use and share their or their child's health information as explained above. If they don't agree to the collection, use and sharing of their or their child's health information, they cannot participate in this study.

Person Obtaining Consent

Signature of Person Obtaining Consent

Date:

Witness/Interpreter

By signing this form, you are indicating that

- The information in the Summary Document as well as any additional information conveyed by the person obtaining consent was presented to the subject in a language preferred by and understandable to the subject; and
- The subject's questions were interpreted and the responses of the person obtaining consent were presented in a language preferred by and understandable to the subject.
- At the conclusion of the consent conference, the subject was asked in a language preferred by and understandable to the subject if s/he understood the information in the Summary Document as well as any additional information conveyed by the person obtaining consent (including responses to the subject's questions) and responded affirmatively.

Name of Witness/Interpreter

Signature of Witness/Interpreter

Date:

Child Assent to Take Part in this Research Study *(Non-English Speaking Subjects)*

For children capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

Witness/Interpreter

By signing this form, you are indicating that

- The information in the Summary Document as well as any additional information conveyed by the person obtaining assent was presented to the subject in a language preferred by and understandable to the subject; and
- The subject's questions were interpreted and the responses of the person obtaining assent were presented in a language preferred by and understandable to the subject.
- At the conclusion of the consent conference, the subject was asked in a language preferred by and understandable to the subject if s/he understood the information in the Summary Document as well as any additional information conveyed by the person obtaining assent (including responses to the subject's questions) and responded affirmatively.

_____ _____
Name of Witness/Interpreter Signature of Witness/Interpreter

Date: _____