Study Name: Long-term Outcomes of Children with HLHS and the Impact of Norwood Shunt Type (SVR III)- Protocol

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Long-term Outcomes of Children with HLHS and the Impact of Norwood Shunt Type

PROTOCOL

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Pediatric Heart Network

1. GENERAL INFORMATION

1.1 Protocol Signature Page

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the [insert the word “device”, “drug”, or “biologic”, as applicable] and the conduct of the study.

I will use the informed consent form approved by the National Heart lung and Blood Institute (NHLBI) and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 7.2 of this protocol.

I further agree that the NHLBI and/or its designee has access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including drugs, biologics, and/or devices) provided and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this study protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local regulations and regulatory authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Investigator		
Investigator		
Investigator		
Investigator		

1.2 Protocol Synopsis

Title	**Long-term Outcomes of Children with Hypoplastic Left Heart Syndrome and the Impact of Norwood Shunt Type (SVR III)**
Study Objectives	1. To determine if shunt type at the time of Norwood operation is associated with long-term differences in cardiac function, survival or contributors to quality of life. 2. To characterize long-term outcomes and determine risk factors other than shunt type for adverse long term outcomes in children with hypoplastic left heart syndrome (HLHS) and other related single ventricle anomalies.
Significance	The proposed long-term follow-up of the Single Ventricle Reconstruction (SVR) trial cohort is required to determine the optimal shunt approach for children with HLHS.
Study Design	Prospective follow-up study of the SVR cohort
Primary Aim	To compare direct and indirect measures of right ventricular (RV) systolic and diastolic function between 11 year old subjects who had been randomly assigned to receive a right ventricle to pulmonary artery shunt (RVPAS) vs. a modified Blalock-Taussig shunt (MBTS) at the time of the Norwood operation.
Secondary Aim(s)	1. To compare the incidence of death or cardiac transplantation between those randomized to receive a RVPAS vs. a MBTS at the time of the Norwood operation. 2. To compare exercise tolerance between those randomized to a RVPAS vs. a MBTS. 3. To compare the incidence of arrhythmias between those randomized to a RVPAS vs. a MBTS. 4. To compare neurodevelopmental outcomes at 11 years of age in those randomized to a RVPAS vs. a MBTS 5. To develop risk stratification models for 1) cardiac outcomes, 2) transplant-free survival, and 3) neurodevelopmental outcomes. 6. To collect specimens from subjects and their parents to further develop the biologic specimen repository.
Accrual Objective	Fixed cohort, ideally with a 2 year window for participation (11 $\pm$ 1 year of age), but subjects can be enrolled at any time there is interest in participation up until September 30, 2020.
Study Duration	10.5 years (June 2015 - November 2025)
Inclusion Criteria	Transplant-free survivors of the SVR cohort (All SVR survivors are eligible to be followed for vital status.)
Exclusion Criteria	Participants who received cardiac transplantation or biventricular conversion will be excluded from all outcomes other than vital status.

1.3 Table of Contents

1.4 List of Abbreviations

ABAS	Adaptive Behavior Assessment System
AE	Adverse Event
AUC	Area under the Curve
BRIEF	Behavior Rating Inventory of Executive Function
CEC	Clinical Events Committee
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance Imaging
Connors 3 AI	Connors 3rd Edition Attention Deficit and Hyperactivity Index
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DMP	Data Management Plan
DMS	Data Management System
DSMB	Data and Safety Monitoring Board
DTI	Doppler Tissue Imaging
EC	Executive Committee
Echo	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HRQOL	Health-Related Quality of Life
HLHS	Hypoplastic Left Heart Syndrome
IART	Intra-Atrial Reentrant Tachycardia
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IVC	Inferior Vena Cava
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LPA	Left Pulmonary Artery
MBTS	Modified Blalock-Taussig Shunt
MedDRA	Medical Dictionary for Drug Regulatory Activities
MM	Medical Monitor
MOO	Manual of Operations
MRI	Magnetic Resonance Imaging
ND	Neurodevelopmental
NEPSY-II	A Developmental NEuroPSYchological Assessment – Second Edition
NCBI	National Center for Biotechnology Information
NIH	National Institute of Health
NHLBI	National Heart, Lung and Blood Institute

OHRP	Office for Human Research Protection
Peds-QL	Pediatric Quality of Life Inventory
PC	Phase Contrast
PHN	Pediatric Heart Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RPA	Right Pulmonary Artery
RV	Right Ventricle
RVED	Right Ventricular End Diastolic
RVEDV	Right Ventricular End Diastolic Volume
RVEF	Right Ventricular Ejection Fraction
RVES	Right Ventricular End Systolic
RVESV	Right Ventricular End Systolic Volume
RVPAS	Right Ventricular to Pulmonary Artery Shunt
SAE	Serious Adverse Event
SC	Steering Committee
SMF	Site Master File
SMP	Site Monitoring Plan
SSFP	Steady State Free Precession
SSL	Secure Socket Layer
SVR	Single Ventricle Reconstruction
SVR II	Single Ventricle Reconstruction Extension Study
SVT	Supraventricular Tachycardia
SVC	Superior Vena Cava
TR	Tricuspid Regurgitation
TV	Tricuspid Valve
VO_2	Oxygen Consumption
VO_2 max	Maximum Oxygen Consumption
WIAT	Wechsler Individual Achievement Tests
WISC	Wechsler Intelligence Scale for Children

2. STUDY AIMS AND HYPOTHESES

2.1 Primary Aim:

To compare direct and indirect measures of right ventricular (RV) systolic and diastolic function between 11 year old subjects who had been randomly assigned to receive a right ventricular-to-pulmonary artery shunt (RVPAS) vs. a modified Blalock-Taussig shunt (MBTS) at the time of the Norwood operation.

Hypothesis*: Assignment to the RVPAS compared to the MBTS will be associated with worse RV performance in subjects at age 11 years.*

Primary Outcome: RV ejection fraction (RVEF) at 11 years, as measured by cardiac magnetic resonance (CMR).

Secondary Outcomes: Secondary outcomes will include additional measures of ventricular systolic, diastolic, and global function by CMR and echocardiogram (echo); anatomic measures related to RV function; and physiologic measures affecting RV function. Secondary outcomes of the greatest importance include:

- RVEF (measured by echo)
- RV fractional area change (measured by echo and CMR)
- Cardiac output (measured by CMR)

2.2 Secondary Aims

Secondary Aim 1: To compare the long-term effect of the RVPAS to that of the MBTS on the incidence of death or cardiac transplantation in children with hypoplastic left heart syndrome (HLHS) and other single RV anomalies undergoing the Norwood procedure.

Hypothesis*: The incidence of death or cardiac transplant will be higher in the RVPAS group compared to the MBTS group.*

Outcomes:

- The composite of the earliest occurrence of mortality and cardiac transplantation using all available follow-up (ranging from 10 to 15 years).
- Conditional freedom from death or cardiac transplantation by 11 years among subjects who survived >1 year post-randomization.
- Survival at 11 years post-randomization and when the last enrolled subject is 11 years old.
- Transplant at 11 years post-randomization and when the last enrolled subject is 11 years old.
- The composite of the earliest occurrence of mortality, cardiac transplantation and pacemaker placement, using all available follow-up (ranging from 10 to 15 years).

Secondary Aim 2: To compare exercise tolerance between those randomized to receive a RVPAS vs. a MBTS at the time of the Norwood operation.

Hypothesis: *Subjects assigned to the RVPAS group will have lower exercise performance at age 11 years compared to those assigned to the MBTS group.*

Outcomes:

- Exercise capacity: Maximal Oxygen Consumption (VO_2max), maximal work rate, and anaerobic threshold

Secondary Aim 3: To compare the incidence of arrhythmias between those randomized to receive a RVPAS vs. a MBTS at the time of the Norwood operation.

Hypothesis: *The RVPAS will be associated with a greater prevalence of ventricular arrhythmias, but will not differ from the MBTS in the prevalence of atrial arrhythmias.*

Outcomes:

- History of ventricular arrhythmias by age 11 years by parent report and with medical record confirmation.
- History of atrial arrhythmia by age 11 years, including intra-atrial reentrant tachycardia (IART) or supraventricular tachycardia (SVT), by parent report and with medical record confirmation

Secondary Aim 4: **To compare neurodevelopmental outcomes at 11 years of age in subjects randomized to a RVPAS vs. MBTS at the time of the Norwood operation.**

Hypothesis: *Impaired neurodevelopment will not be associated with Norwood shunt type but mean scores will be lower in single ventricle patients compared to the normative population.*

Outcomes:

- Achievement, as measured by the Wechsler Individual Achievement Tests (WIAT) (Math and Reading)
- Intelligence, as measured by the Wechsler Intelligence Scale for Children (WISC)
- Other domains of neurodevelopmental function including assessment of language, executive function, visual spatial skills, motor function, memory, social skills, behavior, health-related quality of life (HRQoL) and adaptive function.

Secondary Aim 5: To develop risk stratification models for the following classes of long term outcomes: 1) cardiac outcomes, 2) transplant-free survival, and 3) neurodevelopmental outcomes.

Hypothesis: *Long-term outcomes at 11 years will be worse for participants with a higher frequency of medical events.*
Analyses for this aim will:

- Provide information about the association of events and interventions other than the randomized surgical procedure with late outcomes.
- Identify early cardiac and neurodevelopmental surrogate endpoints that might be useful in future studies of management strategies.
- Determine if correlates of long-term outcomes vary according to patient subgroup factors.

Secondary Aim 6: To collect specimens from subjects with HLHS and other single RV anomalies and their parents in whom DNA samples either were not collected previously or are of insufficient quality or quantity, to further develop the biologic specimen repository (biorepository).

Purpose: *To build on the collection of genetic material from the SVR cohort, to leverage the careful phenotyping of the SVR cohort to provide an opportunity for future phenotype-genotype studies and to make samples available for future hypothesis-driven studies aimed at identifying genetic determinants of outcome in HLHS and related single RV lesions.*

3. BACKGROUND INFORMATION

3.1 Overview

Hypoplastic left heart syndrome (HLHS) remains among the highest risk congenital cardiac malformations, with significant mortality and morbidity throughout childhood and early adulthood. Prior to 1980, when William Norwood described the palliative operation now commonly known as the Norwood procedure,[1,2] children born with HLHS had virtually no chance of survival. By the late 1990s, early post-operative survival approached 80-85% in some centers.[3,4] Despite this improvement, the ongoing risk of mortality in the early period, including 10-20% interstage mortality,[5,6,7] resulted in one-year survival rates of only 60%-70%.[8-10] Furthermore, among survivors, the morbidity associated with single ventricle physiology is substantial, with major negative consequences for quality of life and long-term survival.

3.2 Prior Studies

The Single Ventricle Reconstruction (SVR) trial was the first multicenter, randomized clinical trial to compare two operations in the field of congenital heart disease.[8,11] Children with HLHS and other related single RV lesions were enrolled and randomized to receive either a MBTS or a RVPAS at the time of the initial Norwood procedure. This landmark study provided extraordinary insight not only into the consequences of both shunt types, but also into the course, treatment responses and short- and mid-term outcomes for these medically complex patients. Through the SVR Trial and SVR Extension Study (SVR II), outcomes, including but not limited to the primary outcome of transplant-free survival, have now been evaluated in this patient cohort when the last enrolled patient reached 12 months and again at 3 years of age. While early post-operative transplant-free survival during the interstage period[7] and at one year[8] was better for those children randomized to a RVPAS, survival by the 3-year evaluation appeared equivalent between the two shunt types. Moreover, RVEF was somewhat diminished and the number of interventions was higher in the RVPAS group.[12] These findings raised concern that the RV dysfunction in the RVPAS group may be progressive, leading to significantly worse long-term outcomes; if so, the benefits of the RVPAS for short-term survival may be outweighed by longer-term morbidity and mortality. Thus, the optimal surgical approach for newborns with HLHS and related single RV lesions remains unclear.

3.3 Rationale for the Study

The Pediatric Heart Network (PHN) Investigators have a unique opportunity and responsibility to analyze the effect of the type of systemic-to-pulmonary artery shunt placed during the Norwood procedure on longer-term survival, as well as to define its effect on other

long-term outcomes in this multi-institutional cohort of exquisitely characterized subjects with single RV lesions. As subjects enrolled in the SVR cohort approach a decade of age, we aim: 1) to determine if shunt type at the time of Norwood operation is associated with any long-term differences in cardiac function, survival, or contributors to quality of life; and 2) to characterize long-term outcomes and determine risk factors other than shunt type for adverse long-term outcomes in children with HLHS and other related single ventricle anomalies.

3.3.1. What is known to date about long-term outcomes of children with single ventricle heart defects?

To enhance our understanding of outcomes among Fontan survivors, the PHN conducted the Fontan Cross Sectional Study, which characterized 546 patients with a spectrum of single ventricle malformations and ranging from 6 to 18 years of age at enrollment.[13] This study and others have noted that after the Fontan procedure, patients experience significant deficits across multiple functional domains. Longitudinal follow-up of the Fontan Cross-Sectional Study cohort has yielded many insights into the medical challenges faced by this population. This work related to the Fontan cohort has been instrumental in informing the aims and design of the current proposal, but it does not include information on single ventricle patients with a RVPAS. Thus, long-term follow-up of the SVR cohort, in particular, is needed to determine the influence of shunt type on important long-term outcomes. Furthermore, unlike the Fontan cohort, the SVR cohort is an inception cohort that has been followed from birth, allowing us to analyze associations between critical early events and later outcomes.

3.4 Rationale for the Study Outcomes

3.4.1 Measurements of Cardiac Function and Assessment of Cardiac Anatomy:

Ventricular dysfunction in patients with single ventricle physiology is common and can lead to symptoms of heart failure, dysfunction of other organ systems, and worse quality of life. Exercise intolerance, ventricular and atrial arrhythmias, protein-losing enteropathy, and hepatic cirrhosis may each be attributable, in part, to ventricular dysfunction. Because of the critical role of ventricular function on the development and progression of these outcomes, and due to the concern that initial shunt type may affect ventricular function, we have chosen RVEF, as measured by CMR, to be the primary outcome for this study.

In the Fontan Cross Sectional Study, ejection fraction was decreased by 2D echo in approximately 27% of subjects. The average RVEF for subjects with a single right ventricle was 56% compared to a left ventricular ejection fraction of 60% in those with a single left ventricle.[14] By CMR, the RVEF was 55% for those with single RV lesions.

Within the SVR cohort, the RVPAS group had a higher mean end-systolic volume compared to the MBTS group (55±17.8 vs. 49.1±6.6 ml/BSA$^{1.3}$, p=0.004) and a lower RVEF (40.9±6.7% vs. 44.2±3.1%, p=0.004) at the pre-Fontan echo.[15] Diastolic dysfunction was even more prevalent than systolic dysfunction, with 81% of all subjects with a single RV having abnormal diastolic filling properties.[14] This is particularly problematic because diastolic ventricular dysfunction, accompanied by higher filling pressures and pulmonary vascular resistance, is a powerful risk factor for morbidity and functional limitation in patients with Fontan physiology. The planned SVR III assessment will include measurements of right ventricular systolic, diastolic, and global function indices.

In addition to direct measures of RV function, other anatomic and physiologic variables will be assessed. For example, atrioventricular valve regurgitation, aortic insufficiency and pulmonary artery size each can affect cardiac output and filling pressures in the single ventricle patient. One recent report described greater tricuspid regurgitation in patients with HLHS and the MBTS.[16] Development of significant neo-aortic root dilatation and neo-aortic valve

regurgitation has been described later in childhood after Norwood palliation with a MBTS.[17] Within the SVR cohort, there was significant neo-aortic dilation by the pre-Fontan echo. Although to date, this has not been associated with significant regurgitation,[15] ongoing dilation may eventually result in aortic insufficiency that is less well tolerated by those in the RVPAS group given their history of a right ventriculotomy.

For the SVR III study, measurements of function and anatomy will be obtained using CMR and echo. While the primary outcome measure for the proposed study is RVEF measured by CMR, some eligible subjects will be unable to undergo CMR because they have a pacemaker or cannot cooperate in the scanner. The inclusion of echo measurements as secondary outcomes allows cardiac function to be evaluated in a greater percentage of the SVR cohort. Knowledge of the relationship between CMR and echo measures will be valuable for the clinical care of patients with HLHS and other single RV disorders, particularly given that serial echoes are performed routinely in single ventricle patients,

3.4.2 Measurement of Exercise Intolerance:

Adolescents with Fontan physiology are recognized to have reduced aerobic exercise capacity.[18-22] Causes of lower exercise capacity include reduced systolic and/or diastolic function, limited ability to maintain adequate preload to the systemic ventricle, chronotropic incompetence, or even the mildest elevation in pulmonary vascular resistance. Consistent with previous findings, the Fontan Cross Sectional Study showed a percent predicted VO_2 max of only 66% at 12 years of age.[20] To the extent that RV function deteriorates in the RVPAS group at older ages, exercise performance may be even further compromised.

3.4.3 Incidence of Arrhythmias:

Abnormalities of cardiac rhythm, including both tachy- and brady-arrhythmias, are common after the Fontan procedure. Supraventricular tachycardia (SVT), most commonly intra-atrial re-entrant tachycardia (IART), occurred in 9.4% of the Fontan Cross Sectional cohort with increasing incidence with age.[23] Atrial stretch, which can result from ventricular dysfunction and high ventricular end diastolic pressure, can exacerbate atrial arrhythmias.[24] Progressive ventricular dysfunction or even stable but reduced ventricular function in the RVPAS group could therefore increase the incidence of atrial arrhythmias.

The potential for promotion of ventricular arrhythmias from scarring around the RVPAS conduit insertion site is even more concerning. Ventricular arrhythmias occurred in 3.5% of Fontan patients in the Cross-Sectional study,[23] and the use of the RVPAS could increase this rate considerably. Both atrial and ventricular rhythm abnormalities can lead to diminished exercise tolerance, lower quality of life, higher risk of thromboembolic events and protein-losing enteropathy, and a possible increase in the incidence of sudden death.

3.4.4 Measurement of Neurodevelopmental (ND) Outcomes:

Children with single ventricle lesions frequently have developmental disabilities. The etiology of ND morbidity is multifactorial and includes low birth weight,[25-27] prolonged cyanosis,[28] congestive heart failure,[29] unstable hemodynamics during the pre-operative period, need for multiple cardiac catheterizations, and a series of operations culminating with Fontan palliation.[30] Impaired cerebral blood flow, even *in utero*,[31,32] as well as structural abnormalities of the brain[33-37] and the presence of genetic and other associated congenital abnormalities,[26,38] also appear to contribute to concerning outcomes reported in numerous studies in infancy and early childhood.

Most findings on ND in this high-risk group of children have derived from single-center or cross-sectional studies. To date, the relationship between early developmental assessments and measures of development for school-age children with HLHS and other forms of single RV remains unknown. The SVR and SVR Extension (SVR II) studies included neurodevelopment as an important outcome[11,26,27] because of its critical role in determining quality of life and

informing optimal treatment approaches. The measurements of the SVR cohort to date are limited by the young age at which in-person testing was performed (14 months) and by the use of home questionnaire instruments in SVR II. An in-person evaluation at age 11 years using a multifaceted battery will allow a richer understanding of ND outcomes in this cohort, refining our ability to discriminate differences based on earlier shunt strategy, as well as to discern other factors influencing long-term neurodevelopment, school function, and quality of life. Given the importance of these outcomes to patients and families, we anticipate excellent motivation to participate in this study.

4. STUDY / TRIAL DESIGN

4.1 Overview of Study Design

The SVR III study is a prospective follow-up study of an existing cohort of children with HLHS and other single RV anomalies enrolled in early infancy in a randomized clinical trial of Norwood procedure with MBTS versus RVPAS. We seek to determine if the shunt assignment at the time of the Norwood operation is associated with cardiac function, transplant free survival, exercise function, and neurodevelopmental outcomes. Families of surviving SVR participants will be contacted and asked to return for multidisciplinary evaluation including performance of a CMR study, echo, exercise testing, and neurocognitive evaluations. All testing will be performed at an SVR enrollment site, either where the Norwood was performed or a site that is closer to the subject's home. Both CMR and echoes will be interpreted in core laboratories by investigators blinded to Norwood shunt type.

4.2 Procedures to Minimize Bias

The eligible SVR III study cohort is defined by the participants in the SVR trial. All eligible subjects will be encouraged to participate, regardless of distance, demographic factors, or earlier medical history. To avoid bias in measures for ventricular function, those performing measurements in the CMR and echo core labs will be masked to the shunt type at the time of the Norwood operation. The psychologist or their surrogate conducting the ND evaluation will also be masked to the original treatment group assignment.

4.3 Study Measures

The battery of evaluations will require approximately two days. Careful coordination will ensure that evaluations are completed efficiently, effectively, and safely.

4.3.1 Measures Related to Primary Aim

4.3.1.a Cardiac Magnetic Resonance Imaging (CMR)

CMR will be performed in all participants without pacemakers or other contraindications. Sedation or anesthesia will not be used for CMR scans performed solely for this research study.

To maximize subject participation, a focused, basic CMR protocol will be performed to assess ventricular morphology and systolic function, with an estimated study length of 10-15 minutes. An expanded research CMR protocol to assess Fontan and collateral flows, systemic arterial anatomy, and Fontan pathways, including pulmonary artery and pulmonary vein size, will be performed when possible in subjects able to comply with an additional 45 minutes of scan time. All CMR studies will be performed on 1.5 T magnets that are available at all sites and will be performed in a free breathing state without anesthesia or intravenous access. To ensure that all measures are performed consistently, and to enhance the precision of study results, CMR images will be analyzed at the CMR core lab.

We have chosen to use CMR as the primary measure of RVEF for this study. CMR is a better, more reproducible method of measuring RVEF than 2D or even 3D echo.[41] Lai and colleagues found that 2D echo measurement of RVEF is particularly limited in the face of a dilated right ventricle, a common finding for patients with HLHS.[42] Comparison of 2D echo to CMR as part of the Fontan Cross Sectional Study demonstrated that CMR is accurate and more reproducible for measurement of RV volume, mass, and ejection fraction.[43] Lower inter-observer variability of measures performed using CMR result in improved power/smaller sample size needs.[43] One potential limitation of CMR in this population is its incompatibility with electronic pacemakers. In the Fontan Cross-Sectional cohort, the incidence of pacemakers was 13% at the time of the initial study and overall 9% in those with a systemic RV.[44] The prevalence of pacemakers increases with age; in the Fontan Cross Sectional study 7-8% of the those 10-11 years of age had undergone pacemaker placement.[44] We anticipate therefore, that at 11 years of age, no more than 5-10% of the SVR cohort will have pacemakers.

Of note, if a **clinical** CMR was performed within the study window using the study protocol, these data will be acceptable for submission to the CMR core lab. If a **clinical** study has required sedation or anesthesia but otherwise is consistent with the study protocol, then the technique will be noted but the data may still be submitted to the core lab.

The battery of CMR measures will include:

1. Evaluation of ventricular morphology and systolic function (all participants):
    - RVEF=(RVEDV-RVESV)/RVEDV
    - Right ventricular end-diastolic volume (RVEDV) and RVEDVi (RVEDV indexed to BSA)
    - RV end-diastolic mass and end-diastolic mass indexed to BSA
    - Right ventricular end-systolic volume (RVESV) and RVESVi (RVESV indexed to BSA)
2. Evaluation of Fontan flows and collaterals by phase contrast imaging:
    - Cardiac output based on inferior vena cava (IVC) and superior vena cava (SVC) flows
    - Comparison of right versus left lung perfusion through pulmonary artery and pulmonary vein flow measurements,
    - Degree of neo-aortic regurgitation
    - Tricuspid regurgitation measured by comparison of TV inflow or right ventricular stroke volume with neo-ascending aorta flow
    - Aorto-pulmonary collateral flow percents: [neo-ascending aorta-(SVC +IVC)]/neo-ascending aorta
    - Fenestration shunt: (SVC+IVC)-(LPA+RPA)/(SVC+IVC)
3. Assessment of systemic arteries (using 3 D Steady State Free Precession (SSFP) navigator-gated imaging)
    - Neo-aortic arch orthogonal dimensions
    - Descending aortic orthogonal dimensions
4. Assessment of Fontan pathways (using 3D SSFP navigator-gated imaging)
    - Right pulmonary artery (RPA) diameter and area
    - Left pulmonary artery (LPA) diameter and area
    - Pulmonary vein assessment (qualitative evaluation for stenosis)

4.3.1.b Two Dimensional Echo

Two-dimensional echocardiograms will be performed on each participant. It is anticipated that all study participants will undergo an echocardiogram within the study window. All images will be sent to the Echo Core Lab, where detailed measures will be performed. Measures of RV systolic, diastolic, and global function will be performed. In addition, measures of anatomy (e.g., neo-aortic root diameter) and measures of physiology affecting RV function (e.g., degree of neo-aortic insufficiency) will be assessed. Subjects will not be sedated for echocardiograms performed solely for research. In the event that an echo was performed clinically within the study window, these data will be included as long as the clinical echo adhered to the echo study protocol.

While the primary outcome measure for the proposed study is RVEF measured by CMR, some eligible subjects will not be able to undergo CMR because they have pacemakers or cannot cooperate with even the basic CMR protocol. The inclusion of echo measurements as secondary outcomes allows the cardiac function related outcomes to be measured in a greater percentage of the SVR cohort. The inclusion of echo measurements will allow for important comparison of echo to CMR measurements in those participants who do undergo both assessments. While the ideal study window is 2 years, 11 years +/- 1 year, we will aim for the CMR and echo to be performed within 6 months of each other. If a cardiac procedure that could affect the correlation between these two imaging studies is performed between the two tests (e.g., a pacemaker is placed after CMR but before echo), or if the CMR and echo are performed more than 6 months apart, we will eliminate that subject from analyses that compare results of these two test modalities.

The battery of echo measures will include:

1. Measures of RV systolic function
    - RVEF (by modified Simpson's method)
    - RVEDV
    - RVESV
    - RV percent area change
    - RV change in pressure/change in time
    - Doppler Tissue Imaging (DTI) peak annular systolic velocity
    - Tricuspid annular peak systolic excursion
    - Peak longitudinal regional and global systolic strain and strain rate
    - Peak circumferential regional and global systolic strain and strain rate
2. Measures of RV diastolic function
    - Tricuspid inflow (peak E velocity, peak A velocity and E/A ratio)
    - Annular DTI (e' velocity, a' velocity, E/e' ratio)
    - Presence and duration of pulmonary vein reversal
3. Global function indices
    - Systolic/diastolic time ratio from tricuspid regurgitant jet
    - Myocardial Performance Index (Tei index)
4. Anatomic measures
    - RVEDV, RVESV, Right ventricular end-diastolic (RVED) area, Right ventricular end-systolic (RVES) area
    - RV shape eccentricity index
    - Neo-aortic indexed annular area
    - Neo-aortic root diameter
    - Ascending aortic diameter
    - Tricuspid indexed annular area

5. Physiologic measures
    - Degree of tricuspid regurgitation (TR) (regurgitant orifice area, largest vena contracta diameter, qualitative assessment)
    - Degree of neoaortic regurgitation (regurgitant orifice area, largest vena contracta diameter, qualitative assessment)
    - Neo-aortic peak distal arch gradient
    - Dyssynchrony (defined as standard deviation of time to peak longitudinal regional strain, and standard deviation of time to peak circumferential regional strain)

4.3.2 Measures Related to Secondary Aims

4.3.2.a Annual Vital Status and Medical History

Through the SVR II study, families have been contacted to assess vital status and interim medical history. This process will be continued through the duration of the SVR III study. Through annual contact with families (e.g., at the time of in-person hospital visits, via telephone or email), vital status will be assessed and medical history including need for cardiac transplantation, need for other surgical procedures or development of a new diagnosis such as stroke, protein losing enteropathy or arrhythmia (atrial or ventricular), will be assessed. Medical records will be obtained from the primary cardiologists to verify medical history. Of note, we will assess vital status for all consenting survivors of the SVR study.

While medical record review and contact with families will serve as the primary means to measure vital status, searches of publicly available death indexes will be performed for all participants who are lost to follow-up. Prior to completion of any of the study evaluations, a medical history will be performed by the study coordinator using a semi-structured interview and standardized data forms. Parents/guardians will be queried related to the interim history since their last SVR/SVR II assessment. Questions will include any additional cardiac operations or interventions (including pacemaker placement), any interim cerebral vascular events, seizures, and diagnosis of atrial or ventricular arrhythmias (See section 4.3.2.c).

An additional touchpoint will occur in 2024-2025 to identify vital status for all eligible to participate; all SVR survivors will be contacted to identify vital status, current contact information and location of current medical care. Information related to planning for longer term follow-up will be shared with the patient and family who will also be queried about potential questions they would like answered through further study. Information related to the conversation will be kept at the study center. Information related to vital status will be shared with the DCC. For any participant over the age of 18 years, if appropriate and required by the local IRB, consent for this portion of SVR III will be requested.

4.3.2.b. Exercise Testing

Cardiopulmonary exercise testing will be performed with a standard ramp cycle ergometry protocol.[45,46] Inclusion in this portion of the study will require participants be able to comfortably reach the pedals enough to effectively pedal the cycle ergometer". This typically, but not always correlates with a height of >/=130 cm.

Electrocardiographic monitoring and breathing by using expiratory gas analysis will be performed throughout the exercise test. Heart rate, blood pressure and oxygen saturation will be monitored continuously. Baseline inspiratory and expiratory flow volume loops will be performed. Subjects will then perform hyperventilation for 10 seconds (3 times for reproducibility) to measure maximal voluntary ventilation. Participants will then pedal in an unloaded state for 3 minutes. Workload will then be increased continuously with exercise watts ramped to achieve each predicted maximal work rate in watts after 10 to 12 minutes of cycling.

All subjects will be encouraged to exercise to exhaustion. This method is safe and allows for adjustment of work rate to optimize performance potential for each individual within 10-12 minutes. VO_2 max will be defined as the highest VO_2 achieved by the subject during the exercise stress test. Maximal aerobic effort will be defined as a peak respiratory exchange ratio (VCO_2/VO_2) of ≥ 1.10. VO_2 max will be indexed to body weight and expressed as a predicted value for healthy age/gender matched subjects per Cooper and Weiller–Ravell.[47]

In addition to VO_2 max, oxygen pulse (maximum VO_2/peak heart rate), and ventilator aerobic threshold (VAT) determined by V-slope method and confirmed by the dual criteria measurements of the ventilatory equivalents of CO_2 and O_2 (VE/ VCO_2 and VE/ VO_2), will be measured/calculated. The battery of exercise measures will include:

1. Maximal work rate: expressed in Watts
    - The maximal work rate reached during exercise test
2. Oxygen consumption (VO_2): expressed in ml/kg/min
    - Resting
    - Maximal –defined as highest oxygen consumption achieved during the exercise test when averaged over 10 second intervals
3. VAT will be measured by V slope method and confirmed with ventilator equivalent method
    - VO_2 at VAT
    - Percent of achieved maximal oxygen consumption (VO_2 at VAT/ max VO_2) x 100
4. Oxygen Pulse measured at rest, VAT and Max VO_2
5. Pulse Oximetry measured at rest, VAT and maximal exercise
6. Heart Rate measured at rest, VAT and maximal exercise
7. Blood Pressure measured at rest and maximal exercise
8. Minute Ventilation measured at rest, VAT and maximal exercise
9. Tidal Volume measured at rest, VAT and maximal exercise
10. Respiratory Rate measured at rest, VAT and maximal exercise
11. Ventilator Equivalents of Carbon Dioxide (VE/VCO_2) measured at rest, VAT, and maximal exercise

If a ramped cycle exercise test has been performed for clinical reasons within the study window, these data will be included if the exercise test protocol was performed using the SVR III exercise test protocol.

4.3.2.c. Incidence of Atrial and Ventricular Arrhythmias

Medical record review and semi-structured interviews, will be employed to determine the percent of participants with atrial and with ventricular tachyarrhythmias.

Participants will be categorized as having had an atrial tachyarrhythmia if they have a history of IART or SVT documented by any type of electrocardiographic recording, have required treatment with an antiarrhythmic, or have required cardioversion at any time for an atrial tachyarrhythmia.

Participants will be considered to have had a ventricular arrhythmia if >5 beat run of ventricular tachycardia has been recorded, if the participant has been treated with an

antiarrhythmic for a ventricular arrhythmia, or if a pacemaker or defibrillator has been placed secondary to a ventricular arrhythmia.

4.3.2.d. Neurodevelopmental and Quality of Life Evaluation

Neurodevelopmental assessment will be performed by a licensed psychologist or supervised psychometrician at each site. Multiple areas will be assessed including intellectual functioning, academic (reading and math) functioning, language, memory, attention/executive functioning, visual spatial, fine motor, social functioning, adaptive skills, emotional/behavioral functioning, and quality of life. A sub-group of instruments included in the battery are based on parent and/or teacher report, including the Behavior Rating Inventory of Executive Function [48] (BRIEF), the Behavioral Assessment System for Children, 2nd Edition (BASC- 2),[49] the Connors 3rd Edition Rating Scale, ADHD Index (Conners 3),[50] the Adaptive Behavior Rating Scale – 3rd Edition (ABAS-3), [51] the Autism Spectrum Rating Scale (ASRS), [52] and the Peds QL (generic and cardiac modules).[53] These will be completed by a parent either before or during the child's evaluation (see details of Consent /Assent Process within Section 5.5 for informed consent procedures related to completion of questionnaires before the in-person evaluation). Teacher report instruments will be mailed to the study site either prior to or following the in-person evaluation. The in-person battery will begin in the morning and will require approximately 5 hours. Breaks will be provided for snacks/lunch as appropriate for the participant. Parents will be given a summary of their child's test results that will be scored based on age-based norms. ND evaluations will need to occur at least 6 weeks after any hospitalization. The psychologist and/or his designate at each site will be blinded to the shunt type at the time of the Norwood operation. The full battery (Table 1) will be extremely valuable to facilitate understanding of long term outcomes; in addition, all measured outcomes will be compared between shunt groups to discern any potential effect of shunt type on ND outcomes.

Table 1: Neurodevelopment Battery

Area	Specific Instruments	In-Person Testing Time	Parent/ Teacher Time
Intelligence	Wechsler Intelligence Scale for Children-V	65-80 min	
Math	Wechsler Individual Achievement III Tests- Math Problem Solving Numerical Operations	15 min 15 min 15 min	
Reading	Wechsler Individual Achievement III Word Reading Reading Comprehension Pseudoword Decoding	 6 min 20 min 6 min	
Language Function	NEPSY-II Comprehension of Instructions Oromotor Sequence	 8 min 5 min	
Executive Function	Delis-Kaplan Executive Function System Verbal fluency Tower Trail Making **BRIEF-Parent Report** **BRIEF-Teacher Report**	 10 min 10 min 15 min	 15 min 15 min
Visual Spatial Skill	Developmental Test of Visual-Motor Integration-6 (VMI-6) and Visual perception	 5 min 3 min	
Motor Function	Lafayette Grooved Pegboard	5 min	
Memory	Wide Range Assessment of Memory and Learning	45 min	
Social Skills	NEPSY II Theory of Mind and Affect Recognition **Autism Spectrum Rating Scale Parent Report**	 11 min	 7 min
Behavior Evaluation ADHD specific measure	**BASC-2 Parent Report** **BASC-2 Teacher Report** **Conners 3rd Edition ADHD Index Parent Forms** **Conners 3rd Edition ADHD Index Teacher Forms**		20 min 20 min 8 min 8 min
Quality of Life	**PedsQL Parent and self report, generic and cardiac modules.**		15 min
Adaptive Function	**ABAS-3 Parent Report**		20 min

Instruments in **bold** text are parent and teacher completed instruments and thus will not contribute to the time the participant needs to work directly with the psychometrician/psychologist.
In person evaluation-approximately 4.5 hours; parent forms 1.5 hours (85 minutes); teacher forms 0.75 hours (43 minutes).

Of note, based on current AHA/AAP guidelines for neurodevelopmental testing in children with congenital heart disease, it is possible that participants will have undergone a clinical ND assessment within the study window. Repetition of the same ND test administered twice within 6 months can affect the score of the second test. For this reason, scores from tests that overlap with our research battery will be incorporated into the research database if the research evaluation takes place within 6 months of the clinical testing. In this circumstance, we will complete the SVR III ND research battery by performing only those research ND tests that were

not done as clinical testing. If more than 6 months has elapsed between clinical and research testing, we will perform the entire research battery, including tests that had been administered earlier for clinical purposes.

A certification process for team members performing the neurodevelopmental battery will include review by the neurodevelopmental consultants of a recording of the team member performing the testing battery on a patient or volunteer of a similar age to the study participants.

4.3.2.e Biorepository

Participants and their parents who have not yet contributed to the SVR Extension biorepository will be offered the opportunity to provide saliva for extraction and storage of DNA. If study participants have consented to participate in the biorepository through the SVR Extension study but not yet contributed a sample, they will be asked to contribute at the time of the SVR III participation. Families who were not previously approached, or who declined participation in the biorepository earlier, may be offered the opportunity to participate at the time of the SVR III participation.

4.3.3. Covariate Measures

The unique nature of this large inception cohort presents the opportunity to examine events that commonly occur in this population as both risks and outcomes. To that end, a number of events will be collected as covariate measures. Covariates that are available from the SVR trial, SVR II and annual visit forms include:

SVR and SVR II:

- Pre-Stage I: prenatal diagnosis, genetic syndrome, socioeconomic status, birth weight/gestational age, occurrence of neonatal shock**.**
- Stage I hospitalization: mechanical ventilation time, cardiopulmonary bypass and deep hypothermic circulatory arrest/regional cerebral perfusion times, ICU/hospital length of stay, delayed sternal closure, use of extracorporeal membrane oxygenation (ECMO), unplanned surgical/catheter interventions**.**
- Interstage, post stage II and post stage III: unplanned surgical/catheter interventions, cardiac arrest, ECMO.
- Stage II/Stage III: mechanical ventilation time, cardiopulmonary bypass and deep hypothermic circulatory arrest/regional cerebral perfusion times, ICU/hospital length of stay, delayed sternal closure, use ECMO, and unplanned surgical/catheter interventions.

Medical history data:

- Treatment with heart failure medications, (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers), treatment for pulmonary hypertension, use of anticoagulants.
- New diagnoses: stroke, plastic bronchitis and protein losing enteropathy will be recorded.
- Weight and height will be measured at the time of the CMR and/or the exercise test.

Procedural history data:

- Unanticipated interventions: catheterization or surgery, (pacemaker implantation, stent implantation, Fontan revision, etc.), use of mechanical circulatory support, and lack of Fontan completion will be noted.

Socioeconomic (SES) data from the SVR and SVR II studies will be included as possible covariates in models for survival and ND outcomes. Educational status of the child, family structure, and language spoken in the home will be collected. In addition, maternal education level and current address information to determine census block variables such as percent within the census block living below the poverty level, will be collected at the time of ND evaluation to allow us to determine and adjust for the contribution of these factors to survival and ND outcomes at 11 years of age.

4.3.4. Schedule of Measurements

Table 2

Measurement	11 ± 1 years*	Annually to 16 years	One time visit after turning 16 years
Vital Status/Medical History including incidence of rhythm abnormalities	X	X	
CMR	X		
Echo	X		
Ramped Cycle Exercise Test	X		
ND Battery	X		
Biorepository Sample	X**		
Vital status			X

** or at study enrollment if >12 years at enrollment

* Included only if no prior adequate sample

4.4 Study Visits

All measures specifically performed for the SVR III protocol will be performed at study enrollment, ideally within a 2 year window defined by 11 years of age ± 1 year; however subjects can be enrolled at any time there is interest in participation up until September 30, 2020. As described above, the optimal window for the CMR and echo is within six months of one another, and comparison of these measures will only be performed if there has been no intervening cardiac operation or interventional catheterization. For those subjects who choose to complete the in-person evaluations within two consecutive days, Figure 1 demonstrates a reasonable schedule for accomplishing this.

Figure 1: Preferred Schedule of In-Person Evaluations

	8A	9A	10A	11A	12P	1P	2P	3P	4P
Day 1	Cardiac MRI		Exercise Test		Lunch		Echo		
Day 2	ND Battery				Lunch		ND Battery cont.		

Vital status and medical history will be performed annually beginning at age 10 years and through the conclusion of the study. The oldest participants will be 16 years of age at the time that the youngest participants reach the conclusion of the study window. An additional visit will

occur in 2024-2025 to identify vital status for all eligible to participate; all SVR survivors will be contacted to identify vital status, current contact information, location of current medical care, and potential questions they would like answered through further study.

4.5 Repeat Study Evaluations

If any of the evaluations are deemed incomplete either at the clinical site if the relevant imaging core lab assesses and finds that the images are inadequate, the evaluation may be repeated by the site if the patient, family and site personnel all agree to repeat the assessment.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Subject Inclusion:

All SVR study cohort members will be contacted to assess for vital status. Transplant free survivors will be approached to participate in the in-person assessment.

5.2 Subject Exclusion:

We will exclude patients who have undergone cardiac transplantation or biventricular conversion from all outcomes other than vital status. Those with pacemakers will be excluded from the CMR, and patients unable to comfortably reach the exercise bike pedals enough to effectively pedal the cycle ergometer will be excluded from the exercise test.

5.3 Subject Withdrawal Criteria

Subjects may withdraw from the study at any time if:

- Subject, parent, or legal guardian declines further participation.
- The investigator or physician judges that it is in the subject's best interest to withdraw from the study.

If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review of vital status and medical history outcomes unless the subject specifically refuses such follow-up.

5.4 Subject Availability

Through the SVR and SVR II studies vital status has been collected annually for the entire SVR cohort. As of June 2014, 352 subjects were alive, 18 had undergone cardiac transplantation, and 3 had undergone biventricular conversion, leaving 331 transplant-free survivors with single ventricle physiology. Conservatively assuming only 80% retention of this cohort secondary to additional mortality, transplantation or loss to follow-up, we anticipate at least 264 participants will be available for this study to participate in the proposed protocol.

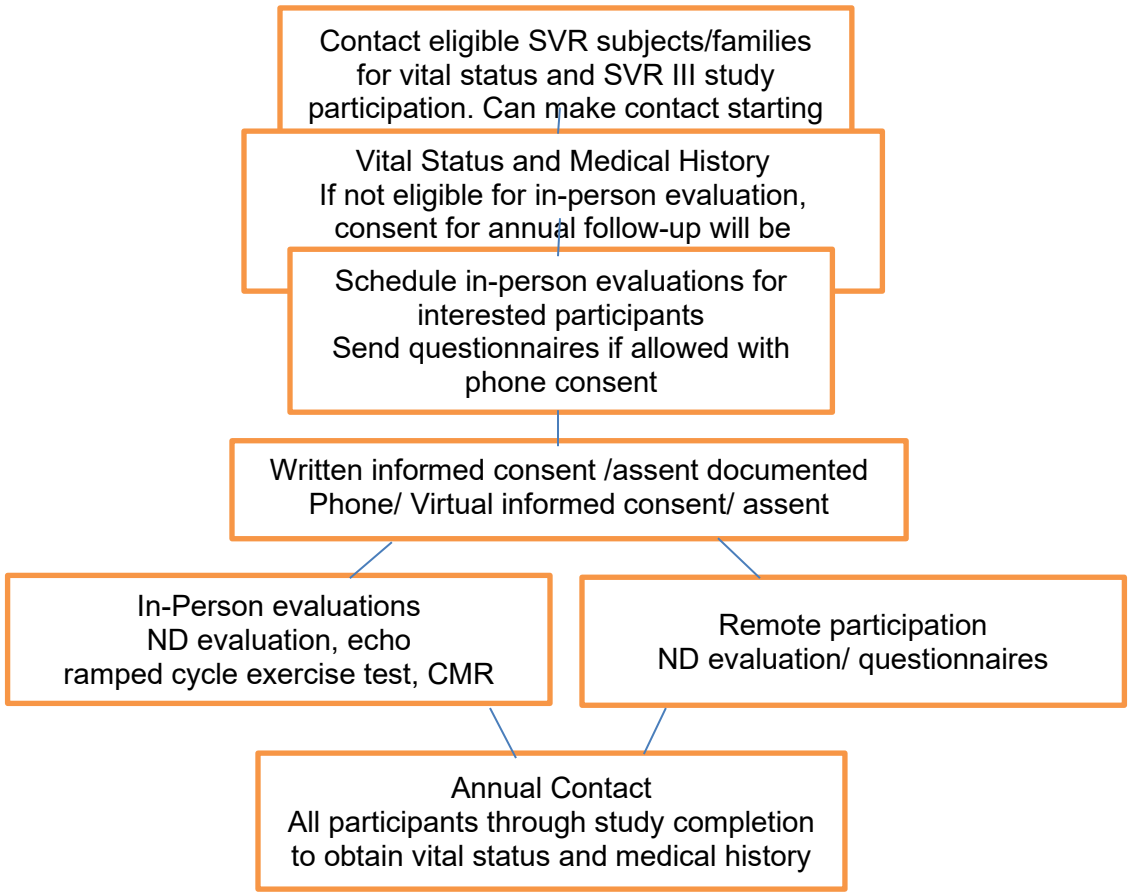
5.5 Recruitment/Enrollment Procedures

The ideal study window will extend from 10 to 12 years of age for each participant (11 years ± 1 year), but subjects can be enrolled at any time there is interest in participation up until September 30, 2020. The Principal Investigator (PI) at each site, his or her designees, and the study coordinator will be responsible for subject recruitment. Parents/guardians of participants will be contacted by the team up to 6 months prior to the opening of the study window to introduce families to the study and to coordinate participation in all relevant portions.

Consents for the SVR and SVR II studies include ongoing permission to contact the families up to patient age 11 years. A letter will be mailed out to the families of eligible participants briefly describing the SVR III study. After approximately 2 weeks, we will telephone or email potential participants to discuss the study and address questions. The consent document will be mailed out to each family who has expressed interest in SVR III participation and the information will be reviewed subsequently by phone by the site PI and /or the research coordinator. Subjects may also be contacted in person at the time of a clinic visit at the study center. Data on all screened subjects will be entered into the screening log.

Initial consent, enough to schedule the evaluations, will be granted by interested families over the phone or in-person if contacted through the clinic. Neurodevelopmental questionnaires can be completed in advance of the study visit based upon this initial phone consent. If an in-person signature is required prior to completion of parent and /or teacher questionnaires by a site, then these questionnaires can be completed at or after the in-person evaluation. The written consent and assent documents will be reviewed in person with the parent/guardian and patient by the site PI/study coordinator and will be signed in person. If the interested subject/ families are interested in remote participation only, consent will take place over the phone or virtually depending on the sites approved procedures.

Figure 2: Approach to Consent and Study Retention



Details of the Consent/Assent Process:

The consent process may vary slightly depending on the specific site. In general, we anticipate a multistep process:

1) A letter will be mailed to each survivor of the SVR cohort to briefly describe the SVR III study and plans for contact.
2) After two weeks, the family will be contacted via telephone or email to address questions and assess general interest in SVR III.
3) If the participant has undergone a transplant, consent will be mailed to renew the plans for annual follow-up for vital status.
4) If the participant is eligible and interested for the in-person SVR III study, appointments will be scheduled for the in-person evaluation in accordance with the needs of the family, and dependent on the institutions guidelines for in-person visits based on the COVID-19 pandemic.
5) If the participant is eligible and interested in remote participation in SVR III study, phone/ virtual consent and discussion on what study events to be done remotely (ND Questionnaires, annual follow-up for vital status) will be held.
6) All questions from the parent/guardian and participant related to study participation will be thoroughly addressed by the site PI, his or her designees, and/or the study coordinator prior to signing and documentation of the informed consent/assent documents.
7) All signatures and dates will be accurately documented. Any errors will be noted in a note or memo. If mistakes have occurred re-consent/ re-assent may be performed if necessary.
8) Neurodevelopmental questionnaires can be completed before the actual visit and delivered to the study team at the time of the in-person evaluation based on phone consent. They can also be completed at or after the time of the in-person visit and mailed to the study team.

6. SAFETY ASSESSMENTS AND MONITORING

6.1 Specification of Safety Parameters

All individuals eligible for participation have single ventricle physiology and are recognized to be at risk for exercise intolerance, declining ventricular function, and arrhythmias. The small increased risk to study participation is described in detail in Section 11. Any complication during a study evaluation or change in function occurring within 24 hours of a study evaluation, will be considered an adverse event and reported as described below.

6.2 Recording and Reporting Adverse Events

This study is not an intervention study. However, a major component of safety monitoring is ascertainment and reporting of adverse events (AE), including adverse reactions to study procedures. The approach to these activities for this study is summarized in the sections that follow.

6.2.1 Definitions of Adverse Event, Suspected Adverse Reaction and Adverse Reaction

For the purposes of this study, adverse events will include any untoward event that occurs to the child participant during or within 24 hours of any study-related evaluation including the CMR, echo, ramped cycle exercise test or battery of neurodevelopmental assessments.

6.2.2. Classification of Adverse Events

Monitoring AEs requires that they be classified as to seriousness, expectedness, and potential relationship to the study, of which drive the reporting process.

a. Seriousness

A serious adverse event (SAE) is one that:

- Results in death,
- Is life-threatening (the subject was, in the view of the PI, in immediate danger of death from the event as it occurred),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is an important medical event that may jeopardize the subject or may require medical/surgical intervention to prevent one of the serious adverse event outcomes.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 MedDRA 12.1 (http://ctep.cancer.gov) provides a grading system that is used to categorize the severity of adverse events, as follows:

Grade 1	Mild	transient, requires no special treatment or intervention, does not interfere with daily activities
Grade 2	Moderate	alleviated with simple treatments, may limit daily activities
Grade 3	Severe	requires therapeutic intervention and interrupts daily activities
Grade 4	Life-threatening Or disabling	
Grade 5	Death	

A SAE, as defined above, encompasses CTCAE grades 4 and 5, and any Grade 3 event that requires or prolongs hospitalization, or that substantially disrupts the ability of the subject to conduct normal life functions.

b. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- *Unexpected*: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, or consent form. An AE or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.
- *Expected*: An event is considered expected if it is known to be associated with the particular evaluation. Expected adverse events could include 1) falling from the bicycle exercise test, 2) developing an arrhythmia during exercise testing, 3) anxiety during the CMR, and 4) frustration at the time of the neurodevelopmental testing.

c. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- *Not Related*: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.
- *Possibly Related*: The event follows a compatible temporal sequence from the time of study evaluation, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.
- *Probably Related*: The event follows a reasonable temporal sequence from the time of study evaluation, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

6.2.3. Identification and Data Collection Procedures

AEs that are not considered adverse reactions or suspected adverse reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

6.2.4. Reporting Procedures (Table 3)

Fatal or life-threatening AEs are to be reported to the Data Coordinating Center (DCC) within 24-hours of first knowledge of the event. Those that are unexpected and considered possibly, probably, or definitely related to the study will be reported by the DCC to the Data Safety and Monitoring Board (DSMB) Chair, the Medical Monitor (MM), the National Heart, Lung, and Blood Institute (NHLBI), and all study Investigators as soon as possible, but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15 calendar days. All other fatal or life threatening events that are unrelated to the study will be reported semiannually to the DSMB and the NHLBI.

All other *SAEs (i.e., non-fatal or not life-threatening)* that are unexpected and considered possibly, probably, or definitely related to the study will be reported to the DCC within 24-hours of learning of the event. The DCC will report the event to the NHLBI, DSMB and all study Investigators within 15 calendar days after first knowledge of the event.

All other *AEs* not meeting the criteria for expedited reporting will be reported to the DCC within 7 calendar days of first knowledge of the event. The DCC will report these AEs quarterly to NHLBI.

Table 3. Reporting of Adverse Events

Seriousness	Reporting Timeframe
Fatal or life threatening	Within 24-hours of learning of the event
Serious, but not fatal or life threatening, and pregnancy	Within 24-hours of learning of the event
All other	Within 7 calendar days of learning of the event

6.2.5. Reporting Adverse Events to Institutional Review Boards (IRB) for National Institutes of Health (NIH)-Supported Multi-Center Clinical Trials

The site Investigator or designee is responsible for reporting all serious adverse events to the local IRB in accordance with local policies and procedures.

6.2.6. Follow-up of Subjects after Adverse Events

For AEs with a causal relationship to the study conduct, follow-up by the PI is required until the event or its sequelae resolve or stabilize at a level acceptable to the PI.

6.3 Safety Monitoring

The Data and Safety Monitoring Plan for this trial will follow standard PHN monitoring principles. Oversight of data and safety is provided by the PHN DSMB, appointed by NHLBI. The DSMB meets at least twice a year to review data on AEs, adverse reactions, suspected adverse reactions, patient-reported outcomes, data quality, and study recruitment at regular intervals, and makes recommendations about study conduct to the Director, NHLBI.

The DSMB and NHLBI are assisted by a MM in reviewing serious adverse events in PHN studies. The PHN MM is the NHLBI's designee for determining causality and expectedness of all SAEs.

7. STATISTICS

7.1 Analysis Plan

The surviving participants and non-participants will be compared to assess representativeness of the SVR III cohort. The primary comparison of outcomes between shunt types will be performed according to the intention-to-treat principle. Secondary analyses of each aim will be performed using non-intention to treat, defined as the shunt in place at the end of the Norwood operation.

7.1.1. Analysis of the Primary outcome for Primary Aim: *To compare cardiac function at 11 years of age between subjects randomized to receive either of a RVPAS vs. a MBTS at the time of the Norwood operation*

RVEF as measured by CMR is the primary outcome for this study. Descriptive statistics will be presented across all patients and by randomized shunt type. Distribution of the RVEF will be examined with histogram and compared by shunt type with either a Student's t-test or a Wilcoxon rank sum test as appropriate. If the distribution of RVEF is found to be skewed or otherwise non-normal, non-parametric tools will be used or RVEF will be transformed appropriately to obtain a close to normal distribution.

7.1.2. Analyses of Secondary Outcomes

7.1.2.a Additional Measures of the Primary Aim

For all additional CMR and echo measures related to Aim 1, the distribution of each measure will be assessed. Continuous measures will be compared between randomized shunt types with either a Student's t-test or a Wilcoxon rank sum test as appropriate. Categorical measures will be compared with a Fisher exact test, Chi-square test or the Mantel-Haenszel test for trend.

In addition, subjects with CMR and echo performed within a 6 month window without an intervening cardiac procedure will be selected to assess the agreement between the two techniques. The continuous measures will be compared using Bland-Altman limits of agreement and Pearson's correlation coefficient. The Kappa statistic will be used to evaluate the agreement in the categorical measures in Echo and CMR.

7.1.2.b Secondary Aim 1: *To compare the long-term death/transplant rates of subjects randomized to receive either a RVPAS vs a MBTS*

Transplant-free survival rate will be calculated using the Kaplan-Meier method. The logrank test will be performed to determine if time since randomization to the composite endpoint of death or transplantation is different between the two shunt types. Cox proportional hazard regression will be used to model the time to death or transplant by shunt type; to determine if the shunt difference varies by time and to identify risk factors of the endpoint.
In addition, nonparametric competing-risks methodology will be used to estimate the cumulative incidence rate of death and transplant. Proportional subdistribution hazards model will be fit to assess the effect of covariate on death and transplant in a competing risk setting.

7.1.2.c Secondary Aim 2: *To compare exercise tolerance between those randomized to receive a RVPAS vs a MBTS*

VO_2 max, work rate VAT and items 4-11 from section 4.3.2.b, from ramped cycle ergometry will be compared between the two shunt groups. The distribution of the variable will be determined with descriptive statistics. If the variable is normally distributed, Student's t-test will be used to compare shunt groups. If non-parametric, then Wilcoxon Rank-Sum will be used.

7.1.2.d Secondary Aim 3: *To compare the incidence of atrial and ventricular arrhythmias between those randomized to receive a RVPAS vs a MBTS at the time of the Norwood operation*

Arrhythmias will be classified as atrial tachyarrhythmias or ventricular tachyarrhythmias. The rate of atrial and of ventricular tachyarrhythmias will be compared between the shunt groups with the Fisher exact test.

7.1.2.e Secondary Aim 4: *To compare neurodevelopmental outcomes at 11 years of age in subjects randomized to a RVPAS vs MBTS*

Descriptive statistics will be performed for each scale included in the ND battery. Student's t-test will be used to compare normally distributed measures, Wilcoxon Rank-Sum for non-parametric continuous measures and Fisher exact test for all dichotomous measures. Adjustment will be included for measures of socioeconomic status.

7.1.2.f Secondary Aim 5: *To determine if early perioperative events other than type of systemic to pulmonary artery shunt are related to long-term outcomes*

To determine if early events after the Norwood operation are related to long-term outcomes, comprehensive models will be explored for each of the primary outcome measures for each aim (RVEF by CMR, transplant-free survival at 11 years, VO_2 max at ramped cycle ergometry, incident atrial tachyarrhythmias, incident ventricular tachyarrhythmias, Wechsler full scale IQ, and Language and Math Achievement Tests). Candidate predictors for these models will include previously collected early events and additional medical and surgical variables since the last SVR/SVR II contact.

7.2 Number of Subjects to be Enrolled

The proposed study is a prospective observational design of a previously determined, fixed cohort. Out of the 549 subjects randomized in the original SVR trial, 334 subjects are currently alive, free from heart transplant and 331 have single ventricle physiology. Study sample size will depend on the ability to contact families and on the consent rate for contacted subjects. Conservatively assuming 80% retention of this cohort (N=265) and 10% excluded from the primary measure of RVEF by CMR, either because CMR is not possible due to a pacemaker or because CMR data are not obtainable without general anesthesia or sedation, we anticipate the

primary outcome will be collected and adequate for 239 participants. If there is 90% retention and 10% without CMR, the primary outcome will be obtained in 269 participants.

7.3 Level of Significance

We anticipate that by 11 years of age the overall rate of transplant free survival will be approximately even between the two shunt groups. However, if even 60% of survivors are from one shunt group, with 239 total eligible participants there is 85.5% power to detect a 4% absolute difference in RVEF between the two groups (Table 4). If total N=269, there is 80% power to detect a 3.5% mean absolute difference in RVEF between groups. If the transplant-free survival rates in the two shunt groups are closer, then all power estimates in Table 4 increase by 1 percentage point. Thus, the proposed study has ample power to detect effect sizes smaller than one-half of a standard deviation, which is typically considered to be a minimum clinically significant effect.

The exercise aim will also be amply powered; utilizing the above assumptions and a SD=16 for percent predicted VO_2max there is approximately 85% power to detect a 6% point difference between groups (e.g., 57% for RVPAS vs. 63% for MBTS).

The key secondary outcome of long-term transplant-free survival is hypothesized to be lower in the RVPAS group, although the difference may not be large. The size of the original SVR trial cohort limits our ability to detect true survival differences that are very small. The proposed study, with 10-16 years follow-up per participant depending on time of enrollment into the original trial will have approximately 80% power using a logrank test to detect a hazard ratio of 0.67. For example, after accounting for loss to follow-up and shunt crossover, a transplant-free survival difference of 13% (50% vs. 63%) at study end will be detectable.

Table 4. Power to Detect RVEF Mean Differences of 0.5-3% points by Shunt Type (Assuming Total Evaluable RVEF Sample Sizes of N=239 and N=269, SD=10*, Two-Sided α=0.05).

Group N		Mean RVEF		Power
MBTS	RVPAS	MBTS	RVPAS	
Assuming 80% retention, 10% without CMR				
143	96	55	50.0	96.5%
143	96	55	50.5	92.5%
143	96	55	51.0	85.5%
143	96	55	51.5	75.2%
143	96	55	52.0	62.0%
Assuming 90% retention, 10% without CMR				
161	108	55	50.0	98.0%
161	108	55	50.5	95.0%
161	108	55	51.0	89.3%
161	108	55	51.5	80.1%
161	108	55	52.0	67.1%

*SD based on Fontan Cross-Sectional Study data, RV subgroup

7.4 Interim Analyses and Stopping Rules for Termination of the Study

As this is an observational study and inclusion of the entire cohort will be valuable, there are no preconceived stopping rules for early termination of the study. However, we would like to reserve the right to look at an interim analysis at some time point such as when all participants have reached 10 years of age (2018). Premature termination of this study may occur because of a regulatory authority decision, or withdrawal of study approval by clinical site IRBs, In addition,

NHLBI retains the right to discontinue the study prior to the inclusion of the intended number of subjects, but intends to exercise these rights only for valid scientific or administrative reasons.

7.5 Spurious Data Procedures

Consistency checks and range checks will be built into the data management system. This will allow many errors to be identified and corrected at the time of data entry. Queries regarding any problems with data will be sent to site coordinators regularly throughout the course of the study. Sites will also be monitored during the study. Therefore, spurious data are expected to be rare. Any data which are judged by the MM to be definitely incorrect, and which cannot be resolved, will be set to missing.

The study report will indicate the number of subjects who have missing data on each study endpoint. For covariate-adjusted analyses, the number of subjects who have missing data on the covariates will be reported.

Throughout the study, the rate, timing, and reasons for subject withdrawal will be monitored by site and treatment arm. Any site with a pattern of differential withdrawal by treatment arm will be queried. If necessary, retraining will take place or the site may be barred from enrolling additional subjects to the study.

7.6 Deviation Reporting Procedures

Any modifications or deviations from the statistical plan described in this protocol will be documented in a "Revised Statistical Plan" document.

7.7 Subjects to be Included in Analyses

All participating subjects will be included in the appropriate analyses, though only participants who have undergone CMR will be included in the analysis for the primary outcome measure of CMR RVEF. The participants who have not had a CMR will be included in analyses related to the secondary outcomes of the primary aim.

8. DATA MANAGEMENT

An Electronic Data Capture (EDC) system will be used for the study that is designed to support reliable and secure data entry for clinical research purposes. The system also provides seamless integration of eCRFs and paper-based CRFs within a single protocol if desired; implementation of protocol amendments; and SAS and XML study data exports.

8.1 Data Entry

Data can be entered directly from multiple study sites via a fully validated and 21 CFR Part 11 compliant, secure Web application and stored centrally. A configurable sample-based double data entry system is available. Data are entered by subject study identification number; names will not be linked with subject data in the database. Study sites will maintain records in secure areas linking the subject name with the identification number assigned for the study. Study sites will have full access to their own data and be able to view these data remotely. Study staff will not be able to view subject data associated with other sites.

8.2 Data Validation and Monitoring

Integrated into the data entry system are real time validations, including both inter- and intra-instrument data checks. Inconsistent or questionable values are flagged during entry, and an edit report is automatically generated to the data entry client. These edit reports provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values. Second level query tracking allows monitors and data managers real time access to unresolved queries as well as the date and time of query generation and resolution.

8.3 Data Security and Integrity

All data changes are written to an audit trail. The audit trail identifies the data item by table, column and key field. The entry includes the user, date and time, as well as the old value and new value. Both patient related data as well as trial configuration data are written to the audit trail. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection. In the unlikely event of a major disruption, a backup connection allows full access to the DMS.

Several levels of security are employed to ensure privacy and integrity of the study data, including the following: Study access requires use of assigned user names and passwords. Individual roles and access levels are assigned by the study data manager. Passwords are changed regularly. Web-based entry uses secure socket layer data encryption. Data will not be stored on laptop computers.

9. QUALITY CONTROL AND QUALITY ASSURANCE (QC/QA)

The DCC has primary responsibility for QC/QA activities of the phenotypic data. The DCC also requires that the sites complete certain QC activities, most of which are monitored by the DCC.

The key QC/QA activities are:

- Development of a Study Manual;
- Clearly formatted and carefully constructed Data Forms with clear, up-to-date manuals of instruction;
- Sign-Off Procedures for all CRFs;
- Central protocol training and certification of all site data collection staff with the use of standardized checklists;
- Data management training and certification of site personnel completing data entry and/or data management;
- Verification of patient eligibility;
- On-going monitoring of all protocols/data collection activities;
- Completion of reliability and/or pilot studies for key measurements as appropriate;
- Inclusion of repeat measurements, as feasible, in the course of the study; and
- Monitoring visits to sites as required with pre-specified goals and/or remote monitoring activities.

The DCC may conduct site visits to the Core Laboratories to review QA and QC procedures and data transfer to the DCC. Review of central laboratory-related reports will be conducted at least monthly to identify overall or site-specific problems in data or specimen acquisition and reporting of results.

10. ETHICS AND HUMAN SUBJECTS CONSIDERATIONS

10.1 Potential Risks and Protection Against Risks

Clinical data collection: CMR, Echo, Exercise test, ND battery

For the CMR protocol, procedural risks will be reduced by avoiding use of anesthesia/ sedation or intravenous access. Participants may experience anxiety or claustrophobia in the CMR scanner. This will be limited by availability of entertainment/distraction whenever possible.

The exercise protocol risks are limited, but there is a very small risk of arrhythmia or of low cardiac output related to strenuous exercise. A trained exercise technician will be present throughout the exercise test and cardiac monitoring of the rhythm will be performed throughout the course of the exercise test.

There is no procedural risk to echocardiography or to neurodevelopmental testing. All of the evaluations will require time and thus pose some inconvenience. It is also possible that the participant may become frustrated with the neuropsychological battery, however subjects will be given breaks as needed, and the battery will be administered by an individual trained in the testing of children from a full developmental range and under the supervision of a psychologist.

Biorepository samples will be obtained from saliva samples and thus there will be no physical risk of bruising, bleeding or discomfort.

There is some inconvenience and burden of completing ND questionnaires and some families may feel uncomfortable answering questions. The parent-completed questionnaires will require approximately 85 minutes to complete. In addition, teachers will be contacted and asked to complete two questionnaires. We will aim for questionnaires to be completed prior to the in-person assessment; however, there will be little time pressure required for the completion of the instruments by the parents and teachers as they will be mailed out to parents approximately 3 months prior to the appointment for the in-person evaluation, after initial telephone informed consent.

Clinical testing, including CMR, echo, exercise testing and the administration of the ND battery will be performed by professionals trained to avert risks.

10.2 Confidentiality

Investigators will take all reasonable measures to protect the confidentiality of subjects and their families, including the following:

a) Each subject is assigned a subject identification number (SID). All interview and clinical research data are stripped of identifiers and labeled with the SID. The enrollment log with participant identifiers will be maintained at each site in a secured, locked location available only to the study staff. The informed consent form states that study data will be made available to the DCC and NIH/NHLBI to ensure study safety and QC. The subject's name and any other identifying information will not appear in any presentation or publication resulting from this study.

b) All echoes and CMRs sent to core labs for analyses will be de-identified prior to the data leaving the clinical site. If an incidental finding is found on a study clinical test such as a CMR, or echo, the PI or other qualified member of the research team will take full responsibility for disclosing the findings to the patients/parents, communicating with their primary cardiologist with permission, or making appropriate cardiology referrals as indicated. The subject may choose to seek a second opinion and/or appropriate clinical care. This might change the subject's insurability and employability as it relates to the clinical finding only. The presumption is that detection of a potentially clinically significant finding will prove to be beneficial.

c) Parents will be asked for permission to approach their child's teacher. In the cover letter accompanying the questionnaire instruments, minimal diagnostic/personal information will be shared about the child to explain the benefit of the teacher's participation. By allowing contact, and providing the teacher's name, parents will be granting permission for sharing of this information.

Confidentiality of biorepository samples will be protected as follows:

a) Biological specimens (DNA) will be assigned a repository identification number without other identifying information. All research related information will be maintained in a system completely separate from the hospital's medical record system. Informed consent will state that the subject's data will be made available to the DCC, NIH/NHLBI, IRB and DSMB if necessary for assessment of study safety.

b) To help to protect the privacy of subjects participating in the biorepository, we have a Certificate of Confidentiality. With this Certificate, the researchers of this study cannot be forced to disclose information that may identify a subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The Certificate cannot be used to resist a request for information from the United States government when it is used for evaluating federally funded study projects or for information that must be disclosed to meet the requirements of the Food and Drug Administration (FDA). A Certificate of Confidentiality does not prevent a subject or his/her family from voluntarily releasing information about the subject's involvement in the research. If an insurer, employer, or other person obtains a subject's or family's written consent to receive research information, then the researchers will not use the Certificate to withhold information.

c) Information from DNA analyses and clinical studies or medical records may be placed into a central biorepository in the future such as the National Center for Biotechnology Information (NCBI) repository. The purpose of a central data biorepository is to help researchers work together to learn about ways in which genes affect disease. The NCBI or a similar repository makes data accessible through the Internet. The NCBI repository has two databases, open access and controlled access. The open access database is available to anyone on the Internet and includes DNA sequence traces that are not linked to medical or personal information. The controlled access database includes de-identified medical information and more detailed analyses of de-identified samples that are made available to researchers with IRB approval to conduct human genetic studies and who have received approval from an NIH Data Access Committee.

d) The results of the future tests will not be released to the subject/family. At the end of the study, the results of the genetic testing may be published for all the subjects as a group, but it will not be possible to provide results for an individual subject and medical management will not be changed based on individual results. There is a reasonable possibility that no findings will result from this research effort. If findings are detected it may be years before any utility of these findings are realized. Further if samples are "anonymized" prior to release to other investigators for research, it may not be possible to trace the results back to the subject.

Global Unique Identifiers: A unique subject number, called a Global Unique Identifier or GUID, will be assigned to each study participant. The GUID is a universal subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII) and at the same time be able to match participants across labs, databases or research studies. Personal information does not leave the research site, only a unique set of encrypted codes that are then decrypted to determine if the subject already

exists within the data repository. The GUID is then sent to the enrolling site. This process is the same one used by the National Database for Autism Research. The GUID will allow data from this study to be combined with data from other research studies or databases in an effort to improve outcomes in children and young adults with heart disease.

10.3 Potential Benefits

It is possible that the clinical assessments obtained for research purposes, including the CMR, echo, exercise test, and ND evaluation, may reveal important clinical findings. Families will receive a written report on the ND evaluation that will explain the results and will include recommendations for follow-up if appropriate. Such findings may lead to valuable intervention to improve outcomes for the participant. Results of each of the evaluations will be reported to the subject's cardiologist, and the subject's family will be informed about the transfer of information.

There might be an indirect benefit from the awareness that study results may help to improve the care of children with similar problems in the future. Families may derive a sense of altruism, accomplishment, and contribution to furthering understanding of the problem through their participation.

Currently, there is no known direct benefit from provision of biospecimens by the subject and family. The indirect benefit comes from the potential knowledge about the relationship between genetic factors or biomarkers and longer-term cardiac and neurodevelopmental outcomes. This information may help physicians provide better answers to families' questions regarding causes, risk, and recurrence risks. It may also inform the development of future interventions and/or treatments.

The research using samples and data from the biorepository may result in inventions or discoveries that could create new tests and medicines that have commercial value. Although subjects and their families will not receive compensation now or in the future for their samples or data, income that may be derived from future research or sales of the grouped data may be used to support biomedical research, providing societal benefit and thus may be a benefit to participants and families.

10.4 Risk/Benefit Ratio and Importance of Information to be Obtained

The risk/benefit ratio is favorable for this study, for the following reasons:

1. The baseline risk is minimal because there are no therapeutic interventions. In addition, although an individual subject may not benefit from participation, the results of this study will make important contributions to the design of an optimal management algorithm for infants with single ventricle.
2. The assessments of RV function address important long-term concerns regarding the potential negative effects of a ventriculotomy on the single right ventricle following the RV-to-PA shunt.
3. Extending the length of follow-up of the SVR study up to 11 years to assess right ventricular function and to obtain the incidence of death or cardiac transplantation is crucial to evaluating the potential survival and functional benefit of the RV-to-PA connection.
4. Neurodevelopment and functional status are critical determinants of the child's well-being and have never been studied in such a large population of children with single ventricle, or in a longitudinal fashion. The in-person evaluation proposed in this study, compared to the questionnaires used at the 6-year evaluation, will provide more accurate and richer information about development for use by families and schools.

5. The assessment of the incidence of arrhythmias will address important long-term concerns regarding the potential promotion of ventricular arrhythmias by the ventriculotomy required for the placement of the RV-to-PA shunt.
6. The assessment of exercise capacity will address long-term concerns related to the potential effects of the ventriculotomy on the function of the single right ventricle.
7. Data generated from this study will be unique in terms of the breadth and depth of the guidance that can be provided to parents and medical care providers of children with univentricular hearts who have undergone the Norwood procedure.

11. STUDY LIMITATIONS

The study of the long-term outcomes of this well-defined inception cohort is essential and imperative to discern the optimal shunt type at the Norwood operation for children with HLHS and other related single RV anomalies. Nonetheless there are some limitations to this study that are important to recognize. The primary outcome measure for this study is ventricular function measured by CMR. We anticipate that approximately 7-8% of the SVR cohort will have had pacemakers placed by the age of 10.5 years and will therefore be unable to undergo CMR. Despite the fact that this group will be excluded from the primary aim, we anticipate that we will still have 85% power to detect a 4% absolute group difference in RVEF. In addition, 2D echo will also be utilized to assess RV function. While this is an imperfect tool, no participants will be excluded from the potential in participating in this portion of the evaluation.

To avoid bias, all team members responsible for measurement/interpretation will be blinded to the assigned shunt type at the Norwood. It is possible that Echo and MRI Core Lab readers will be able to deduce which shunt was used based on review of images.

This study will require the coordination of multiple evaluations and the return of participants to their original surgical site for 1.5-2 days. While this will require a significant commitment for families, this cohort of children with HLHS and their families are invested and motivated; a survey of this cohort revealed that at least 88% of families are interested in returning for follow-up for assessment in a SVR related study (9% responded they were unsure and only 3% denied interest; Lynn Sleeper-personal communication, 8-5-2013), and have expressed interest in returning to the surgical site even in cases when travel will be essential.

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