TRIAL OF RIGHT VENTRICULAR VS. MODIFIED BLALOCK-TAUSSIG SHUNT IN INFANTS WITH SINGLE VENTRICLE DEFECT UNDERGOING STAGED RECONSTRUCTION (SINGLE VENTRICLE RECONSTRUCTION TRIAL)

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OVERVIEW (ABSTRACT)

Hypoplastic left heart syndrome (HLHS) and related single right ventricle (RV) anomalies are the highest-risk congenital cardiovascular malformations (CCVM). Surgical palliation for these patients consists of the Norwood procedure during the newborn period, a stage II procedure at 4-6 months and the modified Fontan procedure at approximately 18 to 36 months. The Norwood procedure remains one of the highest risk procedures in congenital heart surgery. Recently, improved outcomes have been reported in a few small, non-randomized studies of a novel approach to the Norwood procedure, which uses a right ventricle to pulmonary artery (RV-to-PA) shunt to provide pulmonary blood flow rather than the standard modified Blalock-Taussig shunt (MBTS). The Pediatric Heart Network's proposed multi-institutional, randomized clinical trial will evaluate early and intermediate-term outcomes for patients undergoing a Norwood procedure with either the RV-to-PA shunt or MBTS.

Infants with a diagnosis of single, morphologic right ventricle anomaly will be eligible for inclusion in this study. Participants will be randomly assigned to receive either a MBTS or RV-to-PA shunt, with randomization stratified by aortic atresia (presence or absence) and obstructed pulmonary venous return (presence or absence). Dynamic allocation will be used to ensure treatment arms are balanced across surgeons. Data will be collected at discharge from the Norwood procedure, prior to the stage II procedure (at approximately 6 months of age), and then again at 12 and 14 months post-randomization. The primary aim of the study will be to compare the effect of the MBTS to that of the RV-to-PA shunt on the rate of death or cardiac transplantation 12 months after randomization. Secondary aims include post-operative morbidity following the Norwood and stage II palliation procedures, RV function and pulmonary artery growth at the time of the stage II palliation, and neurodevelopmental outcome at 14 months. The incidence of adverse events will also be compared between the treatment groups. The total sample size target is approximately 554 participants and the accrual period will continue until the target is reached, estimated to be up to 39 months.

A. SPECIFIC AIMS

Patients with HLHS and other single RV conditions constitute the highest-risk group of patients with congenital cardiovascular malformations; 20 years ago, these conditions were uniformly fatal. The Norwood procedure transformed care of these patients but hospital mortality remains as high as 24% (1). Post-operative deaths can occur in patients who are clinically gravely ill, or unexpectedly, in patients who appear to be making an uneventful recovery (2-4). Furthermore, among infants who are discharged from the hospital, 4-15% die between their first and second palliative procedures (4, 5). In the classic Norwood procedure, pulmonary blood flow is provided by a MBTS, which shunts blood from the innominate or subclavian artery to the pulmonary arteries via a small polytetrafluoroethylene (PTFE, GoreTex™) tube. Although the exact cause of death in both the hospitalized and discharged patients is frequently unknown, coronary arterial insufficiency secondary to the diastolic run-off that occurs with a MBTS may play an important role (2-5).

Recently, a few small, non-randomized studies have reported short-term improvements in survival with the RV-to-PA shunt to provide pulmonary blood flow following the Norwood procedure rather than the standard MBTS (6, 7). The RV-to-PA shunt has the theoretical advantage of eliminating the aortic diastolic run-off and coronary arterial steal. The long-term outcome of these patients is unknown and no data are available comparing their outcome to contemporary outcomes in patients after the Norwood procedure with MBTS. This multi-center, randomized trial will compare outcomes in patients with HLHS or other single RV anomalies who are randomized to the Norwood procedure with either a MBTS or the RV-to-PA shunt.

A.1 Primary Aim

To compare the effect of the MBTS to that of the RV-to-PA shunt on the incidence of death or cardiac transplantation.

Hypothesis: Placement of a RV-to-PA shunt will be associated with a decrease in the frequency of the combined endpoint, mortality or transplantation, when compared to the standard MBTS.

Primary outcome:

- Death or cardiac transplantation at 12 months post-randomization

Secondary outcome:

- Death or cardiac transplantation at trial end based on all available follow-up

A.2 Secondary Aim

To compare the effect of the MBTS to that of the RV-to-PA shunt on ICU morbidity after the Norwood procedure.

Hypothesis: The ICU morbidity after the Norwood procedure will not differ for patients with MBTS and RV-to-PA shunts.

Outcomes:

- Open sternum (yes or no)
- Extracorporeal membrane oxygenation, ECMO (yes or no)
- Cardiopulmonary resuscitation, CPR (yes or no)
- Time to initial extubation (hours)
- Total number of days ventilated
- Length of ICU stay (days)
- Length of hospital stay measured from day of surgery (days)

A.3 Secondary Aim

To compare the incidence of unintended cardiovascular interventional procedures after the Norwood procedure through age 12 months.

Hypothesis: The incidence of unintended cardiovascular interventional procedures during the first 12 months of life will be higher for the patients with a MBTS, as compared to those with a RV-to-PA shunt.

Outcomes:

- Balloon dilatation of the shunt or branch pulmonary arteries
- Stent placement in the shunt or branch pulmonary arteries
- Shunt revision
- Crossover between MBTS and RV-to-PA shunt
- Balloon dilatation, stent placement or surgical revision of the neoaorta
- PA reconstructions, other than those undertaken as a standard component of the stage II procedure

A.4 Secondary Aim

To compare the effect of MBTS versus RV-to-PA shunt on echocardiographic indices of RV function and measurements of the severity of tricuspid regurgitation (TR).

Hypothesis:

The indices of RV function will be superior and the degree of tricuspid regurgitation will be lower in subjects having the RV-to-PA shunt compared with those with MBTS.

Outcomes:

- Right ventricular BSA-adjusted Z-scores for diastolic and systolic volumes and age-adjusted Z-scores for ejection fraction
- Raw values for diastolic and systolic volumes and ejection fraction
- dP/dt obtained from the TR jet
- Severity of TR
- Doppler Tissue Imaging (DTI) of the RV
  - Systolic annular acceleration and peak velocity
  - Isovolumic myocardial acceleration

A.5 Secondary Aim

To compare the effect of the MBTS to that of the RV-to-PA shunt on pulmonary arterial growth by cardiac catheterization before the stage II procedure.

Hypothesis: Placement of a MBTS will result in superior pulmonary arterial growth after the Norwood procedure, when compared to the RV-to-PA shunt.

Outcomes:

- Angiographic PA cross-sectional area, as determined by the Nakata index
- Ratio of distal to proximal PA diameters measured by angiography
- Incidence of angiographic discrete PA stenosis
- Change in echocardiographic Nakata index from randomization to stage II procedure.

A.6 Secondary Aim

To compare the effect of the MBTS to that of the RV-to-PA shunt on stage II perioperative morbidity.

Hypothesis: The postoperative course after the stage II procedure will not differ between patients with the MBTS and RV-to-PA shunts.

Outcomes:

- Cardiopulmonary resuscitation, CPR (yes or no)
- Time to initial extubation (hours)
- Total number of days ventilated
- Length of ICU stay (days)
- Length of hospital stay measured from the day of the stage II surgery (days)

A.7 Secondary Aim

To compare the effect of the MBTS to that of the RV-to-PA shunt on neurodevelopmental outcome.

Hypothesis: The RV-to-PA shunt will be associated with better midterm (14 ± 1 month) neurodevelopmental outcomes when compared to the MBTS.

Outcomes:

- Bayley Scales of Infant Development II (BSID-II):
  Psychomotor Development Index and Mental Development Index
- MacArthur Communicative Developmental Index
- Functional Status II-Revised questionnaire

B. BACKGROUND

B.1 Previous Studies

B.1.1 Hypoplastic Left Heart Syndrome and Other Single Ventricle Defects

Congenital cardiovascular malformations (CCVM) are the most commonly occurring birth defects, impacting 8 per 1000 live births. Of these defects, the most severe are those with only a single functional ventricle. HLHS is the most common form of single ventricle anatomy, affecting approximately 1000 newborns in the United States each year (8). HLHS and similar single, morphologic RV lesions are characterized by an underdeveloped left ventricle, ascending aorta, and aortic arch, leaving the patient with a single functional ventricle (Figure 1). The aortic valve may be stenotic or atretic.

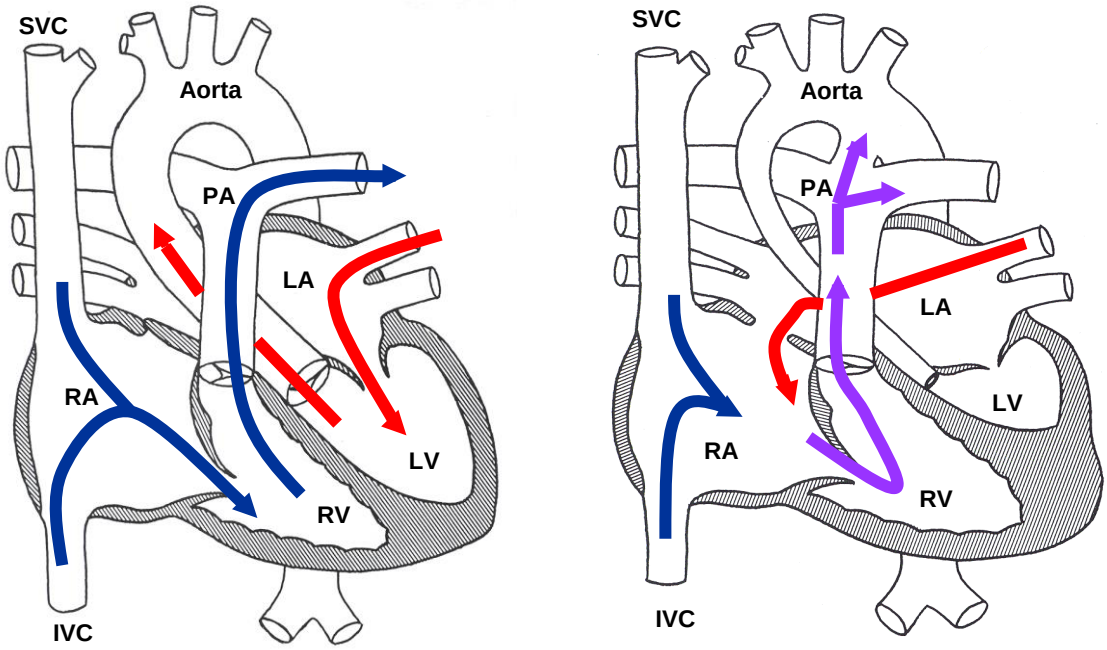
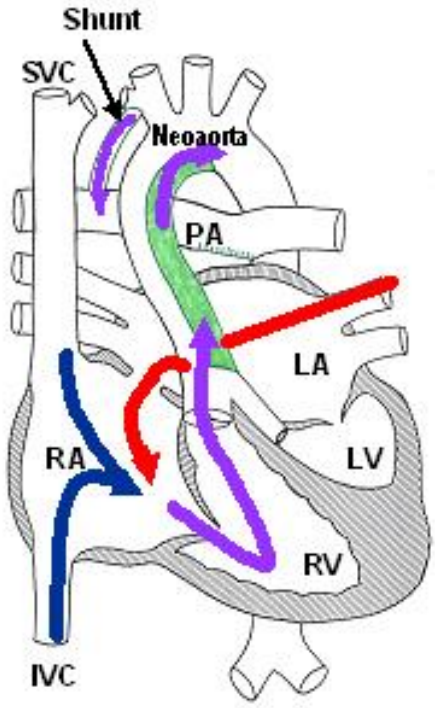


Figure 1. Normal Cardiac Anatomy **Hypoplastic Left Heart Syndrome**
(SVC-superior vena cava, IVC-inferior vena cava, RA-right atrium, RV-right ventricle, LA-left atrium, LV-left ventricle, PA-pulmonary artery)

The surgical palliation of HLHS and other single ventricle anomalies associated with aortic arch hypoplasia requires three operations. The Norwood procedure is the initial operation and is performed within the first 2 weeks of life. The Norwood procedure includes connecting the main pulmonary artery to the hypoplastic aorta and reconstructing the aortic arch (neoaorta) to allow the one functioning ventricle to supply blood to the body. For the pulmonary arteries and lungs to receive blood, a MBTS is inserted from a branch of the aorta to the pulmonary artery (Figure 2a). Alternatively, the RV-to-PA shunt can be used to provide pulmonary blood flow (Figure 2b).



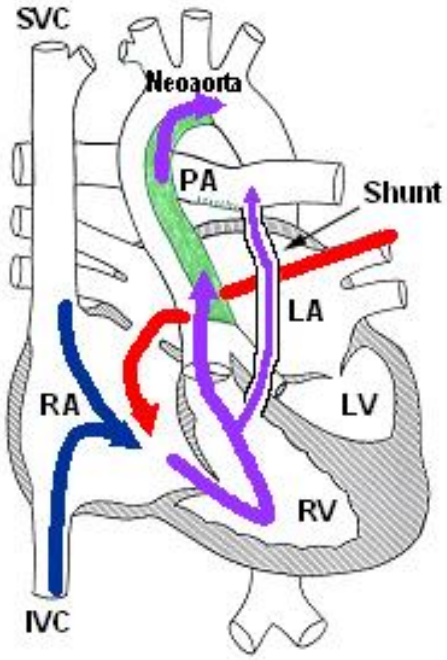


Figure 2a. The Norwood with MBTS

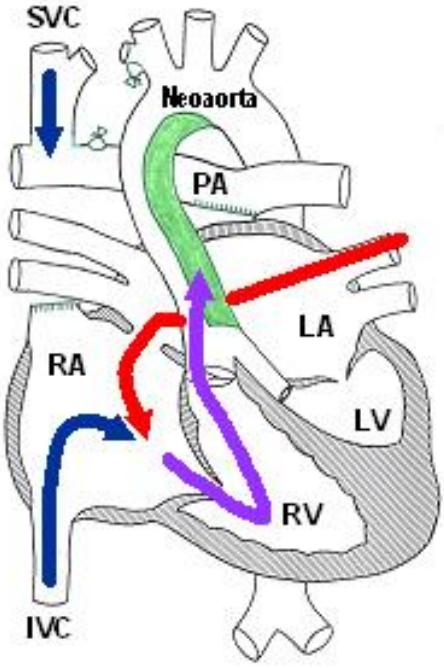


Figure 2b. The Norwood with RV-to-PA shunt

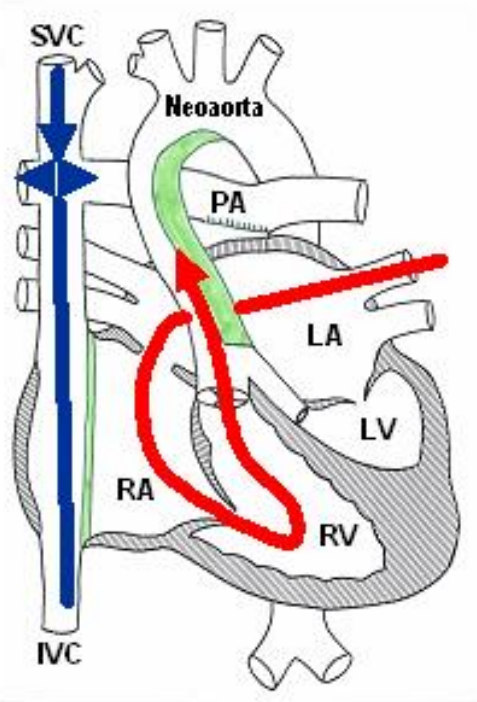


Figure 2c. The Stage II Procedure

Figure 2d. The Fontan Procedure

(SVC-superior vena cava, IVC-inferior vena cava, RA-right atrium, RV-right ventricle, LA-left atrium, LV-left ventricle, PA-pulmonary artery, MBTS-modified Blalock-Taussig shunt)

Approximately 6 months after the Norwood procedure, the infant will undergo a stage II procedure consisting of either a hemi-Fontan procedure or bidirectional Glenn anastomosis (Figure 2c). During the stage II procedure, the MBTS or the RV-to -PA shunt supplying blood to the lungs is ligated and divided. The superior vena cava is connected to the pulmonary artery. Thus, the deoxygenated blood from the upper body is rerouted through the lungs to become oxygenated before it returns to the heart. The deoxygenated blood from the lower half of the body continues to return via the inferior vena cava to the heart. The survival after stage II procedure is excellent at 98% (9).

At 18 to 36 months of age, the Fontan procedure is performed (Figure 2d). This final stage involves routing the deoxygenated blood from the inferior vena cava to the pulmonary artery. After the Fontan procedure, all of the blood returning from the body flows passively to the lungs to pick up oxygen prior to returning to the heart. The functional single ventricle pumps blood only to the systemic (body) circulation. Using current techniques, the survival after the Fontan procedure is 98% (10).

B.1.2 Mortality after the Norwood Procedure

Recent advances in surgical technique and peri-operative management have greatly improved the outlook for single RV anomalies, which were uniformly fatal just 20 years ago. Yet, despite significant gains, the Norwood procedure remains one of the highest risk congenital heart procedures, with hospital mortality as high as 24% (1). Post-operative hospital deaths can occur in patients who appear to be making an uneventful recovery, as well as in those who are gravely ill (2-4); among infants who are discharged from the hospital, 4-15% die before the second palliative procedure (3, 5).

B.1.3 Morbidity after the Norwood Procedure with MBTS

B.1.3.a Short Term Morbidity

Morbidity after neonatal heart surgery impacts the child's short and long term outcome (11). The postoperative course following the Norwood procedure is quite variable resulting in significant range in intensive care support, ICU morbidity, length of stay (LOS) and cost. A recent report (12) showed a mean LOS of 19 days, with 30% of hospital survivors having a hospital stay of > 1 month, and 7% > 2 months. Seizures occurred in 13% of patients, necrotizing enterocolitis in 10%, the need for CPR in 10%, and reintubation in 34%. These

patients consume considerable resources, both human and financial, in the early postoperative period.

B.1.3.b Long-term Morbidity

Long-term outcomes are likely to be related to having a systemic RV, instead of a systemic left ventricle. Such patients may experience problems related to ventricular dysfunction over time because the RV is not designed to pump blood to the systemic circulation. The MBTS may promote run-off from the coronary arteries to the pulmonary circulation, leading to inadequate coronary blood flow and further impairment of ventricular dysfunction. Right ventricular dysfunction can lead to tricuspid regurgitation, which may cause further ventricular dysfunction. Some patients may eventually need heart transplantation because of severe ventricular failure.

B.1.3.c Comparison of Morbidity in Patients with MBTS and RV-to-PA Shunt after the Norwood Procedure

No randomized trials have compared the outcomes for patients undergoing a Norwood procedure with either a MBTS or RV-to-PA shunt. A limited number of small, retrospective reviews provide conflicting data. Of these reports, most focus on mortality, and few address ICU or hospital morbidity. Nemours Cardiac Center found a significant decrease in the need to leave a post-operative open sternum and the use of extracorporeal membrane oxygenation (ECMO) in patients with RV-to-PA shunts (7). Conversely, Sibley Heart Center (13) and the University of California, San Francisco (14) found no difference in the duration of ventilatory support or length of hospital stay between the two groups. No prospective, comprehensive comparison of the RV-to-PA shunt with the MBTS on ICU morbidity has been reported.

B.1.3.d Preliminary Data

Preliminary data from two centers [Children's Hospital Boston (CHB), and Children's Hospital of Philadelphia (CHOP)] are included in Table 1 below.

Table 1 –Morbidity after Norwood Procedure

Variable	RV-PA		MBTS		
	Median (range)	n	Median (range)	n	p Value
Total Days Ventilated	4 (1-49)	59	5.7 (1-69)	91	0.01
ICU Stay (days)	12 (4-55)	63	14 (4-106)	95	0.13
Hospital Stay (days)	15 (6-97)	63	20 (6-133)	93	0.05

B.1.3.e Comparison of Unintended Cardiovascular Intervention Procedures in Patients with MBTS and RV-to-PA Shunt after the Norwood Procedure

Very little data are available from the retrospective reports comparing the need for cardiovascular interventional procedures between patients with the RV-to-PA shunt and those with the MBTS. Sano and colleagues (15) reported the need for angioplasty in 10 of 33 patients with RV-to-PA shunts undergoing stage II palliation. The indications for angioplasty were stenosis in proximal and/or distal anastomosis in 6 patients, coarctation in 3 patients, and restrictive inter-atrial communication in 1 patient. Earlier, Sano (16) also reported a group of 19 patients undergoing a Norwood procedure with an RV-to-PA shunt, with 6/13 patients requiring PA dilatation at the time of the stage II procedure. Two nonrandomized trials comparing the MBTS and RV-to-PA shunt mention inter-stage cardiovascular interventions. Mair, et al. (17) reported the need for balloon dilatation of a recurrent coarctation in 2/10 MBTS patients and 2/13 RV-to-PA shunt patients. In a review of 11 RV-to-PA shunt patients and 22 MBTS patients, Mahle and associates reported 2 patients crossing over from RV-to-PA shunt to MBTS (13).

B.1.4 Concerns Regarding the Use of a RV-to-PA Shunt

The placement of a systemic to pulmonary artery shunt to provide pulmonary blood flow is an integral portion of the Norwood procedure. The traditional method of shunting has been the MBTS. The MBTS consists of a PTFE tube graft (3.0-4.0 mm) placed between the subclavian or innominate artery and the pulmonary artery. The RV-to-PA shunt also provides pulmonary artery blood flow, but originates directly from the free wall of the right ventricle. A shunt diameter of approximately 1-2 mm larger than the traditional MBTS is required to compensate for the added resistance to flow imparted by the additional length necessary to reach from the RV to the PA (6, 7).

In the traditional Norwood procedure with MBTS, the systemic and pulmonary vessels are directly connected, so pulmonary vascular resistance influences coronary artery blood flow. As pulmonary vascular resistance decreases and more flow is directed into the pulmonary vasculature, diastolic runoff from the aorta increases, decreasing flow in the coronary system (coronary artery steal). In contrast, when the RV-to-PA shunt supplies pulmonary blood flow, the pulmonary and systemic vascular systems remain separated, eliminating aortic diastolic run-off and coronary artery steal that occur with the MBTS. Thus, coronary flow is no longer dependent on pulmonary vascular resistance, and myocardial oxygen delivery and RV function should be optimized.

Sano (6) and Pizarro (7) have proposed a benefit of the RV-to-PA shunt in a small non-randomized series of consecutive patients. However, these early reports provide no insight into the possible adverse effects of a small RV incision in the single functioning ventricle. In the patient with HLHS, optimal function of the single functioning RV is critical for the successful completion of the three-stage palliation, and ventricular incisions can interfere with both function and normal heart rhythm. An analogous situation occurred in the evolution of the repair of tetralogy of Fallot. Historically, the repair was accomplished with a large ventriculotomy. Newer techniques have stressed the avoidance or limitation of the size of the ventriculotomy. Several authors have reported greater impairment of ventricular function and a higher incidence of arrhythmia associated with the transventricular approach (18-20).

Other concerns relate directly to the RV-to-PA shunt. All shunts, including the MBTS, are susceptible to occlusion and stenosis. The RV-to-PA shunt may be more prone to occlusion or stenosis because of its length and geometry. Sudden shunt occlusion could lead to unexpected death, and shunt stenosis may require a shunt revision or earlier performance of the stage II procedure. Lower weight and younger age at the time of stage II procedure have been associated with adverse outcome as defined by mortality or unsuitability for later Fontan (10). Pulmonary blood flow relative to the RV volume ejected into the RV-to-PA shunt may also be decreased because of the regurgitant fraction from the unvalved shunt. Decreased pulmonary blood flow may then result in less growth of the pulmonary arteries in the inter-stage period. In addition, the regurgitant fraction adds to the volume load of the single ventricle.

B.1.5 Coronary Arterial Physiology in Patients with Congenital Cardiovascular Malformations

Investigators at the Michigan Congenital Heart Center hypothesized that coronary arterial insufficiency was a factor in the mortality early after the Norwood procedure. Five patients undergoing an anatomic repair for CCVM (Group I) and 5 patients undergoing a Norwood procedure with MBTS for HLHS (Group II) were studied with positron emission tomography (PET) at rest and then after administration of adenosine to evaluate coronary blood flow (21). Coronary arterial flow and oxygen delivery at rest and after administration of adenosine were decreased significantly in patients after Norwood procedure as compared to that in patients after anatomic repair of the CCVM (Table 2). These data suggest that patients with HLHS undergoing a Norwood procedure with the MBTS have lower coronary perfusion and oxygen delivery when compared to patients with other lower mortality lesions.

Table 2. Coronary Blood Flow and Oxygen Delivery after Anatomic or Single Ventricle Repairs for Congenital Cardiovascular Malformations.

	Group I (Anatomic repair)	Group II (Norwood)	p value
Resting coronary flow (ml/min/gm)	1.8 $\pm$ 0.2	1.0 $\pm$ 0.3	0.003
Coronary flow after adenosine (ml/min/gm)	2.6 $\pm$ 0.5	1.5 $\pm$ 0.7	0.02
Resting O2 delivery (ml/min/100gm)	28.9 $\pm$ 4.42	16.1 $\pm$ 4.2	0.02
O2 delivery after adenosine (ml/min/100gm)	42.3 $\pm$ 5.8	25.5 $\pm$ 8.1	0.02

B1.6 Right Ventricular Function

Right (systemic) ventricular function can theoretically be compromised by either procedure. In theory, myocardial oxygen delivery and RV function should be optimized when the RV-to-PA shunt supplies pulmonary blood flow, but RV function has not been systematically evaluated and the long term effects of the RV incision are unknown.

B.1.7 Pulmonary Arterial Growth after the Norwood Procedure

Small PA size is known to be a risk factor for patients undergoing both the stage II palliation and the Fontan operation (9, 10, 22). There is a 50% reported incidence of PA stenosis after MBTS in patients with HLHS, with a 14% incidence of major stenosis; i.e. > 50% narrowing (23, 24). A relatively high incidence of PA stenosis is also seen in patients after the RV-to-PA shunt. Six of 33 patients required balloon angioplasty to relieve stenosis at the RV-to-PA proximal or distal

anastomosis prior to the stage II palliation (15). PA growth is dependent on pulmonary blood flow, so the presence of stenosis can adversely affect PA growth (25). Sano and colleagues (15) compared PA growth between patients with MBTS versus RV-to-PA shunt before stage II palliation. The Nakata index (PA cross-sectional area Z-score based on angiographic data) was not significantly different between the MBTS and RV-to-PA shunt groups (335±200 vs 201±86 mm/m^2, respectively). However, the right PA was smaller in the RV-to-PA shunt group compared to MBTS group (5.6±0.9 vs 7.6±1.8 mm respectively, p=0.009). This may have been related to the lower pulmonary-to-systemic flow ratios in the RV-to-PA shunt group compared to the MBTS group (0.66±0.2 vs 0.88±0.1, respectively, p=0.008). Whether the lower pulmonary blood flow is secondary to shunt stenosis or to regurgitation is unknown.

B.1.8 Neurodevelopmental Outcome after Staged Reconstruction

Multiple studies demonstrate that pre-school and school age children with HLHS have deficits on neurocognitive testing, and behavioral abnormalities (26-29). This is a multifactorial process, and potentially is due to a combination of underlying congenital structural central nervous system (CNS) abnormalities, genetic syndromes, disturbances in fetal cerebral hemodynamics, preoperative CNS hypoxemia and/or ischemia, intraoperative events related to cardiopulmonary bypass with or without deep hypothermic circulatory arrest, and postoperative factors such as low cardiac output syndrome. It is possible that a significant contribution to later neurodevelopmental delay occurs in the postoperative period. The potential beneficial effects on neurodevelopment following an RV-to-PA shunt include improved postoperative oxygen delivery, less “steal” through the shunt into the lungs, and higher diastolic blood pressure.

Genetic polymorphisms likely play a role as well because significant inter-individual variation in developmental outcome exists. An association has been discovered between Alzheimer’s disease and the apolipoprotein E (APOE) $\in$ 4 allele (30-33). An important role of APOE has been found as a determinant of neurologic injury and recovery following a variety of ischemic insults including intracerebral hemorrhage, closed head injury, and acute stroke (30-33). Recent reports have documented preliminary evidence of an association of the APOE $\in$ 2 allele with neurocognitive decline after cardiac surgery in adults (34, 35).

Investigators at Children’s Hospital of Philadelphia have performed a prospective study of patients <6 months of age undergoing cardiopulmonary bypass for repair of CCVM to evaluate the association between APOE genotype and postoperative neurodevelopmental dysfunction (36).

Developmental outcomes were evaluated at 1 year of age using the Bayley Scales of Infant Development in 244 patients. After adjustment for preoperative and postoperative covariates including gestational age, age at surgery, sex, race, socioeconomic status, cardiovascular defect and use of deep hypothermic circulatory arrest (DHCA), the APOE $\in$ 2 allele was associated with a worse neurological outcome as assessed by the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development ($p = 0.036$). Patients with the APOE $\in$ 2 allele had approximately a 7.0 point decrease in the PDI. Thus, the APOE $\in$ 2 allele carriers had significantly lower PDI scores at 1-year of age following infant cardiac surgery. This effect was independent of ethnicity, socioeconomic status, cardiovascular defect, and use of DHCA. An effect of the APOE $\in$ 4 allele was not detected.

B.1.9 Stage II Procedure

B.1.9.a Background

The cavo-pulmonary anastomosis was initially conceived as a means of increasing effective pulmonary blood flow and hence, systemic arterial oxygen saturation. Although it is still a very effective palliation alone or with a limited systemic-to-pulmonary artery shunt, currently it is used primarily as the second stage of the standard 3-stage palliation of functional single ventricle patients that ends with the Fontan procedure.

The surgical goal of the stage II procedure is to remove the shunt (either MBTS or RV-to-PA) supplying pulmonary blood flow and to replace it with the superior vena cava (SVC). After the stage II procedure, the venous return from the SVC becomes the sole source of pulmonary blood flow. There are two surgical methods for achieving this goal that both produce the same physiologic result of diverting the SVC blood flow directly to the PA. The first method is termed a bidirectional Glenn, and entails sewing the SVC directly end-to-side into the PA. The second method, a hemi-Fontan, diverts the SVC return to the PA through the right atrial appendage. Both approaches have been shown to be equally efficacious (37). In the performance of the hemi-Fontan, many surgeons routinely enlarge the left pulmonary artery, as the technique lends itself readily to this additional step. However, occasionally with either technique, it is necessary to address other significant branch PA stenoses with patching, stenting or dilatation, which would not be a usual part of the typical bidirectional Glenn or hemi-Fontan.

Current reported results for the stage II procedure with MBTS demonstrate a hospital survival of 98% (112/114) (9). Studies of patients receiving a RV-to-PA shunt are more limited and show survivals ranging from 85% (11/13) to 100% (32/32) (7, 15).

B.1.9.b Preliminary Data Comparing MBTS to RV-to-PA Shunt

The available non-randomized preliminary data from Medical University of South Carolina (MUSC), Children's Hospital Boston (CHB), and Children's Hospital of Philadelphia (CHOP) are outlined in Table 3. These data suggest that the various advantages and disadvantages of the two shunts are either not significant factors influencing outcome or negate each other, supporting the hypothesis of this secondary aim.

Table 3. Stage II Hospitalization Data

	RV-PA		MBTS		
Variable	Median (range)	n	Median (range)	n	p Value
Total Days Ventilated	1 (0-10)	75	1 (0-83)	87	0.46
ICU Stay (days)	2 (1-42)	75	3 (1-190)	86	0.78
Hospital Stay (days)	6 (2-64)	74	5 (2-190)	85	0.50

B.2 Rationale for this Trial

Techniques used for the operative repair of congenital heart lesions have been adopted based solely on expert consensus rather than clinical trials data. One of the primary goals of the Pediatric Heart Network is to promote evidence-based clinical care. There is at present a unique opportunity to study two surgical procedures for which clinical equipoise exists among surgeons. Early claims of superior survival with the RV-to-PA shunt need to be evaluated prospectively in a randomized trial before conclusions can be reached about the risks and benefits of this new surgical strategy, the RV-to PA shunt. The results of this study will make an important contribution to the management of the highest-risk group of patients and if successful, will establish a model by which other operative interventions for patients with CCVM can be evaluated in the future. In addition, this study will establish a cohort of patients who can be followed prospectively to assess long-term outcome, and will provide important baseline data to enable future evaluation of interventions in this high-risk group of patients.

B.3 Rationale for Selection of Outcome Measures

B.3.1 Death and Heart Transplantation

The average mortality rates for the Norwood procedure for HLHS during the 1990's in the United States was approximately 40% (8). In the currently available retrospective series, the primary advantage that has been proposed for the RV-to-PA shunt is a decrease in operative mortality

compared to the MBTS (6, 7, 17). However, others have not shown a difference in mortality (13), and no randomized trials have been conducted.

Although a relatively small number of patients require cardiac transplantation following the Norwood procedure, it will be important to capture these subjects in the Primary Aim as transplantation essentially amounts to "death of the heart" and a failure of staged reconstruction. A recent review of patients undergoing a Norwood procedure with a MBTS at the University of Michigan from January 2001-December 2003 revealed a 4% (4/98) incidence of transplantation (data unpublished).

B.3.2 Measures of ICU Morbidity

The measures selected for analysis include the proportion of patients with a post-operative open sternum, use of extracorporeal membrane oxygenation (ECMO) or cardiopulmonary resuscitation (CPR), the number of hours to initial extubation, number of days ventilated, length of ICU stay, and length of hospitalization. These are standard ICU measures and were selected because they may be related to surgical strategy, and because decreasing ICU morbidity can improve short- and long-term outcomes, and reduce health care costs.

B.3.3 Incidence of Unintended Cardiovascular Interventional Procedures After the Norwood Procedure through 12 Months of Age

The need for additional interventional procedures carries the risk of further morbidity and may impact long-term outcome as well as increasing health care costs. Care for children with HLHS will improve if either of the shunts is associated with a decrease in the number of required interventional procedures. We have chosen to evaluate those procedures that might differ in frequency between the patient groups including balloon dilation of the shunt or branch pulmonary arteries, stent placement in the shunt or branch pulmonary arteries, shunt revision, crossover between MBTS and RV-to-PA shunt, and balloon dilatation, stent placement, or surgical revision of the neo-aorta. It is a matter of routine to perform some PA augmentation during the stage II procedure at many institutions; however, PA reconstruction not normally associated with the usual conduct of a stage II procedure will also be tracked.

B.3.4 Echocardiographic Evaluation of RV Function and Measurements of the Severity of Tricuspid Regurgitation

Determining whether the type of shunt done at the time of the Norwood procedure impacts later RV function is a crucial component of determining the best surgical management of infants with HLHS. Establishing baseline evaluations and standardizing echocardiographic methods of evaluating RV function will provide early data on a cohort of patients that can be followed serially through and beyond Fontan palliation to determine if a difference in RV function persists long-term and whether it eventually contributes to failure of the palliative procedure.

B.3.4.a Rationale for Assessment of RV Function by Echocardiography

Echocardiography is routinely and universally used as the initial test to evaluate the anatomy and ventricular function of the child with HLHS throughout the initial presentation, surgery and short-and long-term follow-up (38). It is the only cardiac test that is currently considered clinically indicated in virtually all children with HLHS for both diagnosis and serial follow-up. Despite the widespread use of two-dimensional echocardiography, the limitations of echocardiography for evaluating RV function are well known. Although the shape of the right ventricle does not conform to standard geometric models, 2-dimensional methods to overcome these restrictions by assigning various geometric models have been validated (39). As echocardiographic technology has advanced, the process of obtaining the measurements has become less tedious and time-consuming, and therefore more practical for use in this trial. In addition, because the required views are part of the standard examinations and the measurements can be done off-line, data procurement will not significantly increase the examination time.

Volumetric analysis of the right ventricle can be accurately calculated by using three-dimensional echocardiography. Through the use of high spatial resolution and surface reconstruction principles similar to those employed by magnetic resonance imaging, volumes are obtained that are independent of geometric functions. The use of 3-dimensional echocardiography to provide more accurate determination of RV volumes and ejection fraction has been validated both *in vitro* and *in vivo* (40-43). Although this technique is very likely to provide the most accurate evaluation of RV function for this trial, the technology has only relatively recently become available for practical use in the clinical laboratory and some centers do not yet have the necessary equipment. Nevertheless, the field is advancing so rapidly that 3-dimensional echocardiographic analysis of right

ventricular volumes and ejection fraction will almost certainly become the pediatric standard during the time frame for enrollment into this trial. Collection of 3-dimensional data in a standardized fashion by those centers who currently have and those who subsequently acquire this capability has several advantages. First, it will improve measurement accuracy, provide more robust and current data, and allow better interpretation of the effect of the type of surgery on RV function. Second, acquiring data sets requires no additional expense or additional burden of subject time (the imaging data used is routinely obtained and analysis can be done off-line). Third, it obviates the need for volumetric data from magnetic resonance imaging. Finally, we anticipate the technology will be in place at most centers to provide data for the 14-month echocardiogram at the end of subject follow-up. Longitudinal data will be available even from the beginning of the trial for some centers.

Doppler techniques for the evaluation of RV function are attractive because of their independence from ventricular geometric assumptions. In particular, dP/dt from the tricuspid regurgitant jet as well as tricuspid annular motion and myocardial acceleration from DTI have been used to identify RV dysfunction in both adults and children under a wide variety of pathological conditions (44).

Acoustical imaging windows for the neonates and infants included in this trial are likely to be excellent, allowing optimal visualization of the endocardial walls, myocardium, tricuspid valve landmarks and regurgitant jets. Because of the widely accepted use of this noninvasive and safe test, we propose that these variables be obtained on all study subjects.

B.3.4.b Rationale for Selection of Echocardiographic Outcome Measures

Because of the limitations of echocardiography for evaluating the geometry of the RV, the current methods must be used in context with the global picture of the right ventricular hemodynamics. To allow this, the measurements discussed in this section will be collected for this trial.

Measurements of RV volumes are useful to determine if the RV-to-PA shunt regurgitation is sufficient to increase the volume load and adversely affect function. These values are obtained as part of the process of calculating ejection fraction. Although ejection fraction is load dependent, it is widely used and accepted for evaluation of left ventricular performance where the same restrictions apply. It cannot be used to determine the cause of a decreased

value (alteration in preload versus afterload versus contractility), but the studies will be performed in stable patients before and at various time intervals after recovery from surgical procedures and should provide important information regarding ventricular performance. Two-dimensional echocardiographic measurements of RV volumes and ejection fraction have been shown to correlate with angiographic (r = 0.75 – 0.86) (39) and MRI measurements (0.72 – 0.96) (45). Three-dimensional echocardiographic volumetric analysis correlated with *in vitro* laser scanning (0.998) (41). Such correlations are acceptable for clinical practice. Although several methods have been described (45), the biplane Simpson's using orthogonal subcostal views will be used as this technique takes advantage of the excellent subcostal imaging window in this population and was the method used to validate 3-dimensional volumetric analysis (40). It also allows evaluation of the right ventricular outflow tract where the incision is made for placement of the shunt to the pulmonary artery.

Use of the tricuspid regurgitant jet for estimation of dP/dt is technically easy to obtain, reproducible, and has been shown to correlate well with catheter-derived dP/dt (44). dP/dt is afterload-dependent, making it difficult to determine if a decreased value is from diminished contractility or from an increase in afterload and must be interpreted in the context of the other variables obtained as part of the trial. Despite this, dP/dt has proven to be useful as an index of quantifying right ventricular systolic dysfunction in both adults and children. The echocardiographic method for determining dP/dt has already been validated in infants with HLHS (44) and may be useful for the longitudinal tracking of RV function in this population.

Doppler tissue imaging (DTI) allows display of instantaneous changes in myocardial velocities with both high temporal and spatial resolution in the axial direction. DTI measurements overcome the constraints of an abnormal geometry and may largely overcome the restrictions of load dependency. Tricuspid annular displacement toward the apex in systole reflects systolic longitudinal contraction of the heart and correlates with ejection fraction. Normal values for tricuspid annular motion have been published for children (53). Assessment of tricuspid annular motion using DTI has been used in the evaluation of right ventricular dysfunction in patients with repaired tetralogy of Fallot. Isovolumic myocardial acceleration (IVA) is relatively insensitive to loading conditions and may ultimately prove to be the best method for evaluation of these patients. In a study of

patients after atrial repair of transposition of the great arteries, IVA was successfully used to identify RV dysfunction and correlated with invasive measurements of load-independent indices obtained with a conductance catheter (47). The echo laboratories at all centers participating in this trial have experience in obtaining these measurements using DTI.

Both RV dysfunction and RV volume overload may occur after the first stage of palliation and may lead to tricuspid valve annular dilatation and regurgitation (38, 46, 48). The use of echocardiography to grade TR and the standard values for normal TV annular diameters has been published allowing comparisons to normal values and between the two study groups. These imaging views and measurements are part of a standard echocardiogram and will not add to the time needed to complete the study.

B.3.5 Measurement of PA Growth

B.3.5.a Measures of Pulmonary Artery Size

Multiple methods are available for assessing PA size. Muraoka et al. used the ratio of diameter of the pulmonic annulus against the aortic annulus, whereas McGoon et al. used the ratio of the mean diameter of the right and left PA against that of the descending aorta at the level of the diaphragm (49, 50). Neither of these ratios standardize for different body sizes. Since infants will likely come to stage II palliation at different ages and some of the infants will have different growth parameters, it is important to have a measure of PA size that standardizes for body size. Nakata et al. developed and validated an angiographic method to estimate the size of the pulmonary arteries that is indexed to body surface area (51). The Nakata index is calculated as the sum of the cross-sectional areas of the right and left PAs measured immediately proximal to the origin of the first branches divided by the infant's body surface area. Nakata has shown that this index is consistent over a wide range of body surface areas from infancy to adolescence. Since the first report of the Nakata index, many studies have used this ratio to assess PA growth (52, 53). As with any measure, the Nakata index has potential limitations. These include the difficulty in accurately measuring the PAs in a consistent and reproducible manner and the assumption that the PAs are circular. In addition, the influence of varying shunt sizes and variations in systemic and pulmonary vascular resistance on pulmonary blood flow and on PA growth will be difficult to evaluate in an individual patient.

Angiocardiograms are routinely performed as part of pre-Glenn evaluation at most centers. In order to minimize errors in measurement, modern digital angiograms will be measured at

a single core site. Although some reports show excellent agreement between PA measurements obtained by magnetic resonance angiography (MRA) compared to standard cine-angiocardiography (81, 82), patients that have only MRA to image the PAs prior to stage II palliation will be excluded from analysis of PA size to minimize variability related to imaging modality. Since PA growth can be affected by the occurrence of PA or shunt stenosis, the presence, type and severity of stenosis will also be assessed using angiocardiographic images.

Preliminary data from the participating network centers demonstrates the feasibility of performing these measurements. In an ongoing study, Shirali and colleagues have calculated the echocardiographic Nakata index for normal children, and the angiographic Nakata index for children with functionally single ventricles.

B.3.5.b Angiographic Nakata Index

The angiographic Nakata index has been calculated in 84 patients with functional single ventricle prior to cavo-pulmonary anastomosis, and also prior to completion of the Fontan procedure (51). The technique that was employed for this measurement has been described previously and enjoys wide usage. Prior to stage II palliation, the Nakata index was 194 $\pm$ 88 mm^2/m^2 (median 185, range 58 – 424 mm^2/m^2). Prior to completion of the Fontan procedure, the Nakata index was 207 $\pm$ 76 mm^2/m^2 (median 200, range 53-407 mm^2/m^2).

B.3.5.c Echocardiographic Nakata Index

Children and adolescents without heart disease (n=256, ages 7 days -19 years; 134 boys, 122 girls) were studied (72). A commercially available database was used to construct hypothetical patients whose body surface area ranged from 0.1 to 1.0 m^2, in steps of 0.05 m^2 (19 steps). For each 'step' in body surface area, the database was examined for the diameter of each branch PA that corresponded to a Z-score of –2, 0 and +2. For each Z-score at each step, the corresponding diameters of the branch PAs were indexed to body surface area and then added up to provide the echocardiographic Nakata index. The data are presented as a graph (Figure 3). These data show the remarkable consistency of the Nakata index Z-score across different body sizes thereby minimizing the confounding influence of body growth when comparing PA sizes amongst patients of different ages. Since echocardiograms are routinely performed as part of clinical care, it will provide an

opportunity to compare changes in Nakata index from Norwood procedure to stage II procedure between the two surgical groups using each patient as his/her own control.

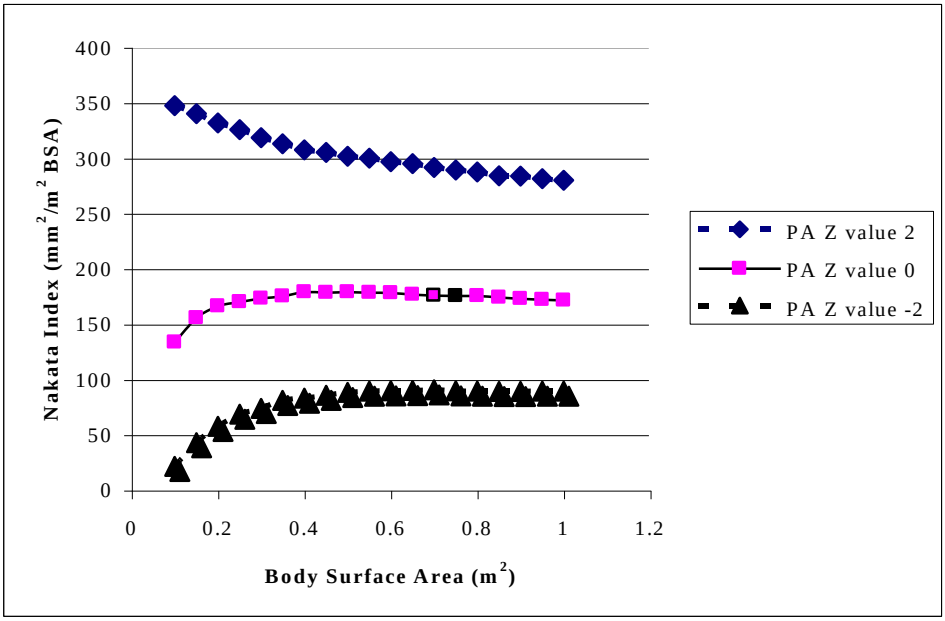


Figure 3: Echocardiographic Nakata Index in Normal Children

B.3.6 Morbidity after Stage II Procedure

The available non-randomized reports comparing patients with MBTS and RV-to-PA shunts have concentrated on the early survival (7, 15, 17). The effect of the RV-to-PA shunt on the stage II procedure remains unknown. Both the MBTS and the RV-to-PA shunt have theoretical advantages and disadvantages for the successful completion of the stage II procedure. Smaller pulmonary artery size, increased PA pressure, and depressed RV function have been identified as a risk factors for the stage II procedure (9, 10, 22). Sano and colleagues (15) found that although the Nakata index was not different between the groups (335±200 vs 201±86 mm/m^2, respectively), the right PA was significantly smaller in the RV-to-PA shunt group (5.6±0.9 vs 7.6±1.8 mm, respectively, p=0.009). Although the smaller PA may increase the risk at the stage II procedure, the same group of RV-to-PA shunt patients had lower PA pressures (11.9±2.7 vs. 15.2±4.4 mmHg) and had evidence of better RV function with lower RV end diastolic pressures (RVEDP) (5.1±2.3 vs. 8.0±6.2 mmHg), which decreases the risk for a poor outcome. With these conflicting data, as well as the excellent currently reported hospital survival of 98% for the stage II procedure with the traditional MBTS (9), the impact of the RV-to-PA on the stage II procedure compared to the MBTS is important to define.

B.3.7 Neurodevelopmental Status

Cognition cannot be measured directly during infancy. However, both psychomotor development and mental development can be assessed for children 1-42 months of age with the Bayley Scales of Infant Development-II (BSID-II) (54). The BSID-II yields both a psychomotor development index (PDI), an assessment of both fine and gross motor function, and a mental development index (MDI), a measurement of other cognitive related tasks. Although these indices are not actual IQ tests, the BSID-II is a widely used and respected measure of neurodevelopment. Scores for each of the indices are standardized for a mean of 100 (standard deviation of 15). For healthy children with normal development, the predictive validity of the BSID-II is limited; however, for groups of children at risk for developmental abnormalities, such as children with complex congenital heart disease, the predictive validity is substantially improved (55). The BSID-II can be performed in infants and small children with congenital heart disease and preliminary data from Children's Hospital Boston, the University of Michigan Congenital Heart Center and Children's Hospital of Philadelphia reflect that infants with HLHS tend to have lower scores than expected for the healthy population on both the PDI and MDI (Table 4). The lower scores on the PDI compared to the MDI are consistent with studies in post-Fontan patients, which consistently demonstrate more deficits in motor and non-verbal skills than in tasks related to verbal cognition (26-29). In addition, one-year PDI scores seem to be generally more affected than MDI scores in children who have undergone open heart surgery in early infancy, perhaps related to selective neuronal vulnerability.

Table 4. Sample of Infants and Children with Complex Congenital Heart Disease: Results of Bayley Scales of Infant Development–II. Mean score for healthy normal children is 100±15.

	Norwood with MBTS
Boston (n=20) *	PDI 74 ±15 MDI 85 ± 14
Michigan (12 months) (n=29) *	PDI 77 ± 21 MDI 94 ±22
Philadelphia (12 months) (n=66) (56)	PDI 71 (50-113) MDI 90 (50-129)

*These data are unpublished.

Neurodevelopmental data are not available for patients who have had an RV–to-PA shunt.

The MacArthur Communicative Development Inventory/Words and Gestures (CDI) is a parent-report instrument for assessing early language skills, designed for use in children 8 to 16 months of age (57). Use of the CDI will complement the Bayley Scales by providing a detailed assessment of

several important aspects of early cognitive development (specifically symbolic) that are difficult to measure in a brief developmental assessment. The CDI/Words and Gestures should be sufficiently sensitive to identify any differences between treatment groups in terms of language development based on previous experience with the MacArthur instruments. In a study from Children's Hospital Boston, children assigned to a vital organ support technique of deep hypothermic circulatory arrest had significantly lower scores than children assigned to low-flow cardiopulmonary bypass on several subscales of the Communicative Development Inventory/Word and Sentences, a similar instrument which is designed for 16 to 30 month old children (58).

The Functional Status II-Revised (FSII-R) is a parent report questionnaire that has been used to assess the health status of children with chronic disorders (59). The instrument measures normal, daily, age-appropriate functions (how well the child eats, sleeps, plays, and temperament, etc.) and has been shown to correlate well with other markers of disease severity such as hospitalization rates, length of hospital stay, and other illness (60). This questionnaire will provide important functional status information on the complete cohort in the event that administration of the Bayley Scales is not well tolerated by or not completed on all subjects.

The BSID-II, MacArthur CDI, and the FSII-R will provide a profile of the motor and cognitive capabilities of the study subjects that will allow us to determine if use of a RV-to-PA shunt results in a difference in functional and neurodevelopmental status as compared to use of a MBTS.

B.3.8 Modifiers of Neurodevelopment

3.8.a Head circumference

Head circumference has also been found to correlate with developmental outcome and will be collected at study visits for analysis as an effect modifier (61).

3.8.b Socio-Economic Status

Socio-economic status will be assessed using the Hollingshead Four Factor Scale as this is a well-defined modifier of neurodevelopment (62).

3.8.c Genetic Evaluation

Inherited syndromes and the presence of other extracardiac abnormalities affecting neurodevelopment are associated with an increased risk of mortality for children with HLHS (63, 64). Furthermore, developmental abnormalities are often associated with inherited syndromes, even when cardiac surgery is not necessary. Thus each family will be given the option of having the subject undergo clinical evaluation by a geneticist before hospital discharge and again at the 14 month follow-up visit to identify any abnormalities not evident during the neonatal period.

Genetic polymorphisms that decrease neuroresiliency and impair neuronal repair after central nervous system injury are important risk factors for neurodevelopmental dysfunction after infant cardiac surgery. These genetic polymorphisms and their effects are a relatively new discovery, and are a rapidly evolving field. Each family will be given the option of having DNA collected from a buccal smear from the subject that will be analyzed for APOE genotype and then the remainder preserved for the duration of the study. As new markers are determined, they will form a valuable library for future analysis. Any additional genetic testing will only be undertaken after obtaining appropriate written informed consent from the subject or guardian.

C. STUDY DESIGN AND METHODS

C.1 Overview

A randomized trial of the RV-to-PA shunt vs. MBTS in patients undergoing a Norwood procedure (Figure 4).

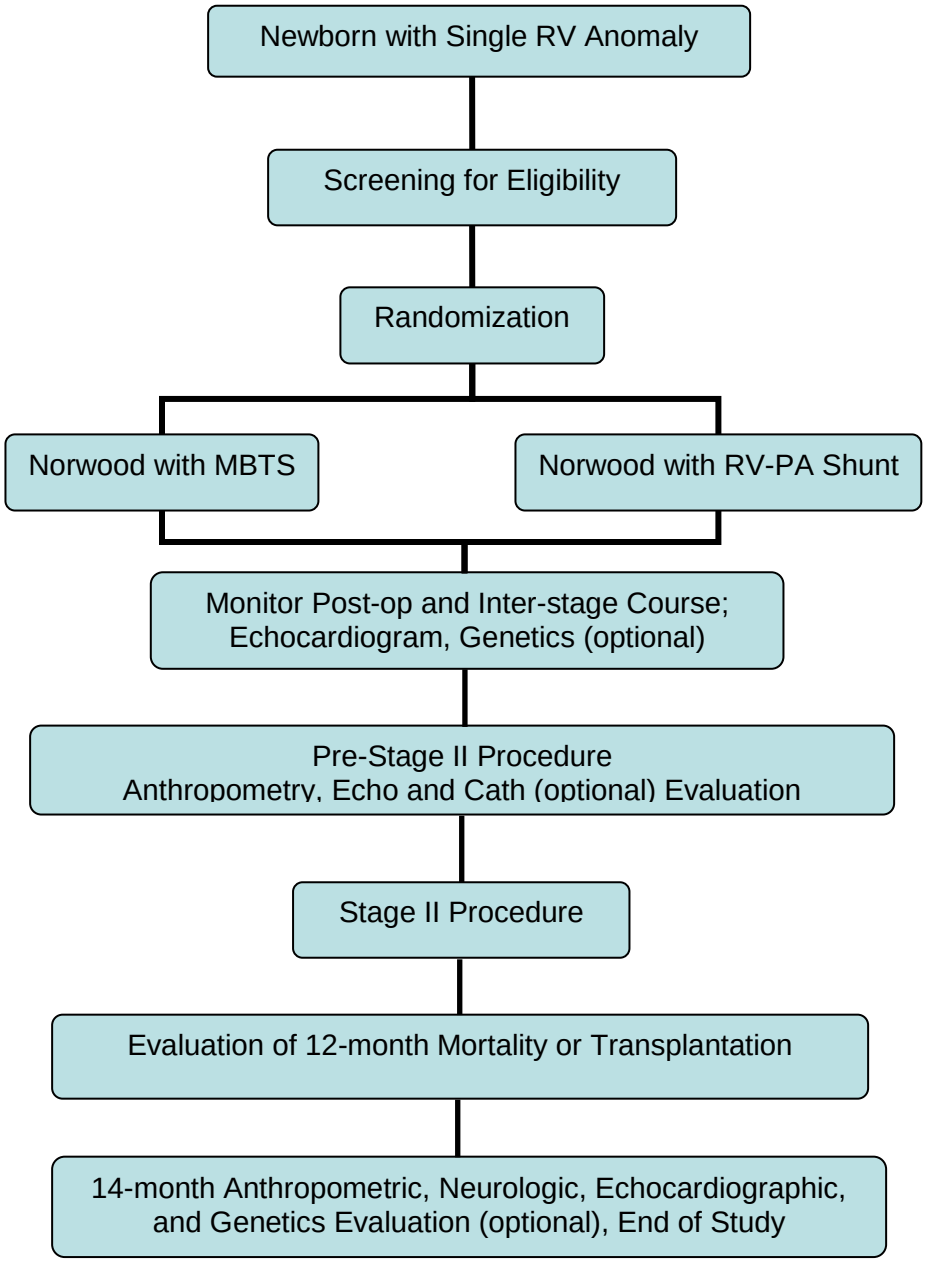


Figure 4. Trial Flow Outline

C.2 Participants

C.2.1 Inclusion criteria

To be eligible for this trial the subjects must meet all of the following inclusion criteria at the time of enrollment:

1) Diagnosis of hypoplastic left heart syndrome or related single, morphologic right ventricle anomaly.
2) Planned Norwood procedure.
3) Informed consent of parent(s) or legal guardian.

C.2.2 Exclusion Criteria

To be eligible for this trial, the patient must meet none of the following exclusion criteria at the time of enrollment:

1) Single, morphologic left ventricle anomaly.
2) Pre-operative identification of anatomy rendering either a MBTS or a RV-to-PA shunt technically impossible.
3) Any major congenital abnormality (i.e. congenital diaphragmatic hernia, tracheoesophageal fistula) or acquired extra-cardiac disorder (e.g. meconium aspiration with need for high frequency ventilation, persistent renal failure requiring dialysis) that, in the opinion of the investigator, could *independently* affect the likelihood of the subject meeting the primary endpoint.

C.2.3 Subject Availability

The estimated number of patients undergoing a Norwood procedure at the 7 PHN centers, Children's Hospital Wisconsin and the Michigan Congenital Heart Center for the years 2002-2003 is approximately 200-250 per year. In addition, other centers including Children's Hospital Los Angeles, and Emory University, University of Cincinnati, Denver Children's Hospital, and Indiana University have expressed strong interest in participating in this study and have submitted preliminary data. These centers will add another 95 patients per year. Based on previous studies in our institutions, fewer than 2% will meet exclusion criteria or have unexpected anatomic findings at the time of operation. We project that 67% will be eligible and will also provide informed consent. With a target sample size of approximately 554 subjects, the accrual period is estimated to be up to 39 months, but will continue until the target is reached.

C.2.4 Recruitment Protocol

The Principal Investigator at each clinical center, his or her designate, and the nurse coordinator will have the responsibility for case finding and subject recruitment. After consultation with the patient's pediatric cardiologist, the parent(s) or legal guardian of potential study participants who have a single right ventricle anomaly will be recruited after the decision has been made to treat with staged surgical palliation beginning with the Norwood procedure. The initial approach may be during the prenatal or postnatal period. The screened population, however, will be all live births for whom a Norwood procedure is planned. The surgeons at all clinical centers are committed to playing an active role in explaining the study and either the surgeon or a cardiologist will be involved in obtaining consent. Data (demographic, eligibility criteria, and informed consent status) will be

recorded on a screening form for all patients undergoing a Norwood procedure, regardless of their inclusion in the study, for definition of the study population.

The medical records of eligible patients, who are not enrolled because of parent or physician preference, will be reviewed through an IRB-approved expedited review procedure to collect data for the primary endpoint and other relevant diagnosis and treatment information.

C 2.5 Human Subjects Considerations

The characteristics of the subject sample and sources of research material are specified in Sections C.2.1-C.2.4. Consent will be obtained from the parent(s) or legal guardian before the subject undergoes a Norwood procedure. The site study investigators, study nurse coordinators, or assigned designates will obtain consents, documented by the parent(s) or legal guardian's witnessed signature on an informed consent document that is compliant with HIPAA regulations (Appendix A). The consent process will require separate signatures indicating consent for genetics evaluation, consent to use the subject's buccal smear for APOE genotyping (Appendix B), and consent to store unused DNA for future research. Assent will not be required because all subjects are <2 years old.

C.2.5.a Potential Risks

1. The overall risks associated with the staged repair of HLHS with the traditional MBTS are well known and are reviewed above in Section B1. These risks are primarily related to excessive or restricted pulmonary blood flow and to the inter-relationship of systemic perfusion, pulmonary blood flow, and coronary arterial and other end-organ perfusion. The risks associated with the RV-to-PA shunt are not well defined. Potential concerns are outlined in Section B1.4. These concerns mainly revolve around the requirement of a ventriculotomy to place the proximal origin of the shunt. This ventriculotomy and the resultant scar may adversely affect intermediate- and long-term RV function, or promote arrhythmias. Other than random assignment to one of the two shunts, all subjects will undergo routine care for patients who have had a Norwood procedure.

2. All echocardiograms except for the study at age 14 months are part of routine care of infants with functional single ventricles. Subjects will be sedated for the echocardiographic examinations according to the practice guidelines at the individual center. All sedation protocols will adhere to practice guidelines for sedation and analgesia (65).
3. The catheterization is part of routine care. No catheterization will be performed for research purposes only.
4. The length of the subject's hospital stay will not be affected by any tests involved in this study.
5. The study sponsor will pay for all testing that is not part of routine care. Investigators from the clinical center will have access to the medical record for 6 years after enrollment to review the results of follow-up clinical course, surgical or catheter intervention, and other relevant studies.
6. Confidentiality concerns are discussed in Section C.2.5.e.

C.2.5.b Potential Benefit

The possible benefits of participation in the proposed study to the subject are:

1. The subject's family, primary care provider, and cardiologist will receive extensive information regarding cardiac status.
2. The evaluation of neurodevelopmental and functional status may provide valuable information to families and primary care providers that would not otherwise be available. This may lead to early intervention if developmental or functional abnormalities are detected.

C.2.5.c Risk/Benefit Ratio

The risk/benefit ratio of the study is favorable. Although an individual subject may not benefit from study participation, the results of this study will make an important contribution to the management of these high risk infants who undergo a Norwood procedure by determining whether the survival of infants who receive a RV-to-PA shunt is better than that of infants who receive the traditional MBTS. In addition, the information obtained concerning the interrelationships of measures of clinical status, laboratory evaluations, and medical and surgical therapies in infants with single RV anomalies will make an invaluable contribution to the overall management of these complex infants.

If parents decline to participate, their child's medical care will not be adversely affected in any way. If they agree to participate, they are free to withdraw from the study at any time.

Patients and their families will be reimbursed for costs associated with participating in the study-related visits and procedures that would not have occurred as part of routine clinical care.

C.2.5.d Gender and Minority Recruitment

Based on current rosters of patients undergoing Norwood procedures at the Network sites, it is estimated that 45% of patients will be female and 15-30% of the patients will be of minority race/ethnicity, depending on geographic location of the clinical center. The overall study population is expected to meet the NIH requirement of 25% minority patients. Because of gender differences in the CCVM under study, the usually NIH requirement that 50% of subjects be female will be modified.

C.2.5.e Patient Confidentiality

Each subject will be assigned a study identification (I.D.) number so that study information will be confidential. The link between subject name and I.D. number will be stored only at the site where the subject received his/her clinical care. All Network procedures are conducted in accordance with HIPAA requirements.

The buccal swabs obtained for APOE genotyping will be sent to the Genetics Core laboratory. APOE genotyping results will be sent by the Genetics Core Laboratory to the Data Coordinating Center. The Data Coordinating Center will send a separate unique genetic identification number to the Genetics Core Laboratory, which will be used to label the sample to be stored for testing. The sample to be stored for testing will not have the original study identification number, subject's name or any other information that could identify the subject. The information at the Genetics Core Laboratory that links the unique genetic identifier to the study number will be destroyed immediately after the sample for future testing is relabeled, making it very difficult for the participating study site or the Genetics Core Laboratory to link future genotyping results with the study subject. Only the Data Coordinating Center will maintain the list linking the genetic identification number to the study identification number.

C.3 Trial Enrollment

C.3.1 Stratification

The study design is a multicenter, randomized trial. Infants with certain anatomic or hemodynamic conditions may have the poorest clinical outcome over the first year of life. Multiple studies have identified the presence of aortic atresia or obstructed pulmonary venous return as risk factors for mortality following the Norwood procedure (66-70). Therefore, we will randomize participating patients to treatment groups using randomly permuted blocks within strata defined by aortic atresia (presence or absence) and obstructed pulmonary venous return (presence or absence). For the purpose of this study, obstructed pulmonary venous return is defined by the use of intervention, including balloon septostomy, open atrial septectomy or urgent Norwood procedure. Due to potential differences in surgeon experience and operative techniques in spite of performing two specific procedures, dynamic allocation by surgeon will be used to ensure that treatment arm totals are balanced within surgeon. Because surgeon will be used as a dynamic rather than explicit stratification factor, this design will not result in excessively small stratum sizes.

C.3.2 Blinding

This trial has an unblinded design with respect to knowledge of treatment assignment. The majority of the personnel caring for the subjects will know which shunt an individual subject has had based on physical exam, as well as on many of the follow-up studies performed for the secondary endpoints such as echocardiography and cardiac catheterization. The exception to the unblinded design is that of the specialist who performs the neurodevelopmental testing.

The DSMB will determine their preference for receipt of blinded or unblinded trial results prior to the interim look. No clinical investigators will review trial outcomes, by arm or in aggregate, until the end of the trial.

C.3.3 Randomization

Patients will be randomly assigned in a 1:1 ratio to receive a MBTS or RV-to-PA shunt during the Norwood procedure using randomly permuted blocks. All eligibility criteria must be confirmed, and written informed consent obtained, before randomization. Although the recruitment process may begin in the prenatal period, randomization will occur only after confirmation of all eligibility criteria after birth. Randomization will be accomplished over the Internet using the randomization computer at the Data Coordinating Center (available 24 hours a day, 7 days a week). There will be a backup sealed envelope system in the event that technical problems prevent computer randomization. After

verifying key eligibility criteria and supplying stratification information (see Section C.3.1), the randomization computer will return the numeric Treatment Allocation Code corresponding to either the MBTS or RV-to-PA shunt. Investigators at each institution will maintain a log containing the subject's study I.D. and name, date of enrollment, date of operation and Treatment Allocation Code.

C.4 Treatment

C.4.1 Technical Considerations of Surgery

Each center will maintain a consistent approach to the conduct of the operation, including techniques of cardiopulmonary bypass, the use of regional cerebral perfusion, methods of pH monitoring, and ICU care.

The MBTS will be constructed of an unvalved PTFE tube graft. It will originate from the innominate or proximal subclavian artery in the subject with normal brachiocephalic branching at the discretion of the surgeon, based upon the subject's individual anatomy. The size of the shunt will also be tailored to the individual subject's needs to assure adequate pulmonary blood flow. In the subject with an aberrant right subclavian artery, the right carotid artery will be assessed as the potential origin of the shunt. If the carotid artery is too small in the opinion of the surgeon, the subject can be considered for intra-operative cross over (see below for details).

The RV-to-PA shunt will also be constructed of an unvalved PTFE tube graft. Shunt size will be individualized, primarily based on the subject's weight. The graft will originate from the free wall of the right ventricle. A ventriculotomy will be made in an area of the ventricle free of significant coronary arteries approximately 1 cm below the pulmonary root to avoid injuring the pulmonary valve. The size of the ventriculotomy will be limited to that which matches the shunt size. Small amounts of muscle may be resected to undermine the ventriculotomy and prevent proximal stenosis from muscular obstruction. All efforts will be made to minimize both the ventriculotomy and the resection of any RV muscle. The shunt may be brought to the left or right of the neoaorta, so as to easily reach the PA without compressing the native proximal aorta. All other aspects of the Norwood procedure will be identical regardless of shunt technique.

There are situations where a MBTS or RV-to-PA shunt is technically not feasible. Although very rare, some of these situations will only be determined by the operating surgeon at the time of the Norwood procedure. An example of a scenario where a MBTS may be contraindicated is the subject with an aberrant right subclavian artery and a right carotid artery that is deemed to be too

small to support a MBTS. An example of a situation in which an RV-to-PA shunt may be technically impossible may occur if there is a significant conal coronary artery in the area of the proposed shunt origin. In these events, a cross-over will be considered. In the extremely unlikely event that neither shunt can be used, a central shunt may be necessary. A central shunt originates directly from the neoaorta and attaches to the PA in the same manner as a MBTS. A central shunt is a systemic artery to pulmonary artery shunt and will be included with the MBTS cohort as it exhibits the same hemodynamic effects as a MBTS. It is also possible that after the placement of the initial randomly assigned shunt, the subject may fail to separate successfully from cardiopulmonary bypass. The surgeon may place another type of shunt in an attempt to salvage the patient. Although every effort will be made to use the shunt to which the subject is randomized, the surgeon may choose an alternative shunt at any time during the operation, if it is deemed to be in the subject's best interest. Such subjects will be included in the group corresponding to the shunt that they were randomized to receive.

C.4.2 Study Completion

Subjects will be considered to have completed the study if they have completed the assessment at age 14 ± 1 months post-randomization. As described in the informed consent form (Appendix A), subjects may also be contacted via a brief telephone call or letter, until 5 years of age to confirm vital/transplant status at the end of the entire trial period, if this information is not available in the medical record. If a patient receives a heart transplant, then *only* genetics data within the trial period (if consented) and vital status until 5 years of age will be collected.

C.4.3 Indications for Withdrawal From the Study

- Patient/guardian refusal to continue in the study
- Participation in the study felt to be not indicated by the attending cardiologist or study investigator

The reason for withdrawal and the circumstances of withdrawal will be documented for all patients withdrawn from the study. Every effort will be made to obtain permission to continue to follow subjects to obtain data for primary outcome variable at 12 months post-randomization.

C.4.4 Other Treatments/Interventions

Subjects will be cared for at the discretion of their surgeon, cardiologist, and primary care provider. The need for additional procedures and all medications will be recorded on study forms.

C.5 Measurements

C.5.1 Schedule of Measurement

Table 5. Schedule of Trial Measurements

	Baseline	Follow-up					
Measurement	Study entry	Norwood hospitalization	Discharge	Pre-stage II	Stage II hospitalization	Age 12 mo	Age 14 mo
Medical History	X		X	X			X
Ht, Wt, head circ	X		X	X			X
Anatomic subtype	X						
ICU/hospital course		X			X		
Echo	X		X	X			X
Catheterization*				X			
APOE genotype†		X					
Death or transplantation						X	
Neuro-developmental evaluation							X
Clinical genetics evaluation†		X					X

*Not mandated by protocol, performed at the discretion of the attending cardiologist.
†Not mandated by protocol, performed only with consent of family.

C.5.1.a Baseline Data

Demographic and pre-operative data will be collected including pregnancy history, birth weight, race, gender, gestational age, APGAR scores, condition and anatomical diagnosis at presentation, occurrence of significant preoperative complications, and age at operation. All echocardiograms performed before enrollment will be reviewed both locally and in the core lab to evaluate anatomic and ventricular function. The results of the clinical evaluation by a geneticist , if performed, will be recorded. Any procedures or significant events will be noted.

C.5.1.b Follow-Up Visits

Follow-up data will be obtained at 5 time points: hospitalization/discharge for Norwood procedure, before the stage II palliation, hospitalization for the stage II palliation, 12 months post-randomization, and age 14 months. In addition, to determine vital/transplant status at the end of the entire trial period, the subject's family may be contacted by phone or letter, if this information is not available in the medical record. This contact will occur annually so that the follow-up information is current, with the number of contacts varying according to the

date of randomization of the subject (i.e., the first subject enrolled in the trial may have 3 contacts after the 12 month time point, but patients enrolled in the final year of the trial period will be contacted at most once after the 12 month study time point). However, to provide for long-term follow-up of this unique patient population, the consent form is written to allow for annual contact of each subject up to age 5 years.

- Echocardiographic images will be obtained for analysis at study entry (see Section C.5.1.a), after the Norwood procedure, before the stage II palliation and at age 14 months. All studies except the one at age 14 months are part of routine care.
- Height, weight and head circumference will be recorded at the time of each echocardiogram.
- A buccal smear for APOE genotype will be obtained on consenting subjects during the hospitalization for the Norwood procedure and sent to the Genetics Core Laboratory.
- If a routine cardiac catheterization is performed before the stage II palliation, data will be recorded, and the images sent to the Angiographic Core Laboratory.
- Data regarding whether the subject is alive and whether heart transplantation has been performed will be collected at 12 months post-randomization.
- The Bayley Scales of Infant Development, MacArthur Communicative Development Index, and Functional Status II-Revised questionnaire will be performed at age 14 months.

C.5.1.c Windows for Visits

- The Norwood procedure, stage II palliation, and cardiac catheterization will be performed at the discretion of the subject's cardiologist.
- The echocardiogram after the Norwood procedure will be performed within 28 days of the surgery.
- The pre-stage II palliation time point will be obtained 2 weeks prior to the surgery with a window of ± 2 weeks, up until the time of the stage II procedure.
- The age 14 month visit will occur with a window of ± 1 month.

C.5.2 Outcome Variables

Outcome variables have been chosen that will reflect the improved coronary perfusion associated with the RV-to-PA shunt compared with the MBTS (Table 6). The primary outcome is death or

cardiac transplantation by 12 months post-randomization. Details regarding the secondary outcome measures are provided in Sections C.5.2.a-e.

Table 6. Outcome Variables

Primary Outcome

Death or cardiac transplantation at 12 months post-randomization

Secondary Outcomes

Death or cardiac transplantation at trial end based on all available follow-up

Morbidity after the Norwood procedure

1. Open sternum (yes or no)
2. Extracorporeal membrane oxygenation, ECMO (yes or no)
3. Cardiopulmonary resuscitation, CPR (yes or no)
4. Time to initial extubation (hours)
5. Total number of days ventilated
6. Length of ICU stay (days)
7. Length of hospital stay from the day of surgery (days)

Incidence of unintended cardiovascular interventional procedures (Composite and Individual)

1. Balloon dilation of the shunt or branch pulmonary arteries
2. Stent placement in the shunt or branch pulmonary arteries
3. Shunt revision
4. Crossover between MBTS and RV-to-PA shunt
5. Balloon dilation, stent placement or surgical revision of the neo-aorta
6. PA reconstructions, other than those undertaken as a standard component of the stage II procedure

Evaluation of RV function by echocardiography

1. Right ventricular BSA-adjusted Z-scores for diastolic and systolic volumes and age-adjusted Z-scores for ejection fraction
2. Absolute values for diastolic and systolic volumes and ejection fraction
3. dP/dt obtained from the TR jet
4. Severity of TR
5. Doppler Tissue Imaging (DTI) of the RV
    - Systolic annular acceleration and peak velocity
    - Isovolumic myocardial acceleration

Table 6. Outcome Variables (continued)

Pulmonary arterial growth

1. Angiographic PA cross-sectional area, as determined by the Nakata index
2. Ratio of distal to proximal PA diameters measured by angiography
3. Incidence of angiographic discrete PA stenosis
4. Change in echocardiographic Nakata index from Norwood procedure to stage II procedure.

Stage II perioperative morbidity

1. Cardiopulmonary resuscitation (CPR) – yes or no
2. Number of hours to initial extubation
3. Total number of days ventilated
4. Length of ICU stay (days)
5. Length of hospitalization from the day of stage II surgery (days)

Neurodevelopmental outcome

1. Bayley Scales of Infant Development II (BSID-II):
   - Psychomotor Development Index and Mental Development Index
2. MacArthur Communicative Developmental Index
3. Functional Status II-Revised questionnaire

C.5.2.a Operative Course and Postoperative Morbidity

Intra-operative variables at the time of the Norwood procedure and the stage II palliation will be recorded including operative, bypass and deep hypothermic circulatory arrest or regional cerebral perfusion times, details of bypass (i.e. lowest temperature, use of modified ultrafiltration), shunt type and shunt diameter. Postoperative data regarding morbidity will be collected by daily review of the hospital chart. Any procedures or significant events in the post-operative period will be recorded. For the stage II palliation, the reason for the timing of the procedure including elective-no interstage problems, progressive hypoxemia, failure to thrive, shunt occlusion, neoaortic arch obstruction, and $\geq$ moderate AVV insufficiency as well as the age at surgery will be tracked. Occasionally, at the time of the stage II palliation, it is necessary to address other significant branch PA stenoses with patching, stenting or dilatation, which would not be a usual part of the typical bidirectional Glenn or hemi-Fontan procedure. These non-routine interventions will be tracked as an outcome as outlined in Secondary Aim A.3.

C.5.2.b Cardiovascular Interventional Procedures

A record of all cardiovascular interventional procedures will be obtained by interview of the parent or legal guardian at the time of study visits and by review of the medical record.

C.5.2.c Echocardiography

All echocardiograms performed before enrollment will be reviewed to evaluate anatomy and ventricular function. Follow-up echocardiograms are planned within 28 days following the Norwood procedure, within 2 weeks prior to the stage II palliation, and at age 14 months. The echocardiogram will consist of a complete two-dimensional echocardiogram and Doppler evaluation. Height and weight will be measured at the time of each echocardiogram as outlined in Appendix C. Systolic, diastolic, and mean blood pressure will be measured using an automatic vital signs monitor. The use of sedation will be managed according to the practice at the individual center. Each clinical center is provided an analog-to-digital conversion system to convert original videotape recordings to digital format, following which they will be transmitted to the DCC according to the procedures described in Appendix G.

Collection of echocardiographic data at all four time points loosely corresponds with current clinical practice. Longitudinal comparisons will allow identification of variables that may impact the randomized surgical outcome as well as information of any differences in RV function that appear either with surgical intervention or as part of the natural history of the particular shunt used.

In addition to the raw measurements and derived index, data will be expressed as Z-scores relative to body surface area or age in normal subjects. Z-scores indicate the position of each measurement relative to the normal population expressed as the number of standard deviations from the population mean. Normal data regarding RV volumes is currently being collected and is expected to be available for the trial. Reporting the data as Z-scores adjusts for the effects of variation in body size or age.

C.5.2.d Assessment of Pulmonary Artery Growth

PA growth will be assessed by echocardiographic and angiographic methods as outlined in Appendix F. Cardiac catheterization will be performed at the time of the stage II palliation as part of standard clinical care in the majority of the study subjects. If the patient does not

have a catheterization, the patient will remain in the study and complete all other required study tests. PA growth will be measured by echocardiography in all subjects.

From the angiogram, the proximal and distal PA diameters will be measured in a standardized manner and used to calculate the ratio as an assessment of discrete PA stenosis (38, 48). One of the benefits of this technique is that it can be used in an equivalent fashion in patients after MBTS or RV-PA shunt, despite variability in camera angle and angiographic technique. While vessel area might be a more desirable way to quantitate stenosis, it is unlikely that most patients would have angiographic data that would allow for a calculation of vessel area for both the proximal and distal PA. The severity of stenosis will be graded based on the ratio of distal to proximal PA.

- Severe stenosis is defined as a ratio of 0.49 or less.
- Moderate stenosis is defined as a ratio of 0.65-0.50.
- Mild stenosis is defined as a ratio of 0.85-0.66.

C.5.2.e Neurodevelopmental and Functional Status

The Bayley Scales of Infant Development-II will be administered at age 14±1 months by trained personnel with the infant in a calm, quiet state. The testing personnel will remain blinded to the treatment assignment of the subject belongs. The MacArthur CDI, and the Functional Status II-Revised are parent report questionnaires that will be completed during the age 14±1 month visit (see Appendix E). Both the MacArthur CDI and the Functional Status II-Revised will be self-administered. A Spanish version will be provided for parents who prefer Spanish. If the parent is unable to read either English or Spanish, the questionnaire will not be completed but the subject will remain in the study.

C.5.3 Effect Modifiers

C.5.3.a Measures of Somatic Growth

Weight, recumbent height and head circumference will be measured as recommended by the CDC and National Center for Health Statistics (see Appendix C). Weights will be obtained on unclothed infants. Height and weight will be used to calculate body surface area for calculation of echocardiographic Z-scores (see Section C.5.2.c). Absolute weight values will also be translated into the corresponding Z-scores for age and height as determined by the National Health and Nutrition Examination Survey for comparison (see

Appendix C). Absolute height values will be transformed into Z-scores for age in a similar manner.

C.5.3.b Apolipoprotein E Subclasses

A buccal smear will be obtained on consenting subjects during the hospitalization for the Norwood procedure and sent to a Core Laboratory for analysis (Appendix D).

C.5.3.c Socioeconomic Status

Socioeconomic status has been identified as associated with scores on standardized developmental assessment tools. For this reason, SES will be measured at the age 14 month study visit using the Hollingshead Four Factor Scale (62).

C.5.3.d Clinical Evaluation by a Geneticist

Each consenting subject will undergo evaluation by a geneticist before hospital discharge. In addition, repeat evaluation will be performed at the 14 month follow-up visit. This second evaluation will provide an opportunity to assess the participants for any abnormalities not evident during the neonatal period. The purpose for this study will be to identify the presence of other inherited conditions. These data will be considered both in evaluating the primary outcome as well as secondary outcomes. The evaluation will be performed by a pediatric geneticist. The parent(s) will receive counseling appropriate to any new diagnosis made during this evaluation and appropriate clinical care will be performed.

C.6 Adverse Events

C.6.1 Definition

An adverse event is any untoward medical occurrence experienced by a subject that occurs in temporal association with the use of an administered investigational intervention, whether considered intervention-related or not. An event can be any sign, symptom, laboratory abnormality, or disease.

C.6.2 Classification of Adverse Events

C.6.2.a Relationship

In non-surgical trials, investigators and monitors are asked to categorize whether adverse events are related to the study intervention. In this trial of two accepted and similar surgical procedures, assessment of relationship of the intervention to any adverse event is at best imprecise. Analysis of adverse event data by the actual shunt received at the conclusion of the trial will provide definitive data on this point, and participant safety is not impaired by waiting for this analysis.

C.6.2.b Seriousness

Consistent with standard clinical trials practice, a Serious Adverse Event is defined generally as any event that:

(a) Is fatal; or

(b) Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred); or

(c) Is severely or permanently disabling; or

(d) Necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or

(e) Necessitates or prolongs hospital admission; or

(f) The Principal Investigator, medical monitor, or DSMB considers a serious adverse event.

Because many normal peri-operative occurrences meet these criteria, only the following six events have been identified as specific Serious Adverse Events for the purposes of this trial, (see also Section C.6.3):

(a) Death

(b) Acute shunt failure requiring intervention

(c) Cardiac arrest requiring CPR and medications

(d) Cardiopulmonary insufficiency requiring ECMO

(e) Cardiovascular re-operation (unplanned)

(f) Necrotizing enterocolitis requiring laparotomy

In addition, any other event that in the opinion of the study investigator is considered to be a Serious Adverse Event may be classified as such and will then adhere to the rules for expedited reported described in C.6.3.1.

If a clinical event or finding does not meet the definition of "serious" per above, these non-serious events will be classified using the M code complications list and will be reported as a complication rather than as an adverse event (see Section C.6.3).

C.6.2.c Expectedness of the Event

All serious adverse events will be evaluated as to whether their occurrence was expected (as described in the protocol and consent form), or whether it was not expected to occur.

1 = "Expected": An event is considered expected if it is known to be associated with the underlying cardiovascular anomaly or with congenital heart surgery, and is mentioned in the protocol, informed consent, or other study documents. An event may be expected despite the study subject's clinical state immediately prior to the event. For this protocol, expected events include:

(a) Sudden cardiac death
(b) Arrhythmias
(c) Tamponade
(d) Postoperative bleeding
(e) Postoperative open chest
(f) Postoperative chest re-exploration
(g) Postoperative electrolyte abnormalities
(h) Postoperative fever
(i) Postoperative renal dysfunction
(j) Postoperative liver dysfunction
(k) Shunt thrombosis
(l) Aortic coarctation with or without associated ventricular dysfunction
(m) Ventricular dysfunction not associated with coarctation
(n) Pericardial effusion
(o) Wound infection
(p) Reintubation after extubation following Norwood surgery
(q) Hypoxia
(r) Respiratory distress
(s) Pleural effusions

(t) Seizures

(u) Renal dysfunction associated with ventricular dysfunction

(v) Liver dysfunction associated with ventricular dysfunction

(w) Malrotation

(x) Failure to thrive

(y) Need for nasogastric tube feedings or gastrostomy

(z) Sepsis or bacteremia

(aa) General pediatric problems such as otitis media, reactive airway disease, gastroesophageal reflux, urinary tract infection, upper respiratory infection, croup, bronchiolitis including respiratory syncytial virus infection, pneumonia, gastroenteritis.

2 = "Unexpected". An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study. Thus, a cardiac death would be expected regardless of timing or the prior condition of the infant, whereas an accidental death in a motor vehicle accident would be unexpected.

C.6.2.d. Outcome

The clinical outcome of the Serious Adverse Event will be characterized as follows:

(a) Death

(b) Recovered: the patient returned to baseline status

(c) Symptoms continue

C.6.3 Data Collection Procedures for Adverse Events

1. In this surgical trial, data on serious adverse events and complications will be obtained using a multi-pronged approach that will ensure comprehensive data without redundant reporting, as follows:

The six events specified as Serious Adverse Events in Section C.6.2.b. are to be reported in an expedited fashion. Any other event that in the opinion of the study investigator is considered to meet the definition of a Serious Adverse Event should also be reported in an expedited fashion.

Significant peri-operative and other in-hospital adverse events will be collected using the Code List M Complications list and be reported as "complications" versus adverse events (Appendix I.).

Between-visit non-serious adverse events will also be recorded as complications using Code List M (Appendix I.).

Anatomic lesions, such as recurrent aortic coarctation or shunt stenosis, for which intervention occurs in the cardiac catheterization laboratory, will be captured on the data collection forms for those procedures, and will not be reported using a Serious Adverse Event form or a complication form. Although collected in a different fashion to minimize redundancy, these lesions will be included in safety analyses.

2. Elective or planned hospitalizations will not be reported as serious adverse events. These include planned hospitalizations for elective procedures.

3. Clinical findings that are present in many study subjects will not be considered complications, adverse events or serious adverse events unless they result in an intervention or treatment. These include but are not limited to:

(a) Gastroesophageal reflux disease (GERD)
(b) Vocal cord paralysis
(c) Diaphragmatic paralysis
(d) Feeding difficulties or failure to thrive

4. Any medical condition or abnormal laboratory value present at enrollment that remains unchanged or improves will *not* be reported as a serious adverse event or complication. However, worsening of a medical condition that was present at enrollment will be considered a new event and reported according to the plan outlined above.

5. The onset of an event/complication from Code List M will be recorded according to the date of the first presenting symptom.

6. Events that are continuing will be identified once as a complication. If the event/complication resolves and recurs as an independent event, only then should it be reported again as a new serious adverse event, or as a new complication using Code List M.

7. Serious adverse events will be reviewed by the Pediatric Heart Network medical monitor, the Chair of the DSMB, and by NHLBI staff.

C.6.4 Reporting

Reports of the serious adverse events in C.6.3 will be submitted to the local Institutional Review Board (IRB) and the DCC by the site investigator within one working day of notification of the event. The DCC will report the serious adverse event to the NHLBI, medical monitor, and DSMB Chair as soon as possible and no later than 7 calendar days after the event.

All events/complications recorded on Code List M during or between hospitalizations, all events recorded on cardiac catheterization and echo forms, and all events reported as serious adverse events will be tabulated and reviewed by the DSMB at their regularly-scheduled meetings, at least twice a year

C.6.5 Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials

A Data and Safety Monitoring Board has been established to oversee all Network studies. The DSMB is composed of experts in pediatric cardiology, congenital cardiovascular surgery, biostatistics and clinical trial design, and ethics, as well as a member of the public, appointed by the Director, NHLBI. The DSMB meets 2-4 times a year to review study conduct, adverse events, and any interim data.

After each DSMB meeting, a Summary Report of Adverse Events will be prepared within 30 days and will be distributed by NHLBI staff to each Principal Investigator and Nurse Coordinator with instructions that each Principal Investigator forward the Summary Report to the local IRB/REB. The Summary Report will contain the following information:

- A statement that a DSMB review of outcome data, adverse events, and information relating to study performance across all centers took place on a given date
- A statement as to whether or not the frequency of adverse events exceeded what was expected and indicated in the informed consent
- A statement that a review of recent literature relevant to the research took place
- The DSMB's recommendation with respect to progress or need for modification of the protocol or informed consent. If the DSMB recommends changes to the protocols or informed consent, the rationale for such changes and any relevant data will be provided
- A statement that if safety concerns are identified, the Program Officer will communicate these promptly to the investigators.

The Summary Reports are in addition to the DSMB minutes, which are posted on the NERI website.

C.6.6 Post-Study Procedures for Adverse Events

All unresolved serious adverse events at the time of the subject's completion of or termination from the study will be followed by the investigators until the events are resolved, the subject is lost to follow-up, or the event is otherwise explained or has stabilized. At the last scheduled contact, the investigator will instruct each parent to report any subsequent event(s) that the parent, or the subject's personal physician, believes might reasonably be related to the shunt. Any death or other clinically serious adverse event that comes to the attention of the study investigators that may be related to the shunt and that occurs at any time after a subject has discontinued or terminated study participation will be reported as in C.6.3.

C.7 Statistical Methods

C.7.1 Background Data for the Primary Endpoint

A review of previous data from the participating centers for infants born 2002-2003 was performed to calculate an estimate of the incidence of death or cardiac transplantation for the primary endpoint. For patients undergoing a Norwood procedure with a MBTS at least 1 year prior, the incidence of death or transplantation by 12 months post-op was 28% (65/236). The expected mortality for the RV-to-PA shunt is based upon the three member centers routinely performing the RV-to-PA shunt exclusively or in a significant proportion of their Norwood procedures (Children's Hospital of Boston, Children's Hospital of Philadelphia and Medical University of South Carolina). Due to a paucity of data on Norwood procedures with RV-to-PA shunts, all deaths and transplants regardless of time since procedure were counted. One-quarter of the cohort had less than 1 yr of follow-up, but the majority of events in 1 year olds occurred in the first 6 months of life. Overall, events after the stage II procedure are rare. Iannettoni et al. (71) reported 73 consecutive patients undergoing a Norwood procedure. Of the 36 patients surviving through the stage II procedure, there were no late deaths. In the single study comparing post-stage II outcomes for the two shunting techniques, Pizarro et al. (7) reported 12/12 patients receiving a MBTS and 32/32 with an RV-to-PA shunt went on to be suitable Fontan candidates. For patients receiving a RV-to-PA shunt at the three centers of interest, the 12-month mortality or transplantation rate is assumed to be 16% (14/87).

Table 7. Incidence of Death or Transplantation for Patients with a Norwood Procedure.

	Norwood Procedures with MBTS at least 1 year post-op.		Norwood Procedures with RV-to-PA shunt	
Center	Number of Procedures	Number meeting endpoint (%)	Number of Procedures	Number meeting endpoint (%)
CHOP	37	10 (27%)	36	6 (17%)
CHB	38	8 (21%)	31	5 (16%)
MUSC	19	6 (32%)	20	3 (15%)
CHW	25	3 (12%)		
MCHC	58	20 (34%)		
Toronto	27	4 (15%)		
Columbia	20	7 (33%)		
Duke	2	0 (0%)		
Utah	10	7 (70%)		
Total	236	65 (28%)	87	14 (16%)

(CHB-Children's Hospital Boston, CHOP-Children's Hospital of Philadelphia, MUSC-Medical University of South Carolina, CHW-Children's Hospital Wisconsin, MCHC-Michigan Congenital Heart Center)

C.7.2 Sample Size and Power

C.7.2.a Primary Endpoint

This study will be powered to detect differences in the primary composite endpoint (death or cardiac transplantation) by 12 months post-randomization. Based on preliminary data (Section C.7.1), the proportion of subjects experiencing an adverse outcome among those undergoing a Norwood procedure with the current standard MBTS is 28%. The proportion of subjects experiencing an adverse outcome is anticipated to be 16% among those receiving a RV-to-PA shunt at the three member centers routinely performing the RV-to-PA shunt exclusively or in a significant proportion of their Norwood procedures. The original trial design was based on 85% power to detect this difference. Using a two-sided, two-sample test of proportions conducted at the 0.05 level of significance, a sample of size 456, or 228 subjects per treatment arm, is required. Using an inflation rate of 2% to maintain a .05 Type I error rate with multiple interim looks at the data, the original target sample size was 466 subjects (233 per treatment arm). However, to account for treatment group crossover observed through mid-2007 (rates not shown due to blinding), the sample size target was increased to 554 subjects (277 per treatment arm) after 2% inflation for interim

looks, to achieve 80% power to detect a group difference equivalent to 28% vs. 16% prior to dilution (reduction of treatment effect in an intent-to-treat analysis) manifested by treatment crossover.

C.7.2.b Secondary Endpoints

In general, sample sizes needed to detect differences in dichotomous outcome variables are larger than those required for either continuous or ordered categorical outcomes. Therefore, this sample will provide at least 75% and for selected endpoints greater than 85% power to detect clinically important differences in secondary outcome variables such as pulmonary artery diameter Z-score, neurodevelopmental test scores, and length of stay. Estimates of the minimum detectable difference between groups for selected specific secondary outcomes follow, assuming an effective sample size based on the original trial design (i.e., the number of expected evaluable patients) of 228 subjects per group and a two-sided test conducted at a 0.05 significance level. Under the modified sample size target which achieves 80% power for the primary endpoint after incorporating dilution due to observed crossover, the minimum detectable group differences for secondary endpoints to be observed with 85% power are 7-10% larger than those reported below; alternatively, comparisons for the detectable differences stated below have approximately 75% power using the modified sample size and incorporating observed crossover.

Stage I Morbidity. Historical data from participating centers indicates that the use of ECMO and the incidence of shunt revision following the Norwood procedure each ranges from 5 to 15%. With 228 evaluable subjects per group and desired power of 85%, assuming an incidence of 10% in one group for either of these events, there is at least 85% power to detect a rate of 3% (or lower) or 20% (or higher) in the other group.

Echocardiographic Outcomes. Based on Colan (72), the standard deviation of RV end diastolic and systolic volume in a comparable pediatric population is, respectively, 27 and 13. With 85% power, the minimum detectable group difference for RV end diastolic and systolic volume is 7.6 ml and 3.6 ml, respectively, approximately a 10% difference between groups. Mean ejection fraction in the Colan cohort was 65±8%. With 85% power, the minimum detectable group difference for ejection fraction is 2.2%, clearly smaller than any clinically significant difference that we desire to detect.

Angiographic Outcome. The incidence of PA stenosis is by coincidence roughly similar to the death/transplant rates assumed for the primary outcome; therefore, we estimate that power will be at least 80% for this secondary outcome. Based on published reports (15, 73), the standard deviation for the Nakata index before stage II palliation determined by angiocardiography is 86 mm/m^2. With 228 evaluable subjects per group and desired power of 85%, the minimum detectable mean difference between the groups for the Nakata index is 24 mm/m^2. This is approximately equivalent to a 12% lower Nakata index for the RV-PA shunt group compared with the MBTS group. Power ranges from 75% to detect a mean group difference of 29 mm/m^2 to 95% power to detect a mean group difference of 21 mm/m^2.

Stage II Morbidity. Data collected at Children's Hospital Boston indicate that the mean duration of ICU stay is 3±4 days (median 2 days). With 85% power and 228 evaluable subjects per group, the minimum detectable mean difference is 1.1 days; there is only 30% power to detect a difference of 0.5 days. A log transformation, perhaps more appropriate but less interpretable, demonstrates a minimum detectable difference of 0.20 log days with 85% power. Total length of stay in hospital following stage II palliation was 10±11 days (median 6 days). With 85% power and 228 evaluable subjects per group, the minimum detectable mean difference is 2.8 days, with 60% power to detect a difference of 2.0 days. In log units, the minimum detectable difference is 0.22 days. Time until extubation was observed to be 25±28 hours (median 16 hours). With 85% power and 228 evaluable subjects per group, the minimum detectable mean difference is 8.4 hours.

C.7.3 Analysis Plan

C.7.3.a Primary Analysis of the Primary Endpoint

All primary analyses will be performed on an intention-to-treat basis. This implies that a randomized subject who received neither trial shunt may remain classified into the assigned surgical group and the vital/transplant status would be counted as an event, if one occurs, in the assigned group. However, if it is clear that the decision of whether or not to go forward with a trial shunt is not influenced by knowledge of the assigned shunt, then no bias is incurred (and intention-to-treat is preserved) by excluding those patients from analysis. A review panel consisting of the study chair, a DCC statistician, and a minimum of two members of the protocol subcommittee, one of whom must be a surgeon, will review each case in which a randomized patient receives neither trial shunt. No panel members will

review a case from their own site. A brief synopsis of the situation will be provided by the DCC to the panel, blinded to site and treatment arm. If the review panel determines that the decision to cancel the assigned trial shunt was clearly not influenced by treatment assignment (e.g. the patient dies prior to surgery), then that patient will be excluded from analysis. Primary outcome data will be collected for these patients so that the impact of the exclusions on primary analysis results can be assessed. Crossovers will not be reviewed and will be analyzed according to treatment assignment.

The proportion of MBTS vs. RV-PA shunt subjects experiencing the primary trial endpoint, death or heart transplantation at 12 months post-randomization, will be compared using a Fisher exact test. Although the primary goal is to assess the relative efficacy of the two surgical strategies at the end of one year, and the exact test above will be considered the primary trial result, it is also of interest to identify whether the failures in the two arms occur at different points in time during the first year of life. Therefore, a comparison of the primary endpoint in the two trial arms will also be conducted using the Kaplan-Meier method for estimation and the Gehan-Wilcoxon test, which places more weight on early failure times due to weights determined by risk set sample size. This weighted logrank test will test the hypothesis that differences in the surgical strategies are present early in time. This test may be significant even if the overall comparison of proportions at one year or an unweighted logrank test is not. Finally, a competing risks analysis will be conducted to fully characterize patient risk by treatment group (74). In this analysis, each subject will be classified into an absorbing state: death, transplantation, stage 2 palliation performed or alive with no transition and the probability of each of these states as a function of time since Norwood (randomization) will be estimated.

C.7.3.b Secondary Analysis of the Primary Endpoint

There are three classes of secondary analyses that will be conducted to compare the two trial arms with respect to the primary trial endpoint (death or transplantation by one year):

1) covariate-adjusted analysis;
2) comparison of groups according to treatment actually received (non-intention-to-treat); and

3) comparison of groups after exclusion of any subjects randomized but found after randomization to have been trial ineligible at the time of enrollment. Such discrepancies will be identified by the echo core laboratory, and final eligibility status will be determined by a review panel, with no panel member reviewing a case from his/her own center.

Due to the use of randomization, any observed differences between the two trial arms with respect to pre-operative characteristics must, by definition, be due to chance; hence statistical inference will be used only as a guideline to assess the magnitude of imbalance between the trial arms with respect to baseline characteristics. Characteristics with an imbalance at the 0.20 significance level in univariate analysis will be included in a multivariate logistic regression model (or Cox model if examining time to event) for the primary endpoint, retained if significant at the 0.10 level, and the covariate-adjusted odds ratio for one-year death/transplant will be reported. This approach will provide an estimate of treatment efficacy that removes the effect of any single or aggregate imbalances that are identified. The second class of secondary analysis is a non-intention-to-treat approach-- the two treatment (surgical) arms will be reconstituted, classifying subjects according to the surgical procedure they actually received at the time of planned palliation. If for some reason a subject did not undergo surgery at all, this subject will be excluded from the non-intention-to-treat analysis.

Both the second and third secondary analyses of the primary endpoint will effectively provide an estimate of treatment efficacy after a) correctly classifying subjects to received surgical technique (outside of the randomization scheme) and b) removing subjects who were immediate crossovers (i.e., were determined to have coronary anatomy that was not suitable for a randomized study).

C.7.3.c Analyses of the Secondary Endpoints

Analytic methods for the secondary endpoints will be varied and depend on the form of the secondary endpoint. For continuous endpoints that are absolute values, Student's t-test will be used to compare group means. In instances of severe skew due to outliers (which may be observed in length of stay for example), a nonparametric test may also be conducted. For length of stay (overall and ICU), a time to event (time to discharge) analysis will also be conducted. For dichotomous endpoints, such as morbidity rates at one year, a Fisher exact test will be employed. For comparison of long-term MBTS vs. RV-to-PA shunt efficacy, a

logrank test will be conducted to compare the event-free survival curves for the two groups, using all available follow-up from the trial; follow-up will range from 14 months for the last randomized subject, to 3-4 years for the first randomized subject, depending on the length of the accrual period. For ordered multinomial variables, such as PA stenosis category, the Mantel-Haenszel test for linear trend will be used to compare the distributions in the two surgical groups. For measures that examine change over time, such as change in RV diastolic or systolic diameters measured by echocardiography, linear regression of the one-year value on the pre-Glenn shunt surgery value will be used to obtain the most powerful test of treatment efficacy. If more than two time points are available, repeated measures analysis of variance will be employed, but interpretation of such analysis will be conditional (that is, those with 3 time points of data represent non-transplanted survivors). Similarly, it should be noted that all analyses of secondary endpoints are conditional—if an infant dies or is transplanted before the stage 2 palliation or the final study visit, then complete case analyses of, for example, PA stenosis or RV function at age 14 months will be based only on non-transplanted survivors. A sensitivity analysis may also be conducted with imputed values based on last value carried forward and/or a 'worse case' value assumed for patients who die or are transplanted. All primary analyses of secondary endpoints will be according to the intention-to-treat principle. Secondary analyses of secondary endpoints will be conducted as described for the primary trial endpoint in Section C.7.3.b.

C.7.3.d Interim Monitoring and Early Stopping

A Data and Safety Monitoring Board (DSMB) has been established by NHLBI to monitor this trial. The DSMB will meet one to two times a year.

Efficacy. In addition to routine data reviews a formal early stopping procedure will be used to monitor the trial for large treatment differences. An O'Brien-Fleming stopping boundary, allowing for flexibility in the exact times of the interim analysis, will be used for this purpose (75, 76). The O'Brien-Fleming plan is conservative in the sense that it is difficult to reach the boundary during the trial. Therefore, most of the Type I error is conserved for the final analysis and the effect on statistical power is minimal. Three formal interim analyses will be conducted when one-quarter, one-half, and three-quarters of patients would be expected to reach the 12 month visit, in addition to one unscheduled look that occurred when 42% of subjects had been randomized one year earlier. The Lan-DeMets methodology (77) will be used to adjust the boundary appropriately if the interim analyses do not fall at exactly the planned information increments. The primary endpoint will be analyzed and the nominal

p-value compared with the stopping boundary to judge the significance of the treatment effect while adjusting for multiple testing. For the information increments used and for those planned, the nominal p-values to reject the null hypothesis at the first to fourth interim looks are 0.00005 (occurred with 28% of information), 0.001, 0.003, and 0.018, respectively, with a p-value of 0.044 required at the final analysis to declare the primary trial result significant, with an overall experiment-wise alpha of 0.05 (Table 8)

Table 8. Early Stopping Rule

Analysis	**First**	**Second**	**Third**	**Fourth**	**Final**
Fraction of total information*	.28	.42	.51	.75	1.00
Nominal p-value to reject null	.00005	.001	.003	.018	.044

*Actual information fraction for first to third looks

Even if there is a statistically significant treatment difference at the interim analysis, the DSMB may decide that an ethical imperative to stop the trial is not present.

Safety. It is possible that the DSMB may consider it necessary to stop the trial early due to safety concerns. Due to the high morbidity of this infant population, adverse event rates cannot be evaluated within a single arm; they must be compared with historical rates for this high risk group and, when sufficient data have accrued, by comparing the adverse event rates of the two trial arms. Early stopping rules are only guidelines; the DSMB may take a more global view of the trial during data monitoring (78-80). To provide this broader perspective, the DSMB reports will include summaries of accrual, patient characteristics, adverse events, compliance rates with therapy, frequency of protocol violations, data quality, primary and secondary endpoints, other information as requested by the DSMB, and any unanticipated special problems that arise during the conduct of the trial.

C.7.3.e Subgroup Analyses

To determine whether the effect of a MBTS vs. Sano technique differs across subgroups, separate treatment comparisons will be made within the following subgroups:

- Birth weight: < 2500 g vs. ≥ 2500 g
- Pre-operative tricuspid regurgitation: Proximal jet width < 2.5 mm vs. ≥ 2.5 mm determined by echocardiography

- Type of cerebral perfusion during Stage I palliation: Deep hypothermic circulatory arrest vs. regional cerebral perfusion. If a patient was administered both types of cerebral perfusion during surgery, the patient will be classified as having undergone deep hypothermic circulatory arrest.
- Experience of the surgeon: Average number of Norwood procedures performed on randomized patients per year (as a continuous variable), and classified as $\leq$ 5, 5-10, 11-15, >15 procedures per year.
- Center volume: Average number of Norwood procedures performed on randomized patients per year (as a continuous variable), and classified as $\leq$ 10, 11-25, 26-40, >40 per year.

Covariate by treatment group interaction tests will be performed to test whether the treatment effect is homogenous across subgroups. Statistical testing within subgroup will not be conducted unless the interaction test p-value is $\leq$ 0.10.

C.7.3.f Site and Cohort Differences

During the ongoing trial, analyses will be conducted on a periodic basis to assess site differences in protocol violation rates, enrollment rates, subject characteristics and adverse event rates. Differences identified may lead to a site visit to review subject data. The characteristics of patients who are screened for but do not participate in the trial will be compared with randomized subjects. This analysis will allow assessment of the generalizability of trial findings and whether the enrolled subject cohort is representative of the entire patient population

C.8 Data Management

C.8.1 Information Flow

Data will be received from several sources, including the clinical sites and Core Laboratories. The flow of data among the units is illustrated in Figure 5.

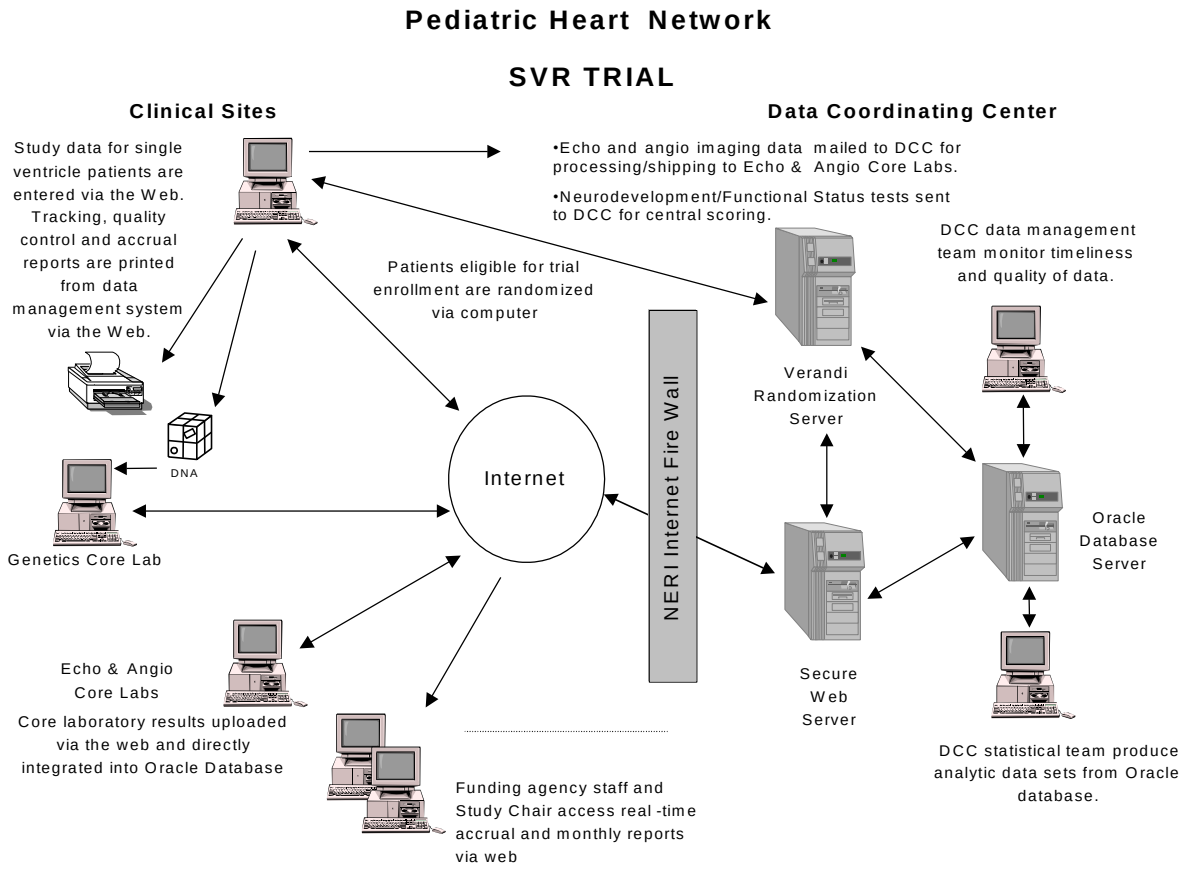


Figure 5. Data Management System and Information Flow

Clinical sites will enter data over the Internet using the Advanced Data Entry and Protocol Tracking (ADEPT) software, a customized and secure Web application (see Section C.8.2). The DCC will also be able to perform central data entry and editing to accommodate sites or central labs that submit paper copies of data forms. Sites will send buccal smear specimens directly to the Genetics Core Laboratory for central processing, and results of tests performed by these laboratories will be electronically transmitted to the DCC and stored in the ADEPT Data Management System (DMS). Echocardiogram and angiogram data files from clinical sites may be transmitted to the DCC via the Web using the PHN File Transfer Program (FTP) site at the New England Research Institutes (NERI) or submitted on other storage media, such as optical disk or CD-ROM. The DCC will forward the echocardiogram and angiogram data to the Echocardiography and Angiography Core

Laboratories, respectively, either electronically or by FedEx. Results of studies performed by the Echocardiography and Angiography Core Laboratories will be directly uploaded to an Oracle database at the DCC or entered electronically using the ADEPT DMS.

C.8.2 Overview of Data Management System

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at NERI, and then stores these data centrally at the DCC. Information entered into the data entry system will be by subject study identification number; names will not be linked with subject data in the database. Clinical sites will maintain records linking the subject name with the identification number assigned for the study in secure areas. Sites will have full access to their own data and be able to view these data remotely, over the Internet.

The ADEPT data entry system will include real-time field level validations and context sensitive help. Electronic data entry forms will be formatted using HTML to resemble closely the paper-based study instruments. These forms will be enhanced with client side JavaScript code to ensure rapid data entry, proper validations of all data fields, and proper skip patterns within study data forms. Data will be 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 of the Internet infrastructure, the ADEPT system has a dial-in backup system to allow for dial-up access to the DMS.

NERI's proprietary VERANDI randomization system, which supports a number of different allocation methodologies, will be used for randomizing subjects. Site personnel will randomize subjects over the Internet as described in Section C.3.3.

Key capabilities of the ADEPT system are described below.

C.8.2.a Data Entry and Editing

The data entry system will include a number of standard features designed to ensure consistently high quality data. Each question on a study form will be associated with a validation, and validations will be executed in real-time during data entry. If the response to a particular question falls outside the range of allowable values specified in the validation for that question, the user will be alerted so that the error can be corrected immediately.

Validations will include both inter- and intra-instrument data checks. In addition to alerting the user to invalid entry of items, edit reports will be automatically generated at the completion of data entry for a form. These edit reports will provide the information necessary to investigate any data entry errors or resolve questions regarding out-of-range or questionable values. Edit reports will list the subject identification number, instrument name, and a detailed description of why each specific data item was flagged. These edit reports can be printed out and reviewed by a supervisor, or returned to the data collector for resolution.

The ADEPT system will track expected, partially completed, and missing data entry forms by instrument and data collector. Data entry quality will be monitored through a sample-based, double data entry quality control system. This quality control system utilizes a self-adjusting algorithm to enforce higher double data entry rates on data entry staff that have higher error rates. This system also allows for a minimum double data entry rate to be specified for each individual study instrument. This minimum rate of double data entry is adhered to regardless of a data entry staff's error rate.

C.8.2.b Reporting

The ADEPT system will produce visit schedules to assist Clinical Site staff in scheduling of appointments, and visit control sheets that will list all of the forms and procedures for a scheduled visit. In addition, the system will produce a variety of reports in both graphical and tabular format, as applicable, for the Study Chair, Program Officer, clinical site and Core laboratory staff. These will include:

- Study Instruments pending entry
- Study Instruments pending edit resolution
- Missing data rates
- Time between collection and entry of data
- Time to physically key each study instrument
- Audit logs for all edits to study data
- Subjects with overdue visits
- Reimbursement information for sites and Core Laboratories
- Other customized reports will be developed within the ADEPT system as needed.

C.8.2.c Data Security and Integrity

The Web-based components of the data management system utilize several levels of security to ensure privacy and integrity of the study data as noted below:

- Web access to ADEPT requires use of assigned user names and passwords;
- Passwords are changed every 90 days;
- Web-based data entry uses secure socket layer (SSL) data encryption;
- Access to any study-specific system features are controlled by Oracle database rights and privileges;
- Oracle archive files are backed up daily;
- There is a full Oracle back up weekly;
- Back-up files are stored off site in safety deposit box;
- Duplicate Windows 2000 servers are available to replace the Oracle or Web Server;
- Primary Identification is via study I.D.;
- Access to electronic linkage limited by Oracle Database Administrator;
- Access to hard copies of linkage kept in locked cabinets by Clinical Center Coordinators;
- NERI firewall limits which internet protocols are allowed to access the Web server;
- No direct access is allowed to the Oracle server from the Internet;
- NERI's firewall monitors for unusual (hacker) activity and automatically notifies NERI IS staff.

All study data will be stored on NERI's Microsoft Windows 2000-based, Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. The Oracle archiving and back-up system ensures minimal data loss, even in the most catastrophic system failure.

C.9 Quality Control

This section describes the quality control program that will be implemented as part of the study to ensure standard implementation of the protocol, protocol compliance, and data integrity. The DCC will develop and update the Manual of Operations in collaboration with study investigators and Core Laboratory directors. In addition, an ADEPT Manual will be developed for clinical site and Core Laboratory personnel who will be using the ADEPT data management system. The two manuals will serve as both training and reference manuals and will be accessible on NERI's PHN website.

C.9.1 Clinical Center Coordinator Training

The DCC, Study Chair, and the Norwood Trial Subcommittee will provide central training of clinical center staff in the areas of protocol implementation, data collection and management, collection and handling of imaging data, medical records abstraction, anthropometric measurement techniques, operative techniques, and quality control expectations. Training manuals will be prepared that reflect clearly and succinctly the learning goals for clinical coordinators and represent the skills and protocol components required to collect quality data. Training follow-up will be completed through conference calls and site visits.

C.9.2 Certification of Personnel

Echocardiography and cardiac catheterization personnel at each center will undergo sessions on standardization of technique as required by the Core Laboratories. All echocardiograms, genetic samples, and cardiac angiograms will be read in a Core Laboratory. Poor quality studies may necessitate site visits.

C.9.3 Data Monitoring/Site Visits

Each clinical site will be visited once by representatives from the DCC and the NHLBI during the study period. The primary roles of the site visit team will be to evaluate general protocol compliance and adherence to Institutional Review Board requirements, review site data files for correct filing of copies of consent forms and study forms, audit a random sample of records to assess data integrity, and identify and resolve general problems with study progress. At each site visit, the site monitor will review procedures, observe form completion and data entry (where applicable), and assess adherence to protocols and flow. A random sample of medical records will be reviewed in order to determine whether reporting of data has been accurate and complete. Follow-up actions by the site coordinator or investigator and a schedule for completion will be identified at each site visit. An evaluation checklist will be completed at each site visit for inclusion in a Site Visit Report to the investigators. New staff will be trained and existing staff will be

retrained, if necessary. Site coordinators will be expected to provide materials and answer questions prior to and during these visits.

The DCC may conduct site visits to each Core Laboratory during the first year to review in-house quality assurance (QA) and quality control (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.

D. STUDY LIMITATIONS

Study limitations include the following:

- Although the study will be a prospective, randomized trial, it will not be possible to blind all of the subject's care providers as to the type of shunt. The subject's surgeon will know the technique. The subject's primary cardiologist will be able to determine the type of shunt from physical exam and routine follow-up echocardiograms; however, the primary trial endpoint is objective and therefore unlikely to be affected by the unblinded design. The neurodevelopmental specialist will remain blinded to treatment assignment.

- The study may be underpowered for subgroup analyses and some secondary endpoints.

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