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Clinical Trials.gov Update

July 14, 2022

Re: Record (NCT) Number NCT03634072
Study Title: Pediatric REPlAcement of the PulmonaRy ValvE in Tetralogy of Fallot – The PREPARE-TOF study
PI Name: Mark Fogel MD
Date of Document:

To Whom It May Concern:

Please see the attached IRB approved protocol version date November 8, 2019 for your review.

If you have any questions or require any further information, please contact me via email@ FOGEL@chop.edu

Thank you for your time,

Principal Investigator
Mark Fogel, MD

Title:	Pediatric REPlAcement of the PulmonaRy ValvE in Tetraology of Fallot – The **PREPARE-TOF** study
Short Title	TOF and PVR
Drug or Device Names(s)	N/A
FDA IND	N/A
Regulatory Sponsor:	NIH/NHLBI
eIRB Number	**18-015046**
Protocol Date:	11/08/2019

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Amendment 2 Date: 1/10/2019	Amendment 5 Date:11.08.2019
Amendment 3 Date: 3/21/2019	Amendment 6 Date:

Sponsor
NIH/NHLBI

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ABBREVIATIONS AND DEFINITIONS OF TERMS

TOF		Tetralogy of Fallot
PVR		Pulmonary Valve Replacement
CMR		Cardiac Magnetic Resonance
MRI		Magnetic Resonance Imaging
VSD		Ventricular Septal Defect
RV		Right Ventricular
LV		Left Ventricular
RVVO		Right Ventricular Volume Overload
PR		Pulmonary Regurgitation
QOL		Quality of Life
DF		Diffuse Fibrosis
PCMR		Phase Contrast Magnetic Resonance
CI		Cardiac Index
EST		Exercise Stress Test
RVEDVi		Right Ventricular End-Diastolic Volume Index
NIH		National Institutes of Health
FDA		Food and Drug Administration

ABSTRACT

Context:

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect and the vast majority of survivors of corrective surgery will be left with some degree of right ventricular (RV) volume overload due to pulmonary regurgitation (PR). TOF patients with significant PR are known to develop RV enlargement with right heart failure, diminished biventricular function, ventricular arrhythmia, sudden death and decreased exercise performance over time. Nearly all studies in this regard are retrospective with much less data in pediatric TOF than adults.

Multiple studies in adult TOF survivors have suggested that pulmonary valve replacement (PVR) may alleviate many clinical symptoms and allow RV remodeling; furthermore, numerous studies have suggested that PVR in the asymptomatic patients may prevent clinical decline. The timing of PVR is crucial as prosthetic valve integrity is limited. If performed too early, the valve will require replacement earlier than it might have otherwise in the future and if performed too late, the patient may experience an adverse clinical outcome and incomplete RV remodeling.

Despite the lack of robust prospective evidence, PVR is nevertheless occurring in adolescent TOF patients. With the advent of transcatheter PVR, an increasing number of patients will undergo this procedure, making knowledge of the benefits and timing of the procedure, which have generally been based on cardiac magnetic resonance (CMR) derived RV volumes mostly in adults, even more critical. Retrospective studies have varied regarding the optimal threshold values for PVR; the practice of when and even if PVR should be performed varies widely between institutions and even within practice groups.

To guide clinicians, a randomized, prospective trial is needed to determine if PVR in adolescents is beneficial both in the short and long terms. We propose to perform a feasibility protocol to obtain preliminary data and to create a structured framework upon which a future, large scale trial can be built. Our long-term goal is to perform a rigorous prospective trial in adolescent TOF patients to determine specific hemodynamic and physiologic criteria in asymptomatic TOF survivors to identify the optimal timing of PVR and to demonstrate its benefit, creating a new paradigm through a targeted approach that identifies subgroups at highest risk for long-term deficits. To design such a trial, the feasibility protocol we propose will obtain pilot data including parameters such as the number of patients to screen, acceptance of a randomized PVR trial, comparisons after 1-1.5 years between those who do and do not undergo PVR in quality of life (QOL) (research procedure), exercise testing and Holter monitoring (clinical procedures) which will inform the endpoints for the larger, longer term trial. This feasibility protocol will use innovative CMR techniques to determine the mechanism of clinical outcome in this patient population.

Objectives:

Specific Aim 1: To determine the operational feasibility of a randomized, multicenter trial of PVR in adolescent TOF survivors to assess its impact on outcome – a main goal of an R34 planning grant. Study teams from Children's Hospital of Philadelphia, Cincinnati Children's

Hospital, Children's Healthcare of Atlanta, Lurie Children's and Children's National Medical Center will recruit asymptomatic TOF patients to be randomized to PVR or "no-PVR" groups based on mostly on CMR RV volumes to prove operational feasibility. There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network). ***Hypothesis: A randomized, multicenter, clinical trial of PVR in TOF survivors is operationally feasible.***

Specific Aim 2: To measure clinical parameters needed to design a large scale clinical trial by performing a short term pilot protocol. At entry, in addition to CMR (clinical procedure), all subjects will undergo exercise testing (clinical procedure), Holter monitoring (clinical procedure) and complete QOL questionnaires (research procedure) which will be repeated 12-18 months later. EST will be performed for research purposes if not performed for clinical purposes. Patients will be randomized to PVR and no-PVR groups. Comparison between PVR and no-PVR groups will be made for parameters including mortality, exercise testing, physical functioning QOL score, prevalence of arrhythmia and medical care utilization. Preliminary data for these parameters would be collected will inform outcome measures in the larger trial. A comparison of biventricular function between groups will also be made. ***Hypothesis: There are clinical metrics that can be utilized to inform the endpoints of a robust longer term, large scale trial of PVR in asymptomatic TOF survivors to discern who would benefit and optimize timing of the procedure.***

Specific Aim 3: To determine mechanisms of the effects of PVR in the definitive trial by obtaining preliminary data on diffuse fibrosis (DF), performing exercise CMR (research procedure) and measuring biventricular strain (post processing of clinical images as a research procedure). Subjects will undergo repeat CMR 12-18 months after enrollment including measurement of DF, exercise CMR and strain measures to determine biventricular function and PR at rest and exercise, comparing PVR and no-PVR groups and correlating with short term outcomes. ***Hypothesis: PVR in asymptomatic TOF survivors who fall within specified guidelines results in improved ventricular function at exercise, improved strain and have less DF when compared to no-PVR and correlates with clinical outcomes.***

Study Design:

This is a prospective, multi-center pilot protocol to assess the operational feasibility of a randomized, multicenter trial of PVR in adolescent TOF survivors.

Setting/Participants:

This is a multi-center study.

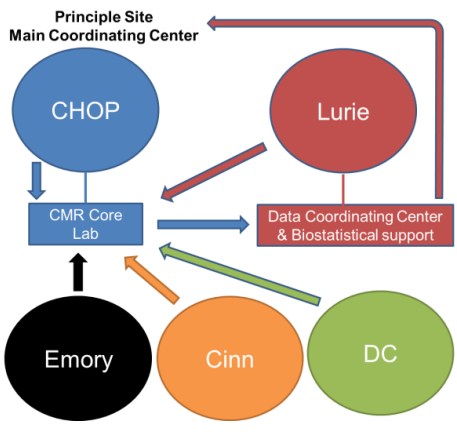
We will enroll 100 patients with TOF from 5 centers: The Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital (Cinn), Emory University School of Medicine/Children's Healthcare of Atlanta (Emory), Lurie Children's (Lurie) and Children's National Medical Center (DC)

Study Interventions and Measures:

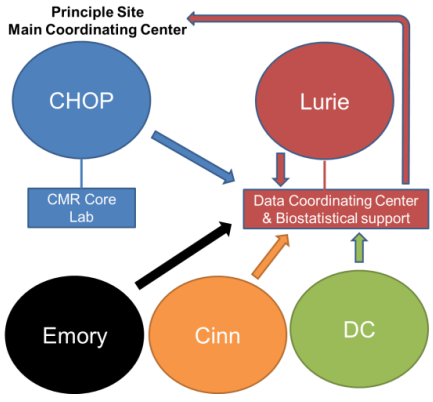
The study team from The Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital (Cinn), Emory University School of Medicine/Children's Healthcare of Atlanta (Emory), Lurie Children's (Lurie) and Children's National Medical Center (DC) will participate in this R34. CHOP, Cinn and Emory have worked successfully together in the past on other projects including a recent RO1 (HL098252-01). CHOP and DC recently began a collaboration using 3D rapid prototyping models, holding their first symposium in February 2014. *This group of 5 centers brings together well published experts in CMR (Drs Fogel, Lang, Slesnick, Rigsby and Cross), exercise (Dr. Paridon), QOL (Dr. Marino), catheterization (Dr. Kim) and surgery (Drs Gaynor and Fuller). Experienced "trialists" such as Drs Paridon and Marino will be complemented by the experience of Dr. Fogel in industry where he ran large scale clinical drug trials for 3 years at Wyeth-Ayerst as well as Dr. Scholtens, biostatistics faculty at Lurie Childrens, who has >10 years of experience in collaborative biostatistics and currently serves as the primary statistician for a large-scale international multicenter epidemiologic study. All are involved in clinical care and have been involved in clinical studies.*

Although five participating centers may seem a large number for a feasibility pilot protocol, there are 2 major justifications for its use. First, because this is a 3 year award, there is limited time for follow-up mandating rapid enrollment, which is more feasible from multiple centers. Second, we intend to demonstrate and fine-tune the multicenter aspects of the trial in preparation for a full study. This includes solidifying functions of a data collection center, imaging core and safety monitoring.

CHOP will be the principle site as well as the CMR Core Laboratory and Northwestern University (NU) will provide the data management and biostatistical support. Dr. Fogel (CHOP) and Dr. Marino (NU) have been the CMR Core Laboratory and data management and biostatistical support respectively for numerous other studies. A strict firewall will be in place at both CHOP and NU to ensure that Drs. Fogel and Marino do not participate in and will be blinded to any site data. Teleconferences monthly will be held between centers to discuss issues and make decisions regarding the conduct of the feasibility protocol. Analysis of CMR data will be performed at each site and in the department of Radiology at CHOP. EST, QOL, echocardiograms and Holter monitoring will be performed at each site. Figures to the right depict the workflow and communications link for CMR data (leftward) and data other than CMR (rightward).



Work flow for CMR data



Work flow for data other than CMR

Overall Approach of this R34: The overall approach of this proposal is to test feasibility of a multicenter, randomized, controlled interventional trial at each of these centers (Aim 1), obtain preliminary data to inform the large scale definitive trial by performing a small pilot protocol of such a trial (Aim 2) and to determine possible mechanistic effects of the results with novel CMR techniques (Aim 3). The small pilot protocol will randomize asymptomatic TOF patients to PVR or "no-PVR" groups based primarily on clinical CMR RV volumes (see entry criteria in Aim 2). PVR groups will be further divided into transcather PVR (where clinically indicated) and surgical PVR (for all others). Recruitment rates will be assessed (Aim 1) and coordination of centers tested (e.g. communication via Skype, etc.; Aim 1). CMR Core lab and data management and biostatistical support performance will be evaluated (e.g. time to process a CMR study; Aims1 and 2). A data safety monitoring board will be established. There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network).

The study intervention is randomization between PVR and no-PVR groups; PVR groups will get catheter-based or surgical based PVR, whichever is clinically indicated. Study measures will include review of medical records including those from CMR (eg ventricular volumes, ejection fraction, PR), exercise testing (eg VO2 at VAT, Work at VAT) and Holter monitoring (eg amount of ectopy). Other research related procedures include patient/family questionnaires, physician questionnaires and Quality of Life testing (QOL), exercise CMR and post-processing of clinical cine images to obtain biventricular strain. EST will be performed for research purposes if not performed for clinical purposes. These will all be performed at the beginning of participation and then 1-1.5 years afterwards. See body of the protocol for more details on specific measures.

PROTOCOL SYNOPSIS

Study Title	Tetralogy of Fallot and Pulmonary Valve Replacement
Funder	NIH/ NHLBI
Clinical Phase	Not applicable
Study Rationale	Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect and the vast majority of survivors of corrective surgery will be left with some degree of RV volume overload PR). TOF patients with significant PR are known to develop right ventricular (RV) enlargement with right heart failure, diminished biventricular function, ventricular arrhythmia, sudden death and decreased exercise performance over time. Nearly all studies in this regard are retrospective with much less data in pediatric TOF than adults. Multiple studies in adult TOF survivors have suggested that pulmonary valve replacement (PVR) may alleviate many clinical symptoms and allow RV remodeling; furthermore, numerous studies have suggested that PVR in the asymptomatic patients may prevent clinical decline. The timing of PVR is crucial as prosthetic valve integrity is limited. If performed too early, the valve will require replacement earlier than it might have otherwise in the future and if performed too late, the patient may experience an adverse clinical outcome and incomplete RV remodeling. Despite the lack of robust prospective evidence, PVR is nevertheless occurring in adolescent TOF patients. With the advent of transcatheter PVR, an increasing number of patients will undergo this procedure, making knowledge of the benefits and timing of the procedure, which have generally been based on cardiac magnetic resonance (CMR) derived RV volumes mostly in adults, even more critical. Retrospective studies have varied regarding the optimal threshold values for PVR; the practice of when and even if PVR should be performed varies widely between institutions and even within practice groups. To guide clinicians, a randomized, prospective trial is needed to determine if PVR in adolescents is beneficial both in the short and long terms. We propose to perform a feasibility protocol to obtain preliminary data and to create a structured framework upon which a future, large scale trial can be built. Our long-term goal is to perform a rigorous prospective trial in adolescent TOF patients to determine specific hemodynamic and physiologic criteria in asymptomatic TOF survivors to identify the optimal timing of PVR and to demonstrate its benefit, creating a new paradigm through a targeted approach that identifies subgroups at highest risk for long-

	term deficits. To design such a trial, the feasibility protocol we propose will obtain pilot data including parameters such as the number of patients to screen, acceptance of a randomized PVR trial, comparisons after 1-1.5 years between those who do and do not undergo PVR in quality of life (QOL), exercise testing and Holter monitoring which will inform the endpoints for the larger, longer term trial. EST will be performed for research purposes if not performed for clinical purposes. This feasibility protocol will use innovative CMR techniques to determine the mechanism of clinical outcome in this patient population. There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network).
Study Objective(s)	***Specific Aim 1:*** *To determine the operational feasibility of a randomized, multicenter trial of PVR in adolescent TOF survivors to assess its impact on outcome – a main goal of an R34 planning grant.* Study teams from Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Children's Healthcare of Atlanta, Lurie Children's and Children's National Medical Center will recruit asymptomatic TOF patients to be randomized to PVR or "no-PVR" groups based on mostly on CMR RV volumes to prove operational feasibility. There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network). ***Hypothesis: A randomized, multicenter, clinical trial of PVR in TOF survivors is operationally feasible.*** ***Specific Aim 2:*** *To measure clinical parameters needed to design a large scale clinical trial by performing a short term pilot protocol.* At entry, in addition to CMR (clinical procedure), all subjects will undergo exercise testing (clinical procedure), Holter monitoring (clinical procedure), complete patient/family questionnaire and complete QOL questionnaires (both research procedures) which will be repeated 12-18 months later. EST will be performed for research purposes if not performed for clinical purposes. Comparison between PVR and no-PVR groups will be made for clinical parameters including mortality, exercise testing, physical functioning QOL score, prevalence of arrhythmia and medical care utilization. Preliminary data for these parameters would be collected will inform outcome measures in the larger trial. A comparison of biventricular function between groups will also be made. ***Hypothesis: There are clinical metrics that can be utilized to inform the endpoints of a robust longer term, large scale trial of PVR in asymptomatic TOF survivors to discern who would benefit and optimize timing of the procedure.*** ***Specific Aim 3:*** *To determine mechanisms of the effects of PVR in the definitive trial by obtaining preliminary data on diffuse fibrosis*

	(DF), performing exercise CMR and measuring biventricular strain. Subjects will undergo repeat CMR 12-18 months after enrollment including measurement of DF, exercise CMR (research procedure) and strain measures (research procedure) to determine biventricular function and PR at rest and exercise, comparing PVR and no-PVR groups and correlating with short term outcomes. ***Hypothesis: PVR in asymptomatic TOF survivors who fall within specified guidelines results in improved ventricular function at exercise, improved strain and have less DF when compared to no-PVR and correlates with clinical outcomes.***
Test Article(s)	PVR or no-PVR in a randomized fashion
Study Design	This is a prospective, multicenter, randomized pilot protocol to assess the operational feasibility and to obtain preliminary data to inform a future large scale randomized, multicenter trial of PVR in adolescent TOF survivors.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** For patients with TOF 1. Males or females with repaired TOF, currently between 13 and 21 years of age. 2. On clinical CMR: RVEDVi between 140 and 180 cc/m2 inclusive with RVEF > 40% and LVEF > 50%. If data available and adequate RV outflow tract peak velocity < 3 meters/second (if not available this can be skipped); there will be no indexed RVESVi criteria; by defining RVEDVi and RVEF, we will be inherently defining RVESVi, at least 10% pulmonary regurgitation fraction. 3. On clinical echocardiogram: If data available and adequate, RV outflow tract peak velocity < 3 meters/second (if not available this can be skipped), at least mild pulmonary insufficiency and tricuspid regurgitation with an RV pressure estimate < 1/2 systemic pressure. 4. On EST, aerobic capacity $\geq$ 60% of predicted. 5. No QRS duration criteria on ECG. For physicians: Any cardiologist who practices at any of the 5 participating sites. ***The Exclusion Criteria*** For patients with TOF 1. Any condition judged by the patient's physician that would cause this trial to be detrimental to the patient. 2. Specific forms of TOF excluded are those with endocardial cushion defects, TOF with absent pulmonary

	valve and TOF with multiple aorto-pulmonary collaterals requiring unifocalization. 3. Unilateral branch pulmonary artery stenosis (one lung receives < 25% of total flow) 4. Contraindication to non-sedated exercise CMR (e.g. pacemaker/implanted cardioverter defibrillator); need for sedation 5. If data available, moderate or greater tricuspid regurgitation on echocardiogram or CMR or Qp/Qs > 1.5 (if not available this can be skipped) 6. Significant strokes/hemiplegia or inability to exercise 7. Genetic syndrome/developmental delay which would make QOL and EST date uninterpretable 8. Pregnancy. 9. Previous pulmonary valve replacement (PVR). For physicians: none.
Number Of Subjects	We will enroll 100 patients with TOF from the 5 centers including CHOP. For physicians agreeing to answer questionnaires, we estimate this will be ~200 subjects will be enrolled.
Study Duration	1. Each subject's participation will last ~ 1-1.5 years from enrollment to followup 2. Exercise CMR component to the CMR scans will last~ 15 minutes. Metabolic exercise test (if not clinically indicated and therefore, research related) will last ~ 60 minutes 3. Assessment of QOL will last ~ 20 minutes 4. Fill out patient questionnaire about this trial will last ~10-15 minutes 5. For physicians answering physician questionnaire, this will last ~20 minutes
Study Phases **Screening** **Study Treatment** **Follow-Up**	1. Screening and subsequent recruitment begins ~3 months after grant approved 2. Patients will be recruited simultaneously 3. Study treatment will be in 2 phases – at recruitment where randomization occurs and then at followup 1-1.5 years later 4. Data entry will be on-going 5. 1.5-2 year enrollment period 6. End recruitment. Data cleaning, analysis and manuscript writing in last few months
Efficacy Evaluations	*Aim 1:* Results of questionnaires, ability to recruit the required number of patients in the time given, Protocol logs demonstrating how many patients were screened, eligible and approached, how many dropped out and for what reason among other metrics. Factors

	which will affect follow-up in a larger trial are also key such as patients moving out of the area, pregnancy and need for pacemaker will be recorded and will be used as preliminary data for dropout rates and sample size for the larger trial. *Aim 2:* Exercise parameters on EST such as maximum oxygen consumption and work at ventilatory anaerobic threshold; Quality of life indexes, CMR parameters such as ventricular volumes, ejection fraction and mass; Holter parameters such as the amount of ectopy. *Aim 3:* Measures of diffuse and discrete fibrosis, myocardial strain and performance parameters on exercise CMR.
Pharmacokinetic Evaluations	Not applicable
Safety Evaluations	Clinical evaluations such as death, transplantation, need for hospitalization and medication, failure of PVR with need to replace or need, in the non-PVR goup for PVR, requirement in general for additional interventions. A data safety monitoring board will be established through the NIH.
Statistical And Analytic Plan	Please see body of this application for a detailed analysis. A data coordinating center will be established at Northwestern University (NU). A REDCAP database will used. For randomization, we will use a 2:1 PVR:no-PVR randomization scheme. The statistician will generate a randomization scheme using blocked randomization with varying block sizes of 3 and 6 within study site. To assess success of randomization in balancing patient characteristics across treatment arms, we will calculate means and standard deviations for relevant continuous variables and tables of counts and frequencies for categorical variables, comparing across PVR and no PVR groups using t- and chi-square tests, respectively. If imbalance is observed, analyses of the outcomes will be conducted with and without adjustment for these covariates. **DSMB interim analysis:** The DSMB will formally review adverse event frequency for the PVR and no-PVR groups after 45 trial participants have completed follow-up data collection; they will be blinded to treatment group status and only frequencies, not sample sizes, will be presented to mask the 2:1 randomization. A statistically significant difference ($p<0.05$) in adverse event frequency will merit further investigation into continuing the trial. This interim analysis is planned for formal evaluation of safety; an interim analysis of treatment effect is not planned due to the pilot and feasibility nature of the study. **Aim 1:** Descriptive statistics appropriate for measures of feasibility and performance will be calculated (eg overall percent and monthly pace of patient recruitment at each site, means and standard

	deviations of patient/physician survey answers). These data summaries will be used to determine whether a large-scale clinical trial is feasible; specific criteria for proceeding with a larger trial are outlined at the end of this proposal. **Aims 2 and 3:** Descriptive statistics for all variables will be computed, including parametric and non-parametric measures of central tendency and variability. Continuous outcome variables for Aims 2 and 3 will be checked for normality using histograms and qplots, both for baseline and follow-up measures at 1-1.5 years after randomization, and for the difference between these two observations. If normality is suspect, we will explore transformations to improve normality or apply non-parametric counterparts for the analyses described in what follows. Data will be analyzed using SAS. The change from enrollment to 1-1.5 years after randomization in each candidate parameter for the intended primary endpoint in the definitive trial will be treated as outcomes which will be summarized for the PVR and no-PVR groups using means and standard deviations; they will be formally compared between groups using linear regression models with a dummy variable for treatment assignment (PVR vs. no-PVR) as the primary variable of interest with adjustment for study site and possibly other covariates that were not balanced across treatment group and might be associated with the outcomes. Treatment differences with $p<0.05$ in regression models will be considered statistically significant. Intent-to-treat analyses will be conducted such that treatment assignment will be assigned as randomized regardless of adherence. Complete data analyses will be conducted initially, but the frequency of missing data within each treatment group will be calculated. Since baseline data determines study eligibility, most missing data will occur at the anticipated follow-up time. We will compare demographic and clinical characteristics of patients with complete data to those without using t- and chi-square tests as appropriate to determine whether "missingness" may be informative. Depending on what we observe, we will perform sensitivity analyses using multiple imputation approaches and compare results to complete data analyses. Importantly, describing "missingness" frequency and potential bias in its occurrence will assist in planning a larger trial by emphasizing areas crucial for follow-up. It will help plan for imputation strategies that may be necessary in the larger trial and could suggest additional variables for in the larger trial to strengthen imputation models in the larger setting if required. Several of the other candidate parameters which will be tested for the definitive trial for both Aims 2 and 3 are continuous variables measured at 2 time points; differences will be analyzed

	using the approach described for the primary endpoints. Comparison of frequency of additional discrete secondary outcome variables for Aim 2 (eg death, hospitalization) will utilize chi-square tests given the sample size followed by logistic regression controlling for site and any other relevant variables. Cox modeling of time-to-event data will be considered if frequencies are higher and event times more varied than expected although this is unlikely given the number of events anticipated. Within the PVR group, we will tabulate frequency of valve failure and re-intervention and in the no PVR group, we will tabulate the frequency of need for PVR or other interventions. These are not comparative analyses but will inform event rates for future trial design. Analyses for comparing the surgical and transcather PVR groups for all candidate parameters for the definitive trial will be adjusted for time since repair will be conducted by performing all analyses as just described. While patients will not be randomized to mode of PVR and this may introduce some bias, we will control for confounding to the extent possible and incorporate the similarities and differences of surgical or transcather PVR group in planning of the larger trial. Pairwise Spearman's correlation coefficients including 95% confidence intervals will be calculated for the variables listed in Aim 3 and the clinical outcomes in Aim 2. All statistical tests will be conducted at nominal 2-sided, 5% significance level. *While we recognize the multiplicity of variables and statistical tests, the purpose of this pilot trial is not to provide conclusive evidence of clinical effect, but rather to indicate possible effect size and use it to plan for a larger trial if the preliminary effect size is clinically relevant. Because of the preliminary nature of this pilot study, no correction for multiple comparisons will be made.*
DATA AND SAFETY MONITORING PLAN	The PI at each site will have overall responsibility for monitoring the overall safety during the study In addition, the study coordinator will be involved in all studies and will also monitor for safety. Each site will be responsible for reporting all adverse events to their respective IRB and to the lead site in a timely fashion in compliance with all applicable regulations. The study investigators will be responsible for data management and accuracy of records. They may assign designated qualified individuals to collect the information. All data will be entered into Redcap. A DSMB will be constituted from the NIH.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

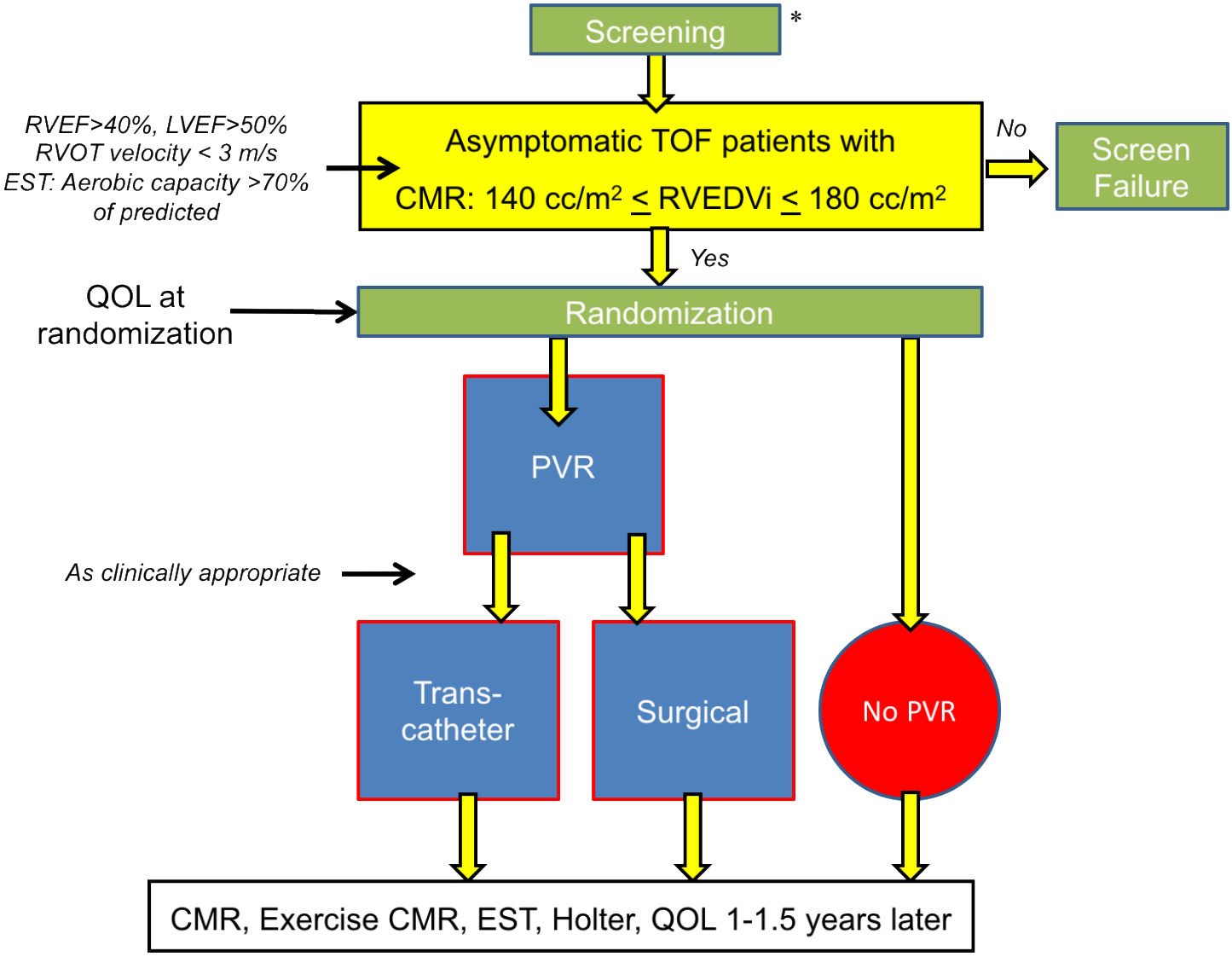
Study Phase	**Screening**	**Study Visit 1**	**Study Visit 2**	**Study Visit 3**
Study Days				
Informed Consent/Assent	X			
Review Inclusion/Exclusion Criteria	X	X*		
Demographics/Review of Medical History	X	X	X	
Randomization to receive PVR or no-PVR		X		
Review medical records	X	X	X	
Exercise Stress Test if not clinically indicated		X	X	
QOL questionnaires		X	X	
Patient/family questionnaire		X	X	
Prior/Concomitant Medications		X	X	
Adverse Event Assessment		X	X	
Exercise CMR [##]		X	X	
Physician questionnaire		X	X	X

*if not done at screening.

[##] this will occur as a pure study procedure and will be added on to at the end to an existing standard of care CMR at the end of the case; this will be done in 10 patients as a subanalysis.

***Screening visit and Study visit can occur on the same day.

STUDY DIAGRAM



To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring are clinical care procedures.

* screening activities are limited to review of medical/investigator records and do not include soliciting information directly from potential subjects

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect and the vast majority of survivors of corrective surgery will be left with some degree of right ventricular (RV) volume overload due to pulmonary regurgitation (PR). TOF patients with significant PR are known to develop RV enlargement with right heart failure, diminished biventricular function, ventricular arrhythmia, sudden death and decreased exercise performance over time. Nearly all studies in this regard are retrospective with much less data in pediatric TOF than adults.

Multiple studies in adult TOF survivors have suggested that pulmonary valve replacement (PVR) may alleviate many clinical symptoms and allow RV remodeling; furthermore, numerous studies have suggested that PVR in the asymptomatic patients may prevent clinical decline. The timing of PVR is crucial as prosthetic valve integrity is limited. If performed too early, the valve will require replacement earlier than it might have otherwise in the future and if performed too late, the patient may experience an adverse clinical outcome and incomplete RV remodeling.

Despite the lack of robust prospective evidence, PVR is nevertheless occurring in adolescent TOF patients. With the advent of transcatheter PVR, an increasing number of patients will undergo this procedure, making knowledge of the benefits and timing of the procedure, which have generally been based on cardiac magnetic resonance (CMR) derived RV volumes mostly in adults, even more critical. Retrospective studies have varied regarding the optimal threshold values for PVR; the practice of when and even if PVR should be performed varies widely between institutions and even within practice groups.

To guide clinicians, a randomized, prospective trial is needed to determine if PVR in adolescents is beneficial both in the short and long terms. We propose to perform a feasibility protocol to obtain preliminary data and to create a structured framework upon which a future, large scale trial can be built. Our long-term goal is to perform a rigorous prospective trial in adolescent TOF patients to determine specific hemodynamic and physiologic criteria in asymptomatic TOF survivors to identify the optimal timing of PVR and to demonstrate its benefit, creating a new paradigm through a targeted approach that identifies subgroups at highest risk for long-term deficits. To design such a trial, the feasibility protocol we propose will obtain pilot data including parameters such as the number of patients to screen, acceptance of a randomized PVR trial, comparisons after 1-1.5 years between those who do and do not undergo PVR in quality of life (QOL), exercise testing and Holter monitoring which will inform the endpoints for the larger, longer term trial. This feasibility protocol will use innovative CMR techniques to determine the mechanism of clinical outcome in this patient population. There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network; http://www.pediatricheartnetwork.org/Studies/CompletedStudies/SingleVentricleStudySurgical.aspx).

1.2 Name and Description of Investigational Product or Intervention

This study does not utilize an investigational product; it is utilizing an intervention. As mentioned in the Introduction above and the Literature and Data sections below, when the RV of a patient with TOF dilates, physicians and patients face a choice of PVR or of not performing PVR with the attendant risks and benefits to each. The intervention this study investigates is PVR vs no-PVR in a randomized fashion.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

Not applicable

1.3.2 Clinical Studies

Please see Relevant Literature and Data section

1.4 Selection of Drugs and Dosages

Not applicable

1.5 Relevant Literature and Data

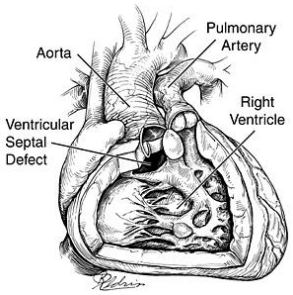


Figure 1: Anatomy of TOF

Tetralogy is the most common cyanotic congenital heart defect and after surgical palliation, often have hemodynamically significant PR. Tetralogy of Fallot (TOF)[1] has an incidence of ~ 6% of all congenital heart defects[2] with ~1660 babies born each year in the US.[3] The main pathologic mechanism is malalignment of the infundibular septum which results in a ventricular septal defect (VSD) and causes pulmonary stenosis. Right ventricular (RV) hypertrophy and an "overriding aorta" are the other 2 components to the "tetralogy" (Figure 1). Repair typically consists of VSD closure and relief of RV outflow tract obstruction typically by placement of a transannular patch, which in most instances, results in severe pulmonary regurgitation (PR) from disruption of pulmonary valve integrity; RV volume overload (RVVO) typically ensues (Figure 2).[4,5] Another commonly used approach is placement of an RV to pulmonary artery conduit instead of a transannular patch which also results in PR and RVVO as most conduits do not have a valve.

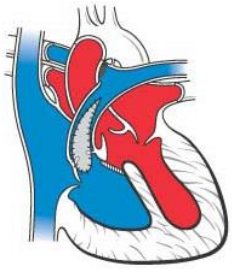


Figure 2: Repair of TOF

Due to PR, TOF survivors have RVVO, reduced RV and left ventricular (LV) performance and are at risk for poor clinical outcomes. Multiple studies that have investigated resting RV and LV function after TOF repair [6,7,8,9,10,11] consistently found diminished RV and LV performance with decreased RV and LV ejection fraction (EF), mostly in patients with PR. There is an increase in indexed RV end-diastolic volume (RVEDVi) which has been the focus of studies with regard to pulmonary valve replacement (PVR). Patients with RVVO are at risk for sudden death, ventricular arrhythmias, increased New York Heart Association (NYHA) class and decreased exercise performance (see below). A recent study suggests that TOF survivors have a higher degree of RV and LV

diffuse fibrosis (DF) compared to normal, raising the possibility of an etiology;[12,13] the degree and time course of this fibrosis has yet to be defined.

Cardiac Magnetic Resonance (CMR) is the gold standard for reliably and accurately measuring ventricular volumes, ventricular performance and PR. Given the above, accurate measurement of ventricular volumes, performance and PR are crucial; toward that end, CMR has been utilized as the non-invasive imaging modality of choice as it can not only visualize 3 dimensional (3D) anatomy but can also determine 3D physiology and function. CMR is tomographic and unencumbered by acoustic windows or overlapping structures; cine CMR measures of ventricular volumes, mass (Figure 3) and cardiac index (CI) are considered the non-invasive "gold standard" for these parameters.[14,15,16] CMR has high reproducibility and decreased variability[17,18] and therefore, less patients are needed to power studies. It has been applied in children for many years by all the imaging laboratories participating in this proposal.[19,20]

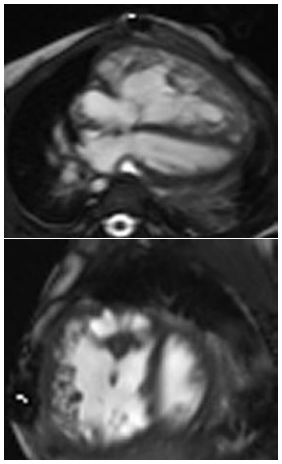


Figure 3: *CMR 4-chamber (top) & short axis views (bottom) of TOF patient with RVVO. Note large RV.*

To determine PR, the CMR technique of phase contrast velocity mapping (PCMR)[21] is employed which has also been applied by our laboratories for many years;[22,23] CI can be directly measured from the cross-sectional area of blood vessels. Internal checks are used (e.g. flow in the main pulmonary artery must equal flow in the branches) making this technique highly accurate in assessing cardiovascular performance.

T1 mapping is a relatively new CMR technique which can determine DF and has been applied in multiple pathologic conditions. In scarred regions, T1 relaxation times (an intrinsic CMR tissue property) is longer without gadolinium and shorter with gadolinium. The LV and RV tissue characteristics in TOF may be different than normals as suggested in recent articles[12,13] and may be a possible reason for decreased biventricular performance in this population. T1 mapping values are have low variability between repeat scans.[24]

Myocardial strain by CMR has been assessed for over 25 years using myocardial tagging,[25] however, the recent development of feature tracking and tissue tracking allows for strain measurements with standard cine.[26] CMR strain has recently demonstrated to be prognostic in adult TOF survivors.[26]

Finally, exercise CMR is also a relatively new technique where individuals undergo lower limb exercise using an MRI compatible ergometer so that ventricular performance and blood flow can be measured under stress conditions.[27] Exercise capacity in TOF patients is impaired and the ability of CMR to determine ventricular function and flows at exercise is an important component to the overall cardiovascular assessment of the TOF survivor.

Exercise capacity is significantly decreased in TOF survivors with PR and RVVO when compared to normal individuals.[28,29,30] This exercise incompetence may result from either primary LV dysfunction or by "ventricular-ventricular" interaction, where the dilated RV impinges on LV geometry causing poor performance. When TOF patients were studied at rest and during exercise testing (EST), the incremental exercise response of LV EF in TOF patients was depressed relative to controls and LV EF during exercise correlated with both RVEDVi and the severity of PR.[30] When comparing exercise performance in TOF patients

and controls, significant differences exist in peak workload, maximal heart rate and systolic blood pressure.[29]

The decreased LV performance at rest and at exercise may also be due to "ventricular-ventricular interaction."[31,32,33,34,35,36,37,38] The LV and RV effect the other's biomechanics by mechanical coupling, mostly through the septum;[35] with RVVO, this interaction may be deleterious and at the root of decreased LV performance and exercise tolerance.[39,40,41,42] For example, correlations of PR and LVEF have been found at rest[39] and at exercise.[30] additionally, significant correlations exist between exercise and the degree of PR.[39,40] A review of 22 exercise studies[43] found that 14 showed a significant relationship between PR with abnormal RV function and decreased exercise capacity. Further implicating RVVO are studies that demonstrate once the RVVO is abolished by PVR, exercise tolerance improved.[41,42]

Diminished ventricular performance in TOF is associated with worse clinical outcomes and is related to important clinical variables. In a study of 100 consecutive TOF survivors,[44] by multivariate analysis, ventricular performance with lower LV EF was one of the strongest predictors of poor clinical outcome (odds ratio [OR]=3.88 for a 10% decrease, P=0.002). Among RV variables, lower RV EF was one of the strongest risk factors (OR= 2.41 for a 10% decrease, P=0.01). A follow-up study performed in 88 of these patients > 4 years later with endpoints of increase NYHA class, sustained ventricular tachycardia and sudden death demonstrated that higher RVEDVi and a lower RV EF correlated with increasing probability of adverse events.[45] Increasing NYHA class has been found to be associated with lower LV EF and RV EF (OR 3.88 and 2.41 for a 10% decrease, $P \leq 0.01$).[46] Decreased biventricular strain by CMR has been demonstrated only recently to be prognostic of adverse outocmes.[26] Numerous studies in the last decade have demonstrated that once the RV becomes too dilated, there is lack of functional recovery - *the threshold of what is "too dilated" remains controversial and varied throughout the studies.*[47,48,49,76]

Health-related quality of life (QOL) in TOF is an important clinical outcome and endpoint for a future clinical trial*:* QOL is defined as the influence of a specific illness or injury, medical therapy, or health services policy on the ability of the patient to both function in and derive personal satisfaction from physical, psychological, and social life contexts.[50] ***It*** has emerged as a high priority not only for patients and their families, but also for the NIH, FDA and insurance providers.[51,52,53]

Given the relative decreasing mortality and prolonged survival in TOF survivors, issues of QOL are increasingly important.[54,55] Morbidity related to underlying physiology and ventricular dysfunction have physical and psychological effects that may have an adverse effect on QOL. Late effects from TOF repair include neurodevelopmental abnormalities,[56,57] diminished physical functioning,[58,59] and psychosocial issues.[60] QOL scores in the pediatric TOF survivor are significantly lower than healthy controls and patients with mild CHD.[61]

Several generic measures of pediatric QOL exist.[62] The *Pediatric Quality of Life Inventory (PedsQL) V. 4.0*[63,64] is a commonly used, self-administered generic pediatric cardiac QOL measure for children and adolescents with CHD or acquired heart disease (8-18 years) which has been validated[65,66] with published norms available.[67] Generic measures, however, may not be responsive to small changes in a child's condition or function and may overlook clinically relevant aspects of a child's life related to a specific disease condition.[68]

Disease-specific measures assess symptoms that are specific to an illness, population, and/or treatment; the main drawback is that it does not allow comparison of QOL among

children and adolescents with different illnesses. Dr. Marino, one of the co-investigators on this proposal, developed and validated the *Pediatric Cardiac Quality of Life Inventory (PCQLI),*[69,70,71,72] which is a self-administered, disease-specific pediatric cardiac QOL measure for children (8-12 years) and adolescents (13-18 years) with CHD or acquired heart disease. Utilizing both instruments allows for a comprehensive QOL assessment.

PVR eliminates PR, decreases RVVO and improves symptoms but the threshold volume above which a PVR should be performed is unknown: The above strongly suggests that PVR may be advantageous to these patients by eliminating PR; RV volumes have been used as the key parameter to determine timing of PVR. Besides decreasing RVEDVi and eliminating PR,[73] PVR generally decreases tricuspid insufficiency, decreases symptoms and increases NYHA class.[74,75] For example, Therrien et al.[76] studied adult TOF patients before and after PVR and found RVEDVi and indexed RV end-systolic volume (RVESVi) decreased 34% and 37% respectively. Importantly, no patient achieved a normal RVEDVi and RVESVi after PVR if their RVEDVi prior to surgery was >170 cc/m^2 and their RVESVi was >85 cc/m^2. In a prospective, non-randomized CMR study[77] in pediatric TOF patients who underwent PVR at an RVEDVi >150 cc/m^2, a significant decrease in RV volumes and mass after PVR (6 months after surgery) was found; no clinical outcomes were reported. Frigiola et al[78] reported an aggressive PVR strategy by operating on patients with an average RVEDVi of 142$\pm$43 cc/m^2, very close to the value of 139 cc/m^2 in the power loss study from our lab on TOF (see preliminary data) and the 135 cc/m^2 our lab found which increased the likelihood of an LVEDP of $\geq$ 12 mm Hg (see preliminary data). They found that early PVR led to RVEDVi normalization, improvement in biventricular function and much improved submaximal exercise capacity. Warner et al found the ability to achieve an increased peak workload after PVR.[79]

Although PVR had clinical benefits in these retrospective studies, the effect on objective exercise performance and arrhythmia is less clear. There are conflicting reports on various exercise stress test parameters with some studies showing improvement[41,47,78] in parameters such as submaximal exercise testing and others not.[80,81] Similarly, some studies have shown a decrease in the amount of ventricular tachycardia and QRS duration increase (e.g. the report by Therrien et al[82]) whereas other reports show no change.[83,84]

The benefit of PVR must be weighed against the interventional risk and the natural history of repaired TOF without PVR. Numerous studies have demonstrated that PVR is very low risk surgically as well as via a transcatheter approach. Available bioprosthetic valves, however, have a limited life span; in one recent study of 227 TOF survivors, freedom from reintervention or structural valve disease after PVR was 94% and 74% at 5 years respectively;[85] younger age increased time to structural valve disease. Undertaking PVR "starts the clock" which will eventually lead to repeat PVR and further interventions. This is balanced by the natural history of TOF survivors without PVR; although mortality rate is only 10% in the first 2 decades of life, it significantly increases afterwards and many patients suffer exercise intolerance, arrhythmia, heart failure, and sudden death. ***A pulmonary valve can be replaced; a failed RV is much more problematic.*** In a study of long term outcomes after TOF repair, the rate of sudden cardiac death was 0.3%/year; sudden cardiac death was the most common cause of late death. A similar study showed that the late mortality risk increased significantly to 0.94%/year.[86,87]

The studies presented above are small, nearly all retrospective and nearly all in adults with little focus on clinical outcome. These limitations are especially true of PVR data; this

has led to varying practices of when and even if PVR is performed between institutions and even within practice groups. *There are strong beliefs on both sides regarding PVR without robust, randomized, prospective data to support either approach. A recent study of 799 over 35 centers found significant between-center heterogeneity in age at PVR.*[88] For example, an asymptomatic TOF patient with an RVEDVi of 161 cc/m^2 may come to clinic on one day and have a cardiologist schedule surgery whereas if the patient serendipitously came on another day to the same clinic but saw a different cardiologist, they would be told adamantly that surgery was not needed. Rationales are based on some data but are mostly anecdotal, experience, or a "gut feeling." Small retrospective studies are variable with regard to what the lower limit should be to undergo PVR to maximize the benefit.

Overall Significance – making a leap forward in TOF survivorship and follow-up care: *The planned large scale trial will be the first prospective, randomized, multicenter trial of PVR in TOF in any age group. The R34 application, which is a clinical trials pilot protocol, is key to obtaining preliminary data to inform that trial. The feasibility protocol which we propose has the potential to not only add to the literature on adolescents with TOF but also holds the potential to begin to definitively answer the question of if and when to perform PVR. This question takes on increasing importance as PVR is increasing across the US*[88] *without robust, randomized, prospective evidence that it ultimately benefits patients.* As an R34, this feasibility protocol will not only be a "proof of concept," it will obtain the necessary information needed to create endpoints for the prospective, randomized, multicenter clinical trial which we envision. It will also obtain much needed data on these children which has not previously been available. *One of the important objectives of this R34 will be to determine the operational feasibility of performing a randomized, controlled, multicenter PVR trial while there is still equipoise on both sides of the randomization scheme*. This application is the first step towards heeding the call for a multicenter dataset which "is clearly needed to assist in management in patients with TOF."[89]

The obvious clinical significance to the proposed trial is that PVR has the potential to change QOL of teenagers and young adults in their daily routine as well as their exercise tolerance, especially in this age group where playing sports, for example, is socially important. The ability to "keep up with their peers," enjoy freedom from arrhythmia, stay in school and out of the hospital on no or minimal medication all play a role in elevating how well a patient after TOF repair feels about himself and appreciates the day. The current proposal, an R34, will yield needed information in the short term but is the first step in a much longer one. As noted above, mortality and other morbidities of TOF repair increase dramatically after the first 2 decades of life. *We hypothesize that intervention as an adolescent may mitigate these complications by decreasing the chronic RVVO, "unloading the RV" at an earlier age and preventing irreversible remodeling and dysfunction.*

There are disadvantages of PVR as mentioned above and risks always need to be weighed against the potential benefit. The patient would need to undergo surgery or transcatheter PVR involving a short hospital stay. Valves can malfunction in the short term and will definitely need to be replaced long term. However, the potential for RV dysfunction and right sided heart failure in the long term looms large; *replacing a pulmonary valve is much easier than replacing or managing a failing or failed RV with its attendant risk of ventricular tachycardia, need for transplantation, poor exercise tolerance and sudden death.*

The proposed trial also has the potential to decrease cost by preventing long-term sequelae. The cost of PVR can be offset by the prevention of heart transplantation, long-

term hospital stays, frequent clinic visits and potentially avoidable pharmacologic therapy. All these may involve the use of expensive tests and diagnostic procedures that may be decreased in frequency by the careful utilization of PVR at the optimal time.

Although this application's primary purpose is to obtain preliminary data for a large scale clinical trial to answer the question of the necessity and optimal timing of PVR, it will also involve a small pilot feasibility protocol which will obtain short term TOF PVR data in a prospective, rigorous fashion. *With PVR becoming more prevalent[88] and easier to perform via catheter, there is a temptation to perform PVR more often; a well-controlled prospective study, supported by this R34 planning proposal, is needed exigently to set boundaries for this temptation.*

Our hypothesis is that PVR benefits outweigh the surgical/transcatheter risks in a select group of TOF survivors and that an optimal timing for this procedure exists. As mentioned above, random events can lead to a patient undergoing PVR or not; instead of serendipity dictating the patient's fate, this proposal will channel these patients into a structured framework to prospectively collect data to determine the benefits of PVR as well as optimal timing. *Importantly, this R34 doesn't pose additional clinical risk; it merely restructures routine clinical practice to obtain badly needed information on PVR to plan for a large multicenter trial.* There is precedence for interventional trials in congenital heart disease (eg Single Ventricle Reconstruction Trial from the Pediatric Heart Network; http://www.pediatricheartnetwork.org/Studies/CompletedStudies/SingleVentricleStudySurgical.aspx).

1.6 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and the HIPAA Privacy Rule and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). Note: Only include the sections of Title 21 if the study is regulated by the FDA. Only include ICH compliance if the study will actually comply with these requirements. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

Specific Aim 1: *To determine the operational feasibility of a randomized, multicenter trial of PVR in adolescent TOF survivors to assess its impact on outcome – a main goal of an R34 planning grant.* Study teams from Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Children's Healthcare of Atlanta, Lurie Children's and Children's

National Medical Center will recruit asymptomatic TOF patients to be randomized to PVR or "no-PVR" groups based on mostly on CMR RV volumes to prove operational feasibility. ***Hypothesis: A randomized, multicenter, clinical trial of PVR in TOF survivors is operationally feasible.***

Specific Aim 2: *To measure clinical parameters needed to design a large scale clinical trial by performing a short term pilot protocol.* At entry, in addition to CMR, all subjects will undergo exercise testing, Holter monitoring and complete QOL questionnaires which will be repeated 12-18 months later. Comparison between PVR and no-PVR groups will be made for clinical parameters including mortality, exercise testing, physical functioning QOL score, prevalence of arrhythmia and medical care utilization. Preliminary data for these parameters would be collected will inform outcome measures in the larger trial. A comparison of biventricular function between groups will also be made. ***Hypothesis: There are clinical metrics that can be utilized to inform the endpoints of a robust longer term, large scale trial of PVR in asymptomatic TOF survivors to discern who would benefit and optimize timing of the procedure.***

Specific Aim 3: *To determine mechanisms of the effects of PVR in the definitive trial by obtaining preliminary data on diffuse fibrosis (DF), performing exercise CMR and measuring biventricular strain.* Subjects will undergo repeat CMR 12-18 months after enrollment including measurement of DF, exercise CMR and strain measures to determine biventricular function and PR at rest and exercise, comparing PVR and no-PVR groups and correlating with short term outcomes. ***Hypothesis: PVR in asymptomatic TOF survivors who fall within specified guidelines results in improved ventricular function at exercise, improved strain and have less DF when compared to no-PVR and correlates with clinical outcomes.***

To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a prospective, multi-center, randomized pilot protocol to assess the operational feasibility and to obtain preliminary data to inform a future large scale randomized, multicenter trial of PVR in adolescent TOF survivors. The general schema breaks down this project into 3 parts as delineate in the Aims:

- Operational feasibility
- Pilot protocol to obtain preliminary data
- Mechanistic effects of the findings

Operational feasibility will involve assessing results of questionnaires, and surveys, ability to recruit the required number of patients in the time given, Protocol logs demonstrating how many patients were screened, eligible and approached, how many dropped out and for what

reason among other metrics. Factors which will affect follow-up in a larger trial are also key such as patients moving out of the area, pregnancy and need for pacemaker will be recorded and will be used as preliminary data for dropout rates and sample size for the larger trial.

The pilot protocol to obtain preliminary data will include exercise parameters on EST such as maximum oxygen consumption and work at ventilatory anaerobic threshold; Quality of life indexes, CMR parameters such as ventricular volumes, ejection fraction and mass; Holter parameters such as the amount of ectopy. Patients will be randomized to PVR via catheter or surgery, whichever is clinically appropriate, or no-PVR.

Mechanistic effects will include measures of diffuse and discrete fibrosis, myocardial strain and performance parameters on exercise CMR.

There will be on-going safety evaluations throughout. Clinical evaluations such as death, transplantation, need for hospitalization and medication, failure of PVR with need to replace or need, in the non-PVR group for PVR, requirement in general for additional interventions will be obtained. IRB review will be obtained every year. A data safety monitoring board will be established through the NIH.

To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring.

3.1.1 Screening Phase

Subjects will be identified from patients who undergo CMR for their TOF and screened to determine if they meet eligibility criteria listed in the *protocol inclusion and exclusion criteria*. If so, they will be approached for informed consent and subject assent. *Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed, including discontinuation of current therapy.*

All cardiologists who treat patients with TOF will be eligible to participate; there is no screening process. They will be approached for informed consent- *this will be obtained prior to any study related procedures being performed – questionnaires.*

3.1.2 Study Treatment Phase (start of the study intervention)

After patients meet eligibility criteria and agree to participate, after informed consent, the patients will be randomized to PVR and no-PVR groups. Both patient groups will undergo research related procedures (eg quality of life questionnaires, review of medical records) at that time. The patients in the PVR group will then undergo PVR. Both patients groups will be followed per standard of care clinical protocols.

Physicians will be given questionnaires to fill out regarding their views of the study.

3.1.3 Phase 2

After 1-1.5 years, both patient groups will undergo research related procedures (eg quality of life questionnaires, review of medical records). This will generally occur when they are seen for their clinical visits per standard of care protocols.

After one year and every year after until study termination, physicians will be given questionnaires to fill out regarding their views of the study and to determine if it has changed at all.

3.1.4 Follow-up Phase

Not applicable

3.2 Allocation to Treatment Groups and Blinding

Patients will be randomized by computer by the statistician and her team at the Data Coordinating Center at Northwestern Univeristy who will maintain the schedule; this will be a 2:1 randomization of PVR to no-PVR. There will be no blinding and the assignment will not be concealed from the investigators. There will be no stratifications within each group.

3.3 Study Duration, Enrollment and Number of Sites

This is a multicenter 3 year project with recruitment to commence when the study team is assembled and the IRB approved. We will enroll 100 patients with TOF (over the 1.5-2 year enrollment period to achieve 1-1.5 year follow-up) from the 5 centers. See statistics section for calculations.

The Study Team and Structure: The study team from The Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital (Cinn), Emory University School of Medicine/Children's Healthcare of Atlanta (Emory), Lurie Childrens (Lurie) and Children's National Medical Center (DC) and Northwestern University will participate in this R34. CHOP, Cinn and Emory have worked successfully together in the past on other projects including a recent RO1 (HL098252-01). CHOP and DC recently began a collaboration using 3D rapid prototyping models, holding their first symposium in February 2014. This group of 5 centers brings together well published experts in CMR (Drs Fogel, Lang, Slesnick, Rigsby and Cross), exercise (Dr. Paridon), QOL (Dr. Marino), catheterization (Dr. Kim) and surgery (Drs Gaynor and Fuller). Experienced "trialists" such as Drs Paridon and Marino will be complemented by the experience of Dr. Fogel in industry where he ran large scale clinical drug trials for 3 years at Wyeth-Ayerst as well as Dr. Scholtens, biostatistics faculty at Northwestern University, who has >10 years of experience in collaborative biostatistics and currently serves as the primary statistician for a large-scale international multicenter epidemiologic study. All are involved in clinical care and have been involved in clinical studies.

Although five participating centers may seem a large number for a feasibility pilot, there are 2 major justifications for its use. First, because this is a 3 year award, there is limited time for follow-up mandating rapid enrollment, which is more feasible from multiple centers. Second, we intend to demonstrate and fine-tune the multicenter aspects of the trial

in preparation for a full study. This includes solidifying functions of a data collection center, imaging core and safety monitoring.

CHOP will be the principle site as well as the CMR Core Laboratory and Northwestern University (NU) will provide the data management and biostatistical support . Dr. Fogel (CHOP) and Dr. Marino (NU) have been the CMR Core Laboratory and data management and biostatistical support respectively for numerous other studies. A strict firewall will be in place at both CHOP and NU to ensure that Drs. Fogel and Marino do not participate in and will be blinded to any site data. Teleconferences monthly will be held between centers to discuss issues and make decisions regarding the conduct of the feasibility protocol. Analysis of CMR data will be performed at each site and in the department of Radiology at CHOP. EST, QOL, echocardiograms and Holter monitoring will be performed at each site. Figures 4A (CMR data) and 4B (data other than CMR) depict the workflow and communications link.

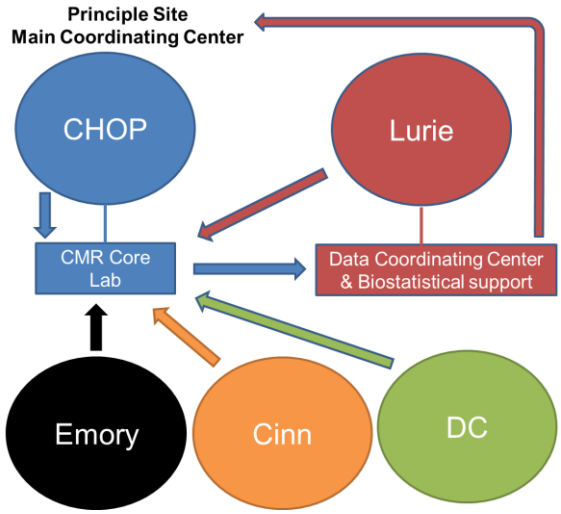


Figure 4A: Work flow for CMR data

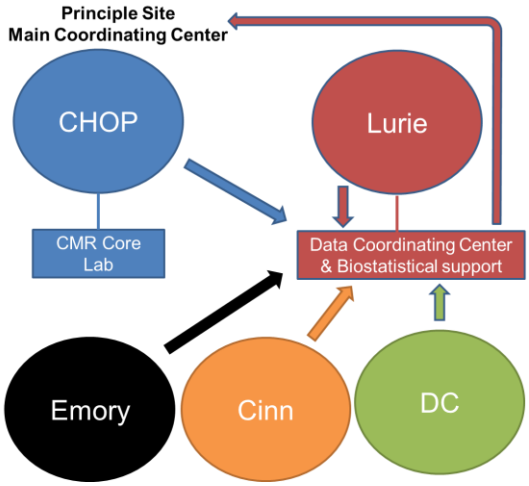


Figure 4B: Work flow for data other than CMR

3.3.1 Duration of Study Participation

- Each subject's participation will last ~ 1-1.5 years from enrollment to follow-up
- Exercise CMR component to the CMR scans will last~ 15 minutes EST will be performed for research purposes if not performed for clinical purposes. Metabolic exercise test (if not clinically indicated and therefore, research related) will last ~ 60 minutes.
- Assessment of QOL will last ~ 20 minutes
- Fill out patient questionnaire about this trial will last ~10-15 minutes
- For physicians answering physician questionnaire, this will last ~20 minutes

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately 5 investigative sites in the United States. The study team from The Children's Hospital of Philadelphia (CHOP), Cincinnati Children's

Hospital (Cinn), Emory University School of Medicine/Children's Healthcare of Atlanta (Emory), Lurie Children's (Lurie) and Children's National Medical Center (DC) will participate in this R34. Recruitment will stop when approximately 100 subjects are enrolled. It is expected that approximately 100 subjects will be enrolled to produce 90 evaluable subjects. See statistical section for addition information. For physicians agreeing to answer questionnaires, we estimate this will be ~200 subjects will be enrolled.

3.4 Study Population

3.4.1 Inclusion Criteria

For patients with TOF

1. Males or females with repaired TOF, currently between 13 and 21 years of age.
2. On clinical CMR: RVEDVi between 140 and 180 cc/m2 inclusive with RVEF > 40% and LVEF > 50%. If data available and adequate RV outflow tract peak velocity < 3 meters/second (if not available this can be skipped); there will be no indexed RVESVi criteria; by defining RVEDVi and RVEF, we will be inherently defining RVESVi, at least 10% pulmonary regurgitation fraction.
3. On clinical echocardiogram: If data available and adequate, RV outflow tract peak velocity < 3 meters/second (if not available this can be skipped), at least mild pulmonary insufficiency and tricuspid regurgitation with an RV pressure estimate < 1/2 systemic pressure.
4. On EST, aerobic capacity $\geq$ 60% of predicted.
5. No QRS duration criteria on ECG.

For physicians: Any cardiologist who practices at any of the 5 participating sites.

3.4.2 Exclusion Criteria

For patients with TOF

1. Any condition judged by the patient's physician that would cause this trial to be detrimental to the patient.
2. Specific forms of TOF excluded are those with endocardial cushion defects, TOF with absent pulmonary valve and TOF with multiple aorto-pulmonary collaterals requiring unifocalization.
3. Unilateral branch pulmonary artery stenosis (one lung receives < 25% of total flow)
4. Contraindication to non-sedated exercise CMR (e.g. pacemaker/implanted cardioverter defibrillator); need for sedation
5. If data available, moderate or greater tricuspid regurgitation on echocardiogram or CMR or Qp/Qs > 1.5 (if not available this can be skipped)
6. Significant strokes/hemiplegia or inability to exercise
7. Genetic syndrome/developmental delay which would make QOL and EST date uninterpretable
8. Pregnancy.
9. Previous pulmonary valve replacement (PVR).

For physicians: none.

4 STUDY PROCEDURES

As a primary purpose of an R34 is to be able to plan for a future study, assessing the operational feasibility of a randomized, multicenter trial of PVR in pediatric TOF to assess its impact on outcome falls under study procedures. The investigators at each center have recruited physicians who are willing to enroll their patients with TOF after repair into this proposal.

Acceptance of a randomized PVR trial, screening and eligibility: Physicians within each institutions, whether they are participating or not in this pilot study, will be asked to complete a brief survey each year to assess satisfaction with the pilot protocol along with physician assessment of patient reaction to the study. This data will be analyzed to determine if and how the approach to recruitment should change. These surveys will include, on a scale of 1-10, questions such as how comfortable both the physician and the patient are to undergoing randomization to PVR, was the need for such a trial adequately explained and free text as to why the patient or physician did or did not want to participate. Pilot protocol logs will demonstrate how many patients were screened, eligible and approached, how many dropped out and for what reason among other metrics; *all this data is critical to designing a future definitive study*.

Any patient approached for the pilot study will be surveyed to determine their reaction to it within the limitations of HIPAA and whether or not they sign an informed consent; there is precedent for this process in other studies.[90] Crucially, patients' rationale for enrolling or not enrolling will be recorded as part of standard practice for study coordinators. This data will be analyzed on an annual basis to determine if and how the approach to recruitment should change. Finally, factors which will affect follow-up in a larger trial such as patients moving out of the area, pregnancy and need for pacemaker will be recorded and will be used as preliminary data for dropout rates and sample size for the larger trial. *Again, all critical information to designing a definitive study.*

Figure 5 depicts the overall schema of study procedures for the pilot protocol. Patients will be screened as they are referred for CMR, EST and Holter monitoring from their cardiologists or other healthcare provider on a clinical basis. If they meet the inclusion criteria and do not meet exclusion criteria, after informed written consent, patients will be randomized to either PVR or no-PVR groups; these patients are ones being followed by physicians who have agreed to the protocol and have equipoise in the PVR vs no-PVR decision. Indeed, multimodality imaging guidelines recently published have recommended yearly CMRs in those patients with moderate RV volume overload.[91] The risks of surgery as well as transcather

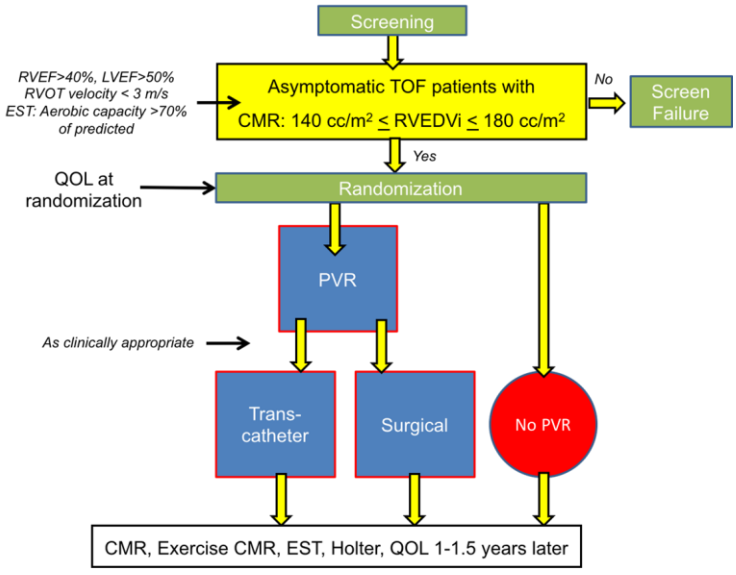


Figure 5: Overall Approach to the pilot protocol.

PVR and the natural history of TOF will be discussed with the patients prior to enrollment. The PVR group will be subdivided into those undergoing transcatheter PVR and those undergoing surgery. If randomized to an intervention, the intervention will occur within 6 months. One to 1.5 years after intervention, clinical history, echocardiogram (if clinically indicated only), CMR, EST and Holter monitor will be repeated as standard of care and QOL questionnaires administered. This data will form the basis for comparison of the effects of PVR clinically and subgroup analysis will be performed between surgical and transcatheter intervention groups to inform the future large scale trial.

To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring are clinical care procedures. Note that the exercise CMR will include CMR sequences that are not FDA approved but have been developed by Siemens Medical Solutions and are "Works In Progress" packages.

4.1 Screening Visit

TOF patients will be recruited from the cohort of patients followed at The Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital (Cinn), Emory University School of Medicine/Children's Healthcare of Atlanta (Emory), Lurie Children's (Lurie) and Children's National Medical Center (DC) Patients will be approached to participate in the study during clinic visits or visits to the hospital for other reasons. In addition, patients may be reached by phone, video (eg Skype) for recruitment. The principal investigator, any of the co-investigators and/or study coordinator will approach the family for consent either by phone, video or in-person. A full understanding of all study related procedures and processes will be explained to the patient, including exercise CMR scans, cardiopulmonary exercise testing (if not performed for clinical reasons) and how the proposed research will help medical practice, although all these tests will be clinically indicated and be performed only on a clinical basis. Child assent will be obtained in the presence of the parents if < 18 years of age. All will be documented by signing the informed consent form which may be done via mail or in-person. The child and his/her parents/guardians will be given a consent form to read and keep, outlining the important details of the study. The consent form will be signed by the parents/guardians (or patient if over 18 years old) prior to enrollment in the study. One of the study physicians will be available to answer all questions concerning the study. The consent process for parents or legal guardians, adult subjects and children who require assent who do not speak English will be facilitated by an interpreter from Language Services at the Children's Hospital of Philadelphia. Each participating site is responsible for adhering to their local governing regulatory bodies, i.e. IRB with regard to administering consent to non-English speaking families.

Please note that CMR parameters are utilized in the inclusion criteria. If the patient meets these criteria, they will then be approached to participate and enrolled and hence, the review

of the medical records associated with those clinically indicated tests will be considered part of the Screening Visit.

Also note that the screening activities themselves are limited to review of medical/investigator records and do not include soliciting information directly from potential subjects; only when subjects meet inclusion criteria and do not meet exclusion criteria will the patient be approached.

4.2 Study Treatment Phase

4.2.1 Visit 1

Patients will be randomized to PVR or no-PVR; PVR group will undergo valve replacement by catheter or surgery, whichever is clinically indicated.

To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring are clinical care procedures.

Extraction of the following parameters. This data includes:

Name

MR number

Date of Birth

<u>Demographics/Medical History:</u>

Age at MRI

Height

Weight

Gender

Ethnicity, birth order, social class, etc

Body surface area

Type of tetralogy (tetralogy, tetralogy with pulmonary atresia, tetralogy with absent pulmonary valve leaflets, tetralogy with conoseptal hypoplasia), coronary anomaly

Type of repair (transannular patch, no transannular patch, conduit)

Number of other cardiovascular or cardiovascular related surgeries, date, type

Pulmonary artery angioplasty (yes, no, and if yes – which PA) (stent: PA/conduit, RPA, LPA)

Residual VSD (yes,no) (small vs mod/large)

Residual pulmonary stenosis (yes, no)

Date and age of definitive repair

Cardiopulmonary bypass time, circulatory arrest time, cross clamp times

Complications, hospital length of stay, hospitalizations with causes and results,

Date of MRI(s)

Years between repair and MRI

Years between MRI and followup (outcomes)

Years between MRIs

Other medical diagnoses (eg 22Q11 deletion status)

Physical exam and Vital Signs

Any abnormal physical exam finding other than routine findings for a patient with TOF

Temperature

Blood pressure

Heart rate

Respiratory Rate

Oxygen saturation

CMRs:

BOTH right ventricle and left ventricle from cine imaging:

End diastolic volume (indexed)

End systolic volume (indexed)

Stroke volume (indexed)

Ejection fraction

Cardiac index

RV/LV ratio of End diastolic volume and end systolic volume

RV mass/volume ratio

LV mass/volume ratio

Velocity maps:

Cardiac index (aortic)

Aortic regurgitation fraction

Pulmonary regurgitation fraction

Pulmonary regurgitant volume (indexed)

Net flow to right pulmonary artery

Net flow to left pulmonary artery

LPA/RPA ratio (% flow to each PA)

Regurgitant fraction of RPA

Regurgitant fraction of LPA

LPA/RPA ratio regurgitant fraction

Right pulmonary artery stenosis if moderate or severe (yes, no)

Left pulmonary artery stenosis if moderate or severe (yes, no)

T1 Mapping: Native T1, post-gadolinium T1, the partition coefficient and, if a hematocrit is available, the extracellular volume (ECV) will be calculated.

Exercise performance qualitative (intolerance, poor or good?)

Exercise performance data

aVO2 (indexed (ml/kg/min), unindexed (ml/min), and percent predicted at peak exercise and AT

Oxygen pulse

VE/VCO2 slope

Pulmonary function parameters: forced expiratory volume in 1 second (FEV1), Functional vital capacity (FVC)

Peak physical work capacity

Hospitalizations

Diagnostic/interventional caths

Other procedures

Medication (yes, no and if so, free text what meds)

Arrhythmia on holter monitoring (yes, no and if so, what)

Echocardiographic data

Diagnoses

Amount and degree of tricuspid insufficiency

RV pressure estimate

Pulmonary stenosis and/or regurgitation estimate

Biventricular function parameters (eg left ventricular shortening fraction, qualitative estimate of RV shortening, myocardial velocities)

Catheterization data

Diagnoses and interventions (if any)

Amount and degree of tricuspid insufficiency

Saturations in various chambers and vessels (eg RV, LV, right atrium)

Pressures in various chambers and vessels (eg RV, LV, right atrium)

Flow measurements (eg cardiac index, Qp/Qs)

Research CMR evaluations

Exercise CMR Protocol: Supine exercise using an MRI compatible ergometer (Figure 6) will occur for 3-5 minutes immediately outside the bore to achieve 80% of the maximum heart rate on metabolic EST; CMR imaging will then take place within 10 seconds. The patient will do this multiple times for a total time in the scanner of approximately 15 minutes to obtain: a) "Real-time" ECG gated cine SSFP across the short axis of the both ventricles from atrioventricular valve to apex to obtain ventricular volumes and cardiac index and b) "real time" and segmented PCMR in the MPA and branch pulmonary arteries and aorta.

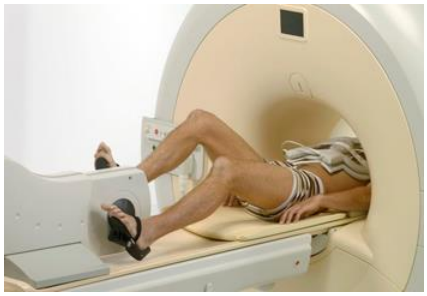


Figure 6: MRI compatible ergometer. Patient exercises outside the bore and then moved into scanner for measurements in < 10 seconds.

Biventricular strain: Cine short axis and 4-chamber images, which were obtained clinically, will undergo tissue tracking (post-processing on computer, after the study) to analyze biventricular circumferential, radial (cine short axis) and longitudinal strain (4-chamber view). The global and regional strain (16 segment model) will be calculated and analyzed (figure 7).

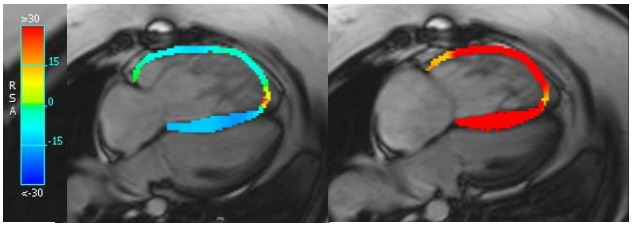


Figure 7: Longitudinal feature tracking strain of the RV at end-diastole (left heart) and end-systole (right heart). Color code for strain map is on the left.

Cardiopulmonary EST Protocol (if not clinically indicated and therefore, research related)

Cardiopulmonary EST Protocol: This will be performed using a standard ramp cycle ergometry protocol with collection of expired gases. Subjects will pedal in an unloaded state for 3 minutes and workload will then be increased continuously with a slope chosen to achieve each subject's predicted maximal work rate in watts after 10 to 12 minutes of cycling. Expired gases will be measured by a mass spectrometer which is FDA approved for clinical use for 3 minutes of quiet rest before unloaded pedaling and throughout the exercise protocol. VO2, carbon dioxide production (VCO2), and minute ventilation (VE) will be measured on a breath-by-breath basis. Maximal VO2 will be defined as the highest VO2 achieved by the subject during the EST. VAT will be measured by V-slope method and confirmed by the dual criteria measurements of the ventilatory equivalents of CO2 and O2

(VE/ VCO2 and VE/ VO2). Values for VO2 will be indexed to body weight and expressed as percentage of predicted values for healthy age- and gender-matched subjects as reported by Cooper and Weiler-Ravell using a similar protocol. The ventilatory equivalents of carbon dioxide (VE/VCO2) will be measured at VAT. The respiratory exchange ratio RER (VCO2/VO2) will be measured continuously. Achievement of a maximal aerobic capacity will be defined as a peak RER of ≥ 1.10.

Please note that the device used to measure expired gas is approved for use at CHOP. This is the same device that is utilized for a standard of care exercise test. The device that is used is a metabolic cart which is a clinically validated and FDA approved piece of equipment that is used in clinical care every day.

Patient/Family Questionnaires: These will be administered to all patients and families who agree to answer questions about this investigation (whether they are participating in randomization or not) at the beginning of their participation and if they decide to participate in trial and be randomized, at the end of their participation. It will take ~ 20 minutes. The questionnaires may be mailed to patients or completed in person at a study visit.

Physician Questionnaires: These will be administered to all physicians who agree to answer questions about this investigation (whether they are participating in allowing their patients to undergo randomization or not) once per year. It will take < 20 minutes. This will be the initial questionnaire.

Assessment of QOL: Utilization of the PCQLI will allow for patient and parent-proxy assessment of QOL using a disease specific tool, allowing for better discrimination between subgroups. The PedsQL Core 4.0 will allow for comparison with healthy and other chronic disease populations. The QOL questionnaires will take ~ 20 minutes for patients to finish. The questionnaires may be mailed to patients or completed in person at a study visit. Patients and parents will be instructed to ensure the inventories are completed independently to minimize contamination resulting from patient-parent discussion. Patients and guardians will be recruited consecutively.

Randomization: See Statistics Section below.

Interventions (Surgical and Transcatheter PVR): Both surgical and transcatheter PVR will be performed per each institutions *clinical* protocol as standard of care. Both surgeon and interventional cardiologist will use their best *clinical* judgment to optimize patient outcome; this approach will make the findings of this proposal widely applicable. PVR, whether surgery or catheter based, requires general anesthesia, insertion of catheters and insertion of a valve in the pulmonary position. Surgery requires a median sternotomy and sealing up the wound with sternal wires and stitches along with cardiopulmonary bypass and circulatory arrest. Catheter based intervention includes inserting a catheter in the groin region generally and then direct pressure on the insertion site after the procedure is completed. Please see Risks section below.

4.3 Phase 2 of the Study – Followup – Visit 2

Between 1 – 1.5 years after enrollment, a follow-up visit will occur with the exact same study procedures as in Study visit above in 4.2.1; this will occur around the time of their clinical visit for their followup CMR and exercise testing. Additional data to be abstracted include:

For all groups:

Death

Transplant

Pacemaker (unlikely)

NY heart association class (if available)

Additional procedures

Additional diagnosis

Need for medication

Hospitalizations with cause and followup

Any additional complications to being in the individual group such as, in the no-PVR group, need for pulmonary valve replacement (surgery vs catheter) or in the PVR group, need for replacement or malfunctioning of the inserted pulmonary valve.

Physician Questionnaires: These will be administered to all physicians who agree to answer questions about this investigation (whether they are participating in allowing their patients to undergo randomization or not) once per year. It will take < 20 minutes. This will be the 2nd questionnaire to be filled out.

4.4 Visit 3 (only applicable to Physician component of this study)

Physician Questionnaires: These will be administered to all physicians who agree to answer questions about this investigation (whether they are participating in allowing their patients to undergo randomization or not) once per year. It will take < 20 minutes. This will be the 3rd questionnaire to be filled out.

4.5 Follow-up Phase

Not applicable

4.6 Unscheduled Visits

All unscheduled visits will be handled as per clinical standard of care as each group is clinically indicated, given the equipoise in the decision.

4.7 Concomitant Medication

All prior and concomitant medications used within 60 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.8 Rescue Medication Administration

Not applicable

4.9 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, or AEs. The Investigator or the Sponsor may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.9.1 Early Termination Study Visit

SUBJECTS WHO WITHDRAW FROM THE STUDY WILL HAVE MEDICAL RECORD REVIEW AS A PROCEDURE AS THE EARLY TERMINATION VISIT.

STUDY EVALUATIONS AND MEASUREMENTS

Randomization to PVR and no-PVR groups will be performed as a research procedure.

4.10 Screening and Monitoring Evaluations and Measurements

4.10.1 Medical Record Review

See 4.2.1 as well. We will extract the following for review:

Demographics/Medical History:

Age at MRI

Height

Weight

Gender

Ethnicity, birth order, social class, etc

Body surface area

Type of tetralogy (tetralogy, tetralogy with pulmonary atresia, tetralogy with absent pulmonary valve leaflets, tetralogy with conoseptal hypoplasia), coronary anomaly

Type of repair (transannular patch, no transannular patch, conduit)

Number of other cardiovascular or cardiovascular related surgeries, date, type

Pulmonary artery angioplasty (yes, no, and if yes – which PA) (stent: PA/conduit, RPA, LPA)

Residual VSD (yes,no) (small vs mod/large)

Residual pulmonary stenosis (yes, no)

Date and age of definitive repair

Cardiopulmonary bypass time, circulatory arrest time, cross clamp times

Complications, hospital length of stay, hospitalizations with causes and results,

Date of MRI(s)

Years between repair and MRI

Years between MRI and followup (outcomes)

Years between MRIs

Other medical diagnoses (eg 22Q11 deletion status)

Physical exam and Vital Signs

Any abnormal physical exam finding other than routine findings for a patient with TOF

Temperature

Blood pressure

Heart rate

Respiratory Rate

Oxygen saturation

CMRs:

BOTH right ventricle and left ventricle from cine imaging:

End diastolic volume (indexed)

End systolic volume (indexed)

Stroke volume (indexed)

Ejection fraction

Cardiac index

RV/LV ratio of End diastolic volume and end systolic volume

RV mass/volume ratio

LV mass/volume ratio

Velocity maps:

Cardiac index (aortic)

Aortic regurgitation fraction

Pulmonary regurgitation fraction

Pulmonary regurgitant volume (indexed)

Net flow to right pulmonary artery

Net flow to left pulmonary artery

LPA/RPA ratio (% flow to each PA)

Regurgitant fraction of RPA

Regurgitant fraction of LPA

LPA/RPA ratio regurgitant fraction

Right pulmonary artery stenosis if moderate or severe (yes, no)

Left pulmonary artery stenosis if moderate or severe (yes, no)

T1 Mapping: Native T1, post-gadolinium T1, the partition coefficient and, if a hematocrit is available, the extracellular volume (ECV) will be calculated.

Exercise performance qualitative (intolerance, poor or good?)

Exercise performance data

aVO2 (indexed (ml/kg/min), unindexed (ml/min), and percent predicted at peak exercise and AT

Oxygen pulse

VE/VCO2 slope

Pulmonary function parameters: forced expiratory volume in 1 second (FEV1), Functional vital capacity (FVC)

Peak physical work capacity

Hospitalizations

Diagnostic/interventional caths

Other procedures

Medication (yes, no and if so, free text what meds)

Arrhythmia on holter monitoring (yes, no and if so, what)

Echocardiographic data

Diagnoses

Amount and degree of tricuspid insufficiency

RV pressure estimate

Pulmonary stenosis and/or regurgitation estimate

Biventricular function parameters (eg left ventricular shortening fraction, qualitative estimate of RV shortening, myocardial velocities)

Catheterization data

Diagnoses and interventions (if any)

Amount and degree of tricuspid insufficiency

Saturations in various chambers and vessels (eg RV, LV, right atrium)

Pressures in various chambers and vessels (eg RV, LV, right atrium)

- Flow measurements (eg cardiac index, Qp/Qs)
-

For all groups in Followup:

Death

Transplant

Pacemaker (unlikely)

NY heart association class (if available)

Additional procedures

Additional diagnosis

Need for medication

Hospitalizations with cause and followup

Any additional complications to being in the individual group such as, in the no-PVR group, need for pulmonary valve replacement (surgery vs catheter) or in the PVR group, need for replacement or malfunctioning of the inserted pulmonary valve.

4.10.2 Physical Examination

Physical examination records associated with visit related to the CMR will be utilized in the review of medical records. See above

4.10.3 Vital Signs

Vital sign records associated with visit related to the CMR will be utilized in the review of medical records. Heart rate would have been captured by either automated device, by pulse or by stethoscope. Respiratory rate would have been measured by stethoscope or visual inspection. Temperature would have been measured by thermometer. Blood pressure would have been measured with an automated device or with an aneroid sphygmoma. See above

4.10.4 Exercise CMR (figure 6)

Data abstracted include: “Real-time” ECG gated cine SSFP across the short axis of the both ventricles from atrioventricular valve to apex to obtain ventricular volumes and cardiac index and b) “real time” and segmented PCMR in the MPA and branch pulmonary arteries and aorta.

4.10.5 Biventricular strain (figure 7):

Data abstracted include: biventricular circumferential, radial (cine short axis) and longitudinal strain (4-chamber view). Time to peak strain will also be included. The global and regional strain (16 segment model) will be calculated and analyzed (figure 7).

4.10.6 Metabolic Exercise Testing (if not clinically indicated and therefore, research related):

Exercise performance qualitative (intolerance, poor or good?)

Exercise performance data

aVO2 (indexed (ml/kg/min), unindexed (ml/min), and percent predicted at peak exercise and AT

Oxygen pulse

VE/VCO2 slope

Pulmonary function parameters: forced expiratory volume in 1 second (FEV1), Functional vital capacity (FVC)

Peak physical work capacity

4.10.7 Assessment of QOL

Assessment of QOL: Utilization of the PCQLI will allow for patient and parent-proxy assessment of QOL using a disease specific tool, allowing for better discrimination between subgroups. The PedsQL Core 4.0 will allow for comparison with healthy and other chronic disease populations. The QOL questionnaires will take ~20 minutes for patients to finish. The questionnaires may be mailed to patients or completed in person at a study visit. Patients and parents will be instructed to ensure the inventories are completed independently to minimize contamination resulting from patient-parent discussion. Patients and guardians will be recruited consecutively.

4.10.8 Patient Questionnaries:

Answers to questions in free text:

How old are you (your child)?

Did you (your child) have: no PVR? Surgery for PVR? Catheterization for PVR?

Why did you (your child) decide to participate in this trial?

Before participating in this trial, what had your physician told you or what have you read about PVR in TOF?

What one aspect convinced you to participate in this trial?

What are the positive aspects of this trial from your standpoint?

What are the negative aspects of this trial from your standpoint?

What would you change about this trial and how to improve it for a future trial?

Is there anything else you'd like to tell us about this trial?

4.10.9 Physician Questionnaires:

Answers to questions as free text:

A. For those not participating in the trial

How many TOF patients do you see on a monthly basis?

Approximately what are their age ranged? 0-13 years old 13-21 >22

Do you think TOF patients at some point should undergo PVR and if so, what criteria do you use, if any, for PVR?

If you do feel PVR is indicated, does age play a factor and if so, please elaborate on your criteria

With the advent of transcather PVR, how much more likely are you to have your patients undergo PVR?

Why did you decide not to participate and have your patients not participate in this trial? Is there anything that would change your mind to participate in trial such as this?

B. For those participating in the trial:

How many TOF patients do you see on a monthly basis?

Approximately what are their age ranged? 0-13 years old 13-21 >22

Why did you decide to participate in this trial?

Before participating in this trial, what criteria do you use for PVR?

While participating in this trial, has your criteria changed and if so, how?

Does age play a factor in PVR and if so, please elaborate on your criteria?

With the advent of transcather PVR, how much more likely are you to have your patients undergo PVR?

What are the positive aspects of this trial from your standpoint?

What are the negative aspects of this trial from your standpoint?

What would you change about this trial and how to improve it for a future trial?

What was the reaction of your patients when you first brought up this trial of PVR in TOF?

Can you please list some of the positive things the patients said regarding this trial

Can you please list some of the negative things the patients said regarding this trial?

What did the patients say, if anything, they would change about this trial and improve it for a future trial?

Is there anything else you'd like to tell us about this trial?

To be delineate clearly, research procedures are limited to randomization to undergo or not undergo PVR, exercise stress testing if this procedure is not completed clinically, exercise CMR, post-processing of biventricular strain, administration of questionnaires, medical history interviews, and review of medical records; clinical care procedures are (non-exercise) CMR, echocardiograms, physical exams, pregnancy tests, and Holter monitoring are clinical care procedures.

4.10.10Interventions (Surgical and Transcatheter PVR)

Both surgical and transcatheter PVR will be performed per each institutions clinical protocol as standard of care. Both surgeon and interventional cardiologist will use their best clinical judgment to optimize patient outcome; this approach will make the findings of this proposal widely applicable. PVR, whether surgery or catheter based, requires general anesthesia, insertion of catheters and insertion of a valve in the pulmonary position. Surgery requires a median sternotomy and sealing up the wound with sternal wires and stitches along with cardiopulmonary bypass and circulatory arrest. Catheter based intervention includes inserting a catheter in the groin region generally and then direct pressure on the insertion site after the procedure is completed. Please see Risks section below.

4.11 Efficacy Evaluations

Please see Statistics section for analysis

Aim 1: Results of questionnaires, and surveys, ability to recruit the required number of patients in the time given, Protocol logs demonstrating how many patients were screened, eligible and approached, how many dropped out and for what reason among other metrics. Factors which will affect follow-up in a larger trial are also key such as patients moving out of the area, pregnancy and need for pacemaker will be recorded and will be used as preliminary data for dropout rates and sample size for the larger trial.

Aim 2: ***Principle parameters to be tested for the intended primary endpoints:*** *The difference between values at enrollment and 1-1.5 years after randomization between those TOF patients with and without PVR for* ***a)*** *Exercise performance parameters such as oxygen consumption (VO_2) at ventilatory anaerobic threshold (VAT)[41] normalized for age, weight, and sex as well as VAT, peak workload and % predicted peak workload[47] as well an New York Heart Association Class and* ***b)*** *Disease Specific QOL - Pediatric Cardiac Quality of Life Inventory (PCQLI) Patient and Parent Scores.* Although some retrospective studies in symptomatic adults have failed to demonstrate improvement and PVR in VO_2, Eysken et al. found improvement in VO_2 and VAT in children 8-18 years of age;[41] Warner et al. found an increase in peak workload and % predicted peak workload.[47] Length of follow-up for patients is limited by the duration and funding of this award but *will provide critical information as pilot data for a future trial.*

Other parameters to be tested for the intended primary or secondary endpoints: The difference between PVR and non-PVR patients at enrollment and 12-18 months later with: ***a)*** Other measures of EST performance such as forced vital capacity, forced expiratory volume at 1 second (FEV_1), maximum voluntary ventilation, maximal work rate, maximal respiratory exchange ratio, breathing reserve, and maximum heart rate, ***b)*** *Disease Specific PCQLI:* Disease Impact and Psychosocial Impact subscale scores as well as *Generic QOL Measure - Pediatric Quality of Life Inventory (PedsQL) Version 4.0 Generic Core* (total and both Physical and Psychosocial Health Summary scores) and ***c)*** change in QRS duration or arrhythmia on Holter monitor (eg ectopy burden).

Other key parameters to be taken under consideration will be the difference between those with and without PVR for: ***a)*** Death, hospitalization, need for medication, ***b)*** additional surgical or catheter based procedures, ***c)*** in the PVR group, failure of the valve and need for re-intervention and ***d)*** in those patients without PVR, need for valve placement or other interventions. In addition, the difference between those patients with surgical and transcatheter PVR for the intended endpoints mentioned will be analyzed.

Other metrics to be obtained will include biventricular performance parameters (eg ventricular volumes and mass, ejection fraction) and hemodynamics such as pulmonary regurgitant fraction and cardiac index.

Aim 3: Primary parameters to be tested for the definitive clinical trial: The difference between PVR and no-PVR for a) ***exercise*** RVEDVi, RVESVi, RV EF and RV output, b) measures of global DF and c) measures of myocardial strain.

Other parameters to be tested for the definitive clinical trial include the difference between those with and without PVR for: a) Global measures of LV performance such as CI, LV EF, indexed LV EDV and LV ESV ***at exercise***, b) Measures of pulmonary blood flow (eg PR fraction and antegrade diastolic flow) ***at exercise***, c) Regional DF using the 16 segment AHA model and d) longitudinal and regional LV and RV strain. In addition, correlation of exercise ventricular function, strain, physiologic parameters and DF with clinical outcomes (Aim 2) will take place.

4.12 Pharmacokinetic Evaluation

Not applicable

4.13 Safety Evaluation

All study procedures will be monitored for safety. The principle investigator or his designee, study coordinators and other health care professionals will record any issues, problems or concerns along with adverse events that may be associated with this project. Subject safety will be monitored by adverse events, vital signs, physical examinations, and discussions with the patient during surveys and at clinical visits.

Adverse events will be recorded and appropriately assigned to either the PVR or no-PVR group. Record of death, hospitalization, requirement for medication or increase in medication, need for additional interventions, patients in the no-PVR group requiring PVR, patients in the PVR group requiring revision or replacement of the valve will be noted and evaluated statistically.

This project will undergo review by an NIH mandated data safety monitoring board who will oversee the project. All data will follow HIPAA mandated policies and procedures to minimize and eliminate any breach of confidentiality.

5 STATISTICAL CONSIDERATIONS

5.1 Primary Endpoint

Aim 1: a) The ability to recruit the required number of patients in the time given (recruiting the full complement of 90 patients over 18 months across 5 centers (ie 1 patient per month per center) to achieve 500 patients across 8 centers over the course of 2-3 years in the larger definitive trial) **b)** Results of questionnaires and surveys to determine whether a large full scale trial is operationally feasibly

Aim 2: Principle parameters to be tested for the intended primary endpoints of the full scale trial: The difference between values at enrollment and 1-1.5 years after randomization between those TOF patients with and without PVR for **a)** Exercise performance parameters such as oxygen consumption (VO_2) at ventilatory anaerobic threshold (VAT)[41] normalized for age, weight, and sex as well as VAT, peak workload and % predicted peak workload[47] as well an New York Heart Association Class and **b)** Disease Specific QOL - Pediatric Cardiac Quality of Life Inventory (PCQLI) Patient and Parent Scores. Although some retrospective studies in symptomatic adults have failed to demonstrate improvement and PVR in VO_2, Eysken et al. found improvement in VO_2 and VAT in children 8-18 years of age;[41] Warner et al. found an increase in peak workload and % predicted peak workload.[47] Length of follow-up for patients is limited by the duration and funding of this award but will provide critical information as pilot data for a future trial.

Aim 3: Primary parameters to be tested for the definitive clinical trial: The difference between PVR and no-PVR for a) ***exercise*** RVEDVi, RVESVi, RV EF and RV output, b) measures of global DF and c) measures of myocardial strain.

5.2 Secondary Endpoints

Aim 1: Protocol logs demonstrating how many patients were screened, eligible and approached, how many dropped out and for what reason among other metrics. Factors which will affect follow-up in a larger trial are also key such as patients moving out of the area, pregnancy and need for pacemaker will be recorded and will be used as preliminary data for dropout rates and sample size for the larger trial.

Aim 2: Other parameters to be tested for the intended primary or secondary endpoints for the full scale trial: The difference between PVR and non-PVR patients at enrollment and 12-18 months later with: **a)** Other measures of EST performance such as forced vital capacity, forced expiratory volume at 1 second (FEV_1), maximum voluntary ventilation, maximal work rate, maximal respiratory exchange ratio, breathing reserve, and maximum heart rate, **b)** Disease Specific PCQLI: Disease Impact and Psychosocial Impact subscale scores as well as Generic QOL Measure - Pediatric Quality of Life Inventory (PedsQL) Version 4.0 Generic Core (total and both Physical and Psychosocial Health Summary scores) and **c)** change in QRS duration or arrhythmia on Holter monitor (e.g. ectopy burden).

Other key parameters to be taken under consideration will be the difference between those with and without PVR for: **a)** Death, hospitalization, need for medication, **b)** additional surgical or catheter based procedures, **c)** in the PVR group, failure of the valve and need for

re-intervention and **d)** in those patients without PVR, need for valve placement or other interventions. In addition, the difference between those patients with surgical and transcatheter PVR for the intended endpoints mentioned will be analyzed.

Other metrics to be obtained will include biventricular performance parameters (eg ventricular volumes and mass, ejection fraction) and hemodynamics such as pulmonary regurgitant fraction and cardiac index.

Aim 3: Other parameters to be tested for the definitive clinical trial include the difference between those with and without PVR for: a) Global measures of LV performance such as CI, LV EF, indexed LV EDV and LV ESV at exercise, b) Measures of pulmonary blood flow (eg PR fraction and antegrade diastolic flow) at exercise, c) Regional DF using the 16 segment AHA model and d) longitudinal and regional LV and RV strain. In addition, correlation of exercise ventricular function, strain, physiologic parameters and DF with clinical outcomes (Aim 2) will take place.

5.3 Statistical Methods

5.3.1 Baseline Data and Efficacy Analysis

Aim 1: This aim is intended to determine feasibility of a multicenter randomized prospective trial. Descriptive statistics appropriate for measures of feasibility and performance will be calculated, for example, overall percent and monthly pace of patient recruitment at each site, means and standard deviations of patient/physician survey answers, percent of teleconference representation from each center, mean data turn-around times for CMR core lab and frequency and mean time-to-resolution of data queries initiated by the data management and biostatistical support. These data summaries will be used to determine whether a large-scale clinical trial is feasible; specific criteria for proceeding with a larger trial are outlined at the end of this proposal.

Aims 2 and 3: Prior to formal statistical analyses, descriptive statistics for all variables will be computed, including parametric and non-parametric measures of central tendency and variability. Continuous outcome variables for Aims 2 and 3 will be checked for normality using histograms and qplots, both for baseline and follow-up measures at 1-1.5 years after randomization, and for the difference between these two observations. If normality is suspect, we will explore transformations to improve normality or apply non-parametric counterparts for the analyses described in what follows. Data will be analyzed using SAS.

The change from enrollment to 1-1.5 years after randomization in each candidate parameter for the intended primary endpoint in the definitive trial will be treated as outcomes which will be summarized for the PVR and no-PVR groups using means and standard deviations; they will be formally compared between groups using linear regression models with a dummy variable for treatment assignment (PVR vs. no-PVR) as the primary variable of interest with adjustment for study site and possibly other covariates that were not balanced across treatment group and might be associated with the outcomes. Treatment differences with $p<0.05$ in regression models will be considered statistically significant. Intent-to-treat analyses will be conducted such that treatment assignment will be assigned as randomized regardless of adherence. Complete data analyses will be conducted initially, but the frequency of missing data within each treatment group will be calculated. Since baseline

data determines study eligibility, most missing data will occur at the anticipated follow-up time. We will compare demographic and clinical characteristics of patients with complete data to those without using t- and chi-square tests as appropriate to determine whether "missingness" may be informative. Depending on what we observe, we will perform sensitivity analyses using multiple imputation approaches and compare results to complete data analyses. Importantly, describing "missingness" frequency and potential bias in its occurrence will assist in planning a larger trial by emphasizing areas crucial for follow-up. It will help plan for imputation strategies that may be necessary in the larger trial and could suggest additional variables for in the larger trial to strengthen imputation models in the larger setting if required.

Several of the other candidate parameters which will be tested for the definitive trial for both Aims 2 and 3 are continuous variables measured at 2 time points; differences will be analyzed using the approach described for the primary endpoints. Comparison of frequency of additional discrete secondary outcome variables for Aim 2 (e.g. death, hospitalization) will utilize chi-square tests given the sample size followed by logistic regression controlling for site and any other relevant variables. Cox modeling of time-to-event data will be considered if frequencies are higher and event times more varied than expected although this is unlikely given the number of events anticipated. Within the PVR group, we will tabulate frequency of valve failure and re-intervention and in the no PVR group, we will tabulate the frequency of need for PVR or other interventions. These are not comparative analyses but will inform event rates for future trial design. Analyses for comparing the surgical and transcather PVR groups for all candidate parameters for the definitive trial will be adjusted for time since repair will be conducted by performing all analyses as just described. While patients will not be randomized to mode of PVR and this may introduce some bias, we will control for confounding to the extent possible and incorporate the similarities and differences of surgical or transcather PVR group in planning of the larger trial. Pairwise Spearman's correlation coefficients including 95% confidence intervals will be calculated for the variables listed in Aim 3 and the clinical outcomes in Aim 2. All statistical tests will be conducted at nominal 2-sided, 5% significance level. While we recognize the multiplicity of variables and statistical tests, the purpose of this pilot trial is not to provide conclusive evidence of clinical effect, but rather to indicate possible effect size and use it to plan for a larger trial if the preliminary effect size is clinically relevant. Because of the preliminary nature of this pilot study, no correction for multiple comparisons will be made.

5.3.2 Pharmacokinetic Analysis

Not applicable

5.3.3 Safety Analysis

All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study intervention will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

5.4 Sample Size and Power

The sample size is powered on the the EST parameter in Eysken et al[41] and QOL parameters from our preliminary data between PVR and no-PVR groups (table 1). For the EST values, we utilized for VAT (% predicted for age and gender) 86±11% before and 107±14% after PVR (estimated change of 21±21%). For the QOL measurements, we utilized the standard deviation of the patient and parent PCQLI scores of 14.5 and 16.2 respectively. Sample size for Aim 3 based on Oosterhof et al[73] are also included. Enrolling 100 patients with a dropout rate of 10% leaves 90 evaluable patients (60 PVR, 30 no-PVR based on 2:1 randomization). Analysis is on an intent-to-treat basis. We will use 2-sided α=0.05 and 80% power. Table 2 provides the minimal detectable difference with 80% power using the assumed standard deviation and sample size. The width of the 2-sided 95% confidence interval for the difference between the 2 groups is provided, indicating the estimation of accuracy for the group differences.

Endpoint (change from enrollment)	Assumed standard deviation	Minimal Detectable Difference	Width of 95% confidence interval
VAT	21	13.3	± 9.4
PCQLI Total Score (Patient)	14.5	9.2	± 6.5
PCQLI Total Score (Parent)	16.2	10.3	± 7.3
RVEDVi (mL/m²)	37	23.5	± 16.6
RVESVi (mL/m²)	28	17.8	± 12.5
RV EF (%)	8.7	5.5	± 3.9

Table 1: Sample Size Statistics

5.4.1 Endpoints and Statistics in Context

This is an R34 proposal which is intended to obtain pilot and preliminary data to inform a large scale clinical trial. As such, all design components of this protocol are intended to support this overarching goal including the Endpoints and the Statistics. In the end, this project is necessary and needs to be sufficient to support a decision to proceed with a clinical trial of PVR in TOF and to have the necessary preliminary data to design and support the endpoints.

5.4.1.1 Minimum Criteria need to proceed to a large scale trial

The following are minimum criteria needed to move forward with the definitive clinical trial: a) recruiting the full complement of 90 patients over 18 months across 5 centers (ie 1 patient per month per center) to achieve 500 patients across 8 centers over the course of 2-3 years in the larger definitive trial, b) an increase in VAT (or any exercise parameter) of > 15% or QOL measures of > 10% consistent with lower 95% confidence interval bounds of detectable differences based on preliminary data to account for potential sampling error, c) no clinically relevant (as decided by the DSMB) difference in death, hospitalization, need for medication or NYHA class between PVR and no-PVR groups and d) in the PVR group, <10% of patients with PVR failure. Not meeting these criteria would indicate a failed feasibility trial.

5.4.1.2 Expected Health Impact

The definitive study which this feasibility protocol will support has the potential to impact literally thousands of individuals in the United States considering ~1,660 children are born each year with TOF.3 Avoidance of catastrophic RV failure, multiple hospitalizations, arrhythmia (all of which can have an adverse impact on productivity as well as lost wages) and death along with improved exercise performance and QOL in these individuals would

have tremendous value. As mentioned above, although PVR will need future valve replacements, replacing a valve is much easier than replacing or managing a failing or failed RV with its attendant risk of ventricular tachycardia and sudden death. Besides avoiding morbidity and mortality, the investigators believe that PVR will

5.4.1.3 Proposed Environment for the Full Clinical Trial:

The full study will involve a much larger consortium. Dr. Fogel will administer the larger trial from CHOP and Dr. Marino will manage the data management and biostatistical support. Besides the current institutions, others that have expressed interest include Texas Children's Hospital, University of Michigan CS Mott Children's Hospital, Children's Hospital of Wisconsin, New York-Prebyterian Children's Hospital and Children's Hospital Colorado. These are large, experienced pediatric cardiology / cardiac surgery centers capable of ensuring a successful outcome of the full clinical trial. Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

5.5 Interim Analysis

DSMB interim analysis: The DSMB will formally review adverse event frequency for the PVR and no-PVR groups after 45 trial participants have completed follow-up data collection; they will be blinded to treatment group status and only frequencies, not sample sizes, will be presented to mask the 2:1 randomization. A statistically significant difference ($p<0.05$) in adverse event frequency will merit further investigation into continuing the trial. This interim analysis is planned for formal evaluation of safety; an interim analysis of treatment effect is not planned due to the pilot and feasibility nature of the study.

6 STUDY INTERVENTION: PVR OR NO-PVR

6.1 Description

Patients will undergo PVR or no-PVR in a randomized fashion.

6.1.1 Packaging

Not applicable

6.1.2 Labeling

Not applicable

6.1.3 Dosing

Not applicable

6.1.4 Treatment Compliance and Adherence

Not applicable. If a patient in the no-PVR group requires PVR, this will be noted in the efficacy as well as safety evaluations mentioned above.

6.1.5 Drug Accountability

Not applicable

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.2 Adverse Event Reporting

The Investigators are responsible for recording and reporting unanticipated problems related to the research and AE reporting will only occur for events linked to the study and not clinical procedures, the surgery or sequelae of the surgery, and will follow the CHOP IRB Guidelines. All SAEs will be reported to the IRB in accordance with CHOP IRB policies. Adverse Events that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

7.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

7.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but

would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

7.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention will be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

7.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

7.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

7.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with regulatory, sponsor or GCRC requirements

7.7 Medical Emergencies (if applicable)

For any medical emergencies, the primary co-investigator at each site or his designee will be responsible for investigating the emergency and resolving issues surrounding the emergency. Study teams and medical personnel associated with the patient will be in contact with each other to determine the correct way to proceed. For nights and weekends, all sites have cardiology fellows on call who know how to get in contact with the investigator at each site; they will be assigned to be called during those hours. The following is a list of who to notify during regular business hours:

In an emergency at:	Person to notify
CHOP	Mark Fogel
Emory	Tim Slesnick
DC	Russell Cross
Cinn	Sean Lang
Lurie Childrens	Josh Robinson
NU	Brad Marino

8 STUDY ADMINISTRATION

8.1 Treatment Assignment Methods

8.1.1 Randomization

Patients will be randomized by computer by the statistician and her team at the Data Coordinating Center at NU who will maintain the schedule; this will be a 2:1 randomization of PVR to no-PVR. There will be no blinding and the assignment will not be concealed from the investigators. There will be no stratifications within each group.

8.1.2 Blinding

This study will not be blinded

8.1.3 Unblinding

Not applicable

8.2 Data Collection and Management

This plan will be consistent with and follow CHOP Policy A-3-6: Acceptable Use of Technology Resources that defines the requirements for encryption and security of computer systems.

Northwestern University will perform high quality data management and analysis functions. CRFs will be developed in conjunction with the study PI, site PIs and statistician. A Manual of Operations, including instructions for CRF completion and data capture will also be developed to support standardized study operations and data collection. All data will be coded at the sites by assignment of a unique study ID number for all participants and reported on all CRFs and source documents; the key which links this number to identifying information will be stored in a separate, secure location at each site. Data will be entered by the site study coordinators into a web-based REDCap database that will be created and extensively tested by the Northwestern University. Staff responsible for data entry will be granted access only to data from their site through the use of site-specific REDCap User Groups. Access to REDCap is conducted only on NU networks or over SSL VPN and all data are stored on a server encrypted using standard 2048-bit SSL certificate using https protocol. In addition to web-based entry, each site will scan in and upload all CRFs to the NU via a secure FTP site. A set of predetermined critical variables will be checked between the CRFs and the database. For 10% of cases, all data will be cross-checked. A series of range and logic checking scripts will be developed and run routinely for all data. Only study personnel will have access to data for their respective site. Data will be backed up on a separate server at Northwestern University.

The identifiers will be destroyed as delineated in the CHOP data retention policy A-3-9 (available for download at https://at.chop.edu/communities/policyprocedure/administrative/Active/a-3-9.pdf). This laboratory (NU and CHOP) will maintains a file drawer specifically for such archives, each folder labeled “Destroy by….,” with the earliest dates at the front.” Data retention policy will meet NIH/NHLBI guidelines.

8.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

Northwestern University will coordinate data transfer between institutions in a HIPAA compliant manner to ensure privacy. Data sent across institutions will be on secure servers with only individual study team members having the ID and passwords. All data will be coded when crossing to the Northwestern University or to CHOP. Spreadsheets with identifying codes will be password protected and locked in secure files at each institution behind their firewalls.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

8.4 Regulatory and Ethical Considerations

8.4.1 Data and Safety Monitoring Plan

The PI (or a designee if he is away) will have overall responsibility for monitoring the overall safety of the entire project during the study. At each site, each co-investigator will be responsible for safety. A physician will personally be at all CMR and EST studies. The IRB at CHOP will monitor this project and all adverse events will be reported to the IRB in a timely fashion in compliance with all applicable regulations.

A Data Safety Monitoring Board (DSMB) will be organized by the NIH as per the request of Dr Egerson of NHLBI and contain at least 5 individuals, at least one of whom will be a pediatric cardiologist, a CMR physician and a catheterization doctor who will meet once yearly to assess the risk, benefit and safety of the study. The DSMB will review all the scientific data gathered to date as well as all the safety information such as adverse events that have occurred during the study period and will put its recommendations to the principle investigator and the rest of the research team in writing. The study team will be responsible for gathering all the information for the DSMB to review.

8.4.2 Risk Assessment

8.4.3 Potential Benefits of Study Participation

There may be direct benefits to the subjects from this study if PVR is determined to have a salutary effect on QOL and exercise performance as well as decreasing complications of no-PVR. Similarly, there may be direct benefits to the subjects from this study if no-PVR is determined to have a salutary effect on QOL and exercise performance as well as decreasing complications of PVR and avoiding surgery or catheterization. The patient will be contributing the overall scientific knowledge in the field of treating TOF.

8.4.4 Potential Risks of Study Participation

As stated, there is equipoise in the decision making process of PVR placement in TOF. It is so serendipitous that depending on who the patient sees as a physician, with the same clinical and imaging data, 2 very different decisions would be made, even within a given institution. This project simply organizes this disorganized approach to obtain data that will be useful in finally coming to a recommendation based on data. As such, the risk to the patient is no different that the risk of the patient having TOF and being apart of the medical system and not being part of this trial. That is to say, whether the patient enrolls in the study or not, the subject will wind up in one of the groups outlined in the study – PVR or no-PVR. Because of this, the risks to the patient are the same whether the patient and their physician, for example, choose to not have PVR or whether they get randomized to the no-PVR group in the study. Nevertheless, if a subject undergoes PVR who would not have outside of the research, then that subject is exposed to the risks of general anesthesia and the PVR procedure – thrombosis, infection, pain, stroke, and death. The same is true for an individual who would have had PVR but is randomized to medical management as a trial participant. These individuals might experience increase in symptoms, poorer QoL, etc.

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.

8.4.5 Risks for Subjects assigned to have PVR

8.4.5.1 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

8.4.5.2 Risks associated with general anesthesia (GA)

GA generally is required 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.

8.4.6 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
- Hospitalization for heart failure, abnormal heart beats or increasing symptoms for example
- Need to undergo PVR
- Need for medication or additional medication
- Death

8.4.7 Risks for all Subjects

8.4.7.1 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 the patient to continue. There may be some discomfort using the snorkel-like tube. During the study, the subject's

- 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

8.4.7.2 Risks associated with exercise CMR:

For a select group who agree, we may ask the subject to exercise in the MRI scanner with a bicycle lying down which would be in addition to the 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 the subject will hear as they would during your routine MRI scan. The subject may also feel uncomfortable inside the magnet if they do not like to be inside small places or have difficulty lying still, similar to the standard scan. The subject may feel tired after you exercise. During exercise, the subject's heart rate will be monitored by an electrocardiogram and pulse oximetry monitor and 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 the subject's 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.

8.4.7.3 Risks associated with Questionnaires:

Answering the questionnaires may bring up certain emotional feelings and concerns about the subject's condition. The subject does not have to answer any questions that make him or her feel too uncomfortable. If the subject becomes too upset or need to talk to someone, the study will refer the subject to the Department of Psychosocial Services.

8.4.7.4 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 the subject's 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.

8.4.8 Risk-Benefit Assessment

Potential risk to the patient is extremely small (the same as being a TOF in the medical system), however the knowledge to be has the potential to not only add to the literature on adolescents with TOF but also holds the potential to begin to definitively answer the question of if and when to perform PVR. The procedures of this study – randomization with interventions (with attendant risks in each group as when the patient is not enrolled and in standard of care – the choice however being taken away from patient and physician), with medical record review, QOL, metabolic exercise testing (if not part of clinical care), physician surveys, exercise CMR and post-processing clinically obtained cine imaging for ventricular strain present a small risk relative to knowledge to be gained.

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, the subject's symptoms may get worse regardless of which arm they are assigned to.

Treatment Arm	Possible Benefits	Possible Risks
PVR	• Improved exercise capacity	• Complications from PVR procedure including:

	• Improved quality of life	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

8.5 Recruitment Strategy

The Principal Investigator or designee at each clinical center and the study coordinator will be responsible for case ascertainment and subject recruitment. Subjects will be recruited from each of the participating sites. Potential subjects will be identified from patients who are referred to or who are already patients in cardiology clinics at the study sites. Most importantly, patients will be identified from CMR logs and the CMR schedule. Prior to study launch, study staff will conduct informational sessions with all physicians, nurses, and other colleagues at their sites who care for the target population to describe the trial and solicit support for recruitment.

Study staff will review site databases/medical records and the CMR and EST schedule for potentially eligible patients based study specified inclusion criteria. A screening log specifying reasons for exclusion will be kept. Screening will continue throughout the study at participating sites to identify any additional subjects that are new or were missed in the initial screening process.

Please note that the screening activities themselves are limited to review of medical/investigator records and do not include soliciting information directly from potential subjects; only when subjects meet inclusion criteria and do not meet exclusion criteria will the patient be approached**.**

The study team may potentially be utilizing the Recruitment Enhancement Core for recruitment purposes (through the mailing of opt-out cards). The recruitment opt-out cards will include the required REC language.

Identified potentially eligible patients will be approached during a clinic visit or CMR scan, or, if eligibility is determined outside of a clinical visit, parents and potentially eligible patients will be contacted by study staff, as permitted by local IRB regulations, including mailing with opt-out card, a telephone call, video (eg Skype) email and/or other methods of approved initial contact. If a patient is interested in the study, the site personnel will be responsible for enrolling and consenting subjects either in person or via mail for signing the consent form. If the patient declines study participation or does not attend the screening visit, this will be recorded in the screening log. After consent has been obtained, each

subject will be assigned a study identification (ID) number in order to keep study information confidential. The link between subject name and ID number will be stored only at the study site. Screening measures will be performed. Subjects who do not meet study eligibility criteria after screening assessment will be discontinued from study participation, and will not be scheduled for further study visits or measures. The screening data will be recorded and kept. Subjects who meet eligibility criteria at the screening visit and provide informed consent will be scheduled for study visits which can occur on that same day.

Recruitment of physicians to fill out questionnaires will occur during or after meetings or in clinics. The Investigator will comply with IRB SOP 501 (https://irb.research.chop.edu/sites/default/files/documents/irbsop501_2014-9-8.pdf) by not enrolling physicians who report to the investigators, that physicians' participation will not affect their performance evaluations or employment, and that only investigators who are not the physicians' direct supervisors will obtain consent.

8.6 Informed Consent/Assent and HIPAA Authorization

Subject consent or parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed with a member of the study team. The principal investigator or a designee will be able to discuss and answer any questions related to the study with both the parent (if applicable) and the subject (to obtain consent if they are an adult or assent if they are a child); if a designee is obtaining consent, the PI will be available in case more questions arise and the subject or family would like to discuss the questions with the PI. Adult subjects will provide consent for themselves. The principal investigator or qualified designee will obtain written consent either in person at the time of the CMR, at a routine clinic visit or other appropriate venue or via mail. In person consent will be obtained in a private area and families and subjects will be encouraged to ask questions. If consent is obtained via mail, the study team will document that the principal investigator or qualified designee has spoken with the family and subject via telephone call or videoconference to answer any questions related to the study prior to having the family or subject, if they are 18 and older, to sign and return the consent forms. If the subject is under the age of 18 and is not available at the time of the initial phone call, then study team will provide flexibility for follow up phone calls in order to obtain assent. The consent forms will be signed by the PI or qualified designee after the family or adult subject has signed. The study team will provide shipping materials (i.e. stamps, labels, etc.) to return the signed consent forms to the study team. The study team will make sure to mail a copy of the fully executed consent form to the family to keep for their own records. Willingness to participate in the study will be confirmed when the subject is seen in person. The subject and family will not be coerced nor will they need to decide at that time to participate. They can bring the consent form home with them and we will offer the family a contact phone number and email address. A member of the study staff will contact the family approximately one week later to answer any further questions prior to obtaining consent.

Subjects who decline to participate in the main study will be asked for the reason and this will be recorded per standard of practice of the study coordinator group. This data will be used for further research and analysis. Physicians who decline to participate in the study but who are gracious enough to fill out a questionnaire every year will be consented on a

separate consent form by the study team at their convenience and in private; they will not be coerced in any way.

Written informed consent will be obtained from physicians who agree to participate in the questionnaires in a private location.

8.6.1 Waiver of Consent

Not applicable

8.6.2 Waiver of Assent

Not applicable

8.6.3 Waiver of HIPAA Authorization

Not applicable

8.7 Payment to Subjects/Families

8.7.1 Reimbursement for travel, parking and meals

Although nearly all study related procedures are clinically indicated, the investigators recognize that patients and their families still take time out of their day to listen to the study plan and participate. This study is funded on a very limited budget. As such, a token amount of $25 will be given to recognize that fact.

8.7.2 Payments to parent for time and inconvenience (i.e. compensation)

See 8.6.1

8.7.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

See 8.6.1

8.7.4 Gifts

See 8.6.1

9 PUBLICATION

We anticipate the results of this study will be presented at national meetings and/or published in academic journals. We will not disclose PHI in any presentation or publication about the study.

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