# THE RELATIONSHIP BETWEEN FUNCTIONAL HEALTH STATUS AND LABORATORY PARAMETERS OF VENTRICULAR PERFORMANCE AFTER THE FONTAN PROCEDURE

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# Pediatric Heart Network

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## PROTOCOL OVERVIEW (ABSTRACT)

In this cross-sectional study we will determine the interrelationships between health status and measures of cardiac performance in children 6-18 years of age with congenital heart disease who have undergone a Fontan procedure as surgical treatment for functional single ventricle.

Administration of health status questionnaires, maximal exercise testing, cardiac magnetic resonance imaging (MRI), echocardiography and B-type natriuretic peptide (BNP) analysis will be performed prospectively within a single 3-month window for each subject. Fontan procedure characteristics, patient age, ventricular morphology, and clinical history will be obtained to determine whether correlations between health status and measures of ventricular performance vary as a function of these patient and surgical characteristics.

The goal of this study is to identify one or more quantifiable measures of cardiovascular performance that correlate with health status following the Fontan procedure. Achieving this goal will allow appropriate and efficient endpoint selection for clinical trials such as administration of ACE inhibitors to Fontan patients. To be successful, such a measure must provide: 1) a sufficiently high level of precision and range of measurement, and 2) a high degree of correlation with health status such that it can be used as a clinically acceptable and statistically powerful outcome measure in future therapeutic trials.

Development of such a quantifiable measure of ventricular performance will significantly enhance the field of pediatric cardiology. To date, clinical trials in pediatric cardiology and particularly those involving Fontan patients have been hampered by small sample sizes and by the lack of a definable primary clinical outcome that occurs with sufficient frequency to be useful. Consequently, the Pediatric Heart Disease Clinical Research Network views this multi-center cross-sectional study as a critical and necessary first step in developing evidence-based systems for the treatment of children with complex congenital heart disease who have undergone a Fontan procedure.

## A. SPECIFIC AIMS AND HYPOTHESES

### A.1 Primary Aim

The primary aim of this study is to determine the relationship between: a) laboratory measures of exercise capacity and systemic ventricular function, and b) indices of overall health and functional status in Fontan patients 6 to 18 years of age. Specifically:

1. **Exercise Capacity** – To determine the relationship between: a) anaerobic threshold, oxygen pulse and maximal oxygen consumption, and b) Child Health Questionnaire (CHQ) and Congenital Heart Adolescent and Teenager (CHAT) questionnaire scores.
   ***Hypothesis:*** *Exercise capacity is an important determinant of health status.*

2. **MRI Assessment** – To identify the relationships between: a) ventricular mass, end-diastolic volume, mass/volume ratio and ejection fraction, and b) CHQ and CHAT questionnaire scores.
   ***Hypotheses:***
   a) *Lower mass/volume ratio is predictive of better health status;*
   b) *Higher ejection fraction is predictive of better health status.*

3. **Echocardiographic Assessment** – To determine the relationship between: a) diastolic ventricular function and atrioventricular (AV) valve regurgitation, and b) CHQ and CHAT questionnaire scores.
   ***Hypotheses:***
   a) *Impaired diastolic function is predictive of poorer health status;*
   b) *More severe AV regurgitation is predictive of poorer health status.*

4. **Biochemical Assessment** – To determine the relationship between: a) B-type natriuretic peptide (BNP), and b) CHQ and CHAT questionnaire scores.
   ***Hypothesis:*** *BNP level will be negatively correlated with CHQ and CHAT questionnaire scores.*

## A.2 Secondary Aims

1. To determine what associations exist among the results of exercise testing, cardiac MRI, echocardiography and BNP level in order to choose the optimal outcome measure(s) for randomized clinical trials in Fontan patients.
   ***Hypothesis:*** *Because there is extensive overlap in the extent to which the clinical measures of cardiovascular performance reflect the physiologic determinants of health status, a subset of these tests can be used to describe the determinants of ventricular function most efficiently and economically.*

2. To determine the effect of current age, ventricular morphology, type of Fontan procedure, presence of a fenestration and past clinical events on the correlation between measures of ventricular function and health status (CHQ, CHAT).
   ***Hypotheses:***
   a) *Right ventricular morphology and presence of a fenestration will significantly attenuate the correlation between measures of ventricular performance and health status;*
   b) *The patient's current age and surgical procedure type will not affect the correlation between measures of ventricular performance and health status.*

## B. BACKGROUND

### B.1 Introduction

The goal of surgery for the 35,000 infants born each year in the U.S. with congenital heart disease is to separate the pulmonary and systemic circulations and to assure adequate systemic cardiac output over a range of metabolic demand. For most patients, this results in a two-ventricle circulatory system with the right ventricle and left ventricle acting as two pumps in series. For the 3,000-5,000 (10%-15%) children who have a severe defect in which there is only one functional ventricle (1,2), the optimal surgical palliation culminates in the Fontan procedure. This surgical technique connects the systemic venous return directly to the pulmonary arteries (3). The single ventricle pumps blood to the body, while blood flow through the lungs is achieved passively, without the assistance of a second pumping ventricle. As a result, there is an obligate increase in the systemic venous pressure to several times normal values. In addition, flow during ventricular diastole from the pulmonary venous atrium to the

systemic ventricle is significantly dependent on the relaxation rate of the ventricle. The absence of a pulmonary ventricle means that pulmonary vascular resistance and systemic ventricular diastolic compliance are the most important determinants of cardiac stroke volume in the Fontan patient. Therefore, even minor perturbations of either resistance or compliance can be catastrophic. The current hospital mortality for the Fontan procedure is now less than 2% (4-7).

Patients undergoing the Fontan procedure have usually had two prior surgeries; all of these can contribute to significant long-term ventricular abnormalities. The first procedure, initial palliative surgery shortly after birth, improves oxygenation but causes the single ventricle to experience an abnormally high circulatory volume load and develop hypertrophy. At 6 to 8 months of age, the second surgery, a bi-directional Glenn procedure, is performed, which only partially alleviates the volume load on the single ventricle. The Fontan procedure is usually performed at 18 to24 months of age, by which time the heart has experienced and reacted to almost two years of abnormal physiology and oxygenation.

The physiological consequences of single ventricle morphology and the complex surgical approach required may have a significant negative impact on long-term ventricular function. Early volume loading leads to an increase in ventricular mass that may not regress following the Fontan (8). After the bi-directional Glenn procedure, there is an acute, abnormal increase in the ventricular mass-to-volume ratio, due largely to a decrease in ventricular end-diastolic volume. The degree of increase in ventricular mass-to-volume ratio has been shown to predict short-term clinical outcome and surgical mortality (9). Systemic venous pressure is increased in Fontan patients, which may in turn lead to the long-term elevation of neurohumoral peptides and abnormally elevated systemic vascular resistance (10). Finally, the Fontan circuit itself may lead to abnormalities in diastolic ventricular function with a loss in diastolic compliance leading to a limitation in ventricular stroke volume (11).

Fontan patients have a higher incidence of late complications than other congenital heart patients, likely due to the abnormal hemodynamic state imposed by the Fontan circulation. For example, exercise performance is significantly impaired following the Fontan procedure (see Section B.3.4 for detailed discussion). There is also an increased risk of intracardiac thrombosis and embolic phenomena, likely attributable to low-velocity flow through the Fontan circuit (12,13). Arrhythmias, including both bradycardia and tachycardia, are common following the Fontan procedure, with progressive loss of normal sinus function, and a progressive

increase in atrial flutter, junctional rhythm, and complete heart block, with many patients requiring pacemaker placement (14-16). Finally, Fontan patients are uniquely at high risk for the development of protein losing enteropathy (PLE), which occurs in 5-25% of patients following a Fontan procedure and can be life-threatening (17,18).

## B.2 Rationale for this Study

The Fontan procedure has been remarkably successful in restoring near-normal systemic oxygen saturation, reducing the demands on the systemic ventricle, and extending the lives of patients with even the most complex forms of congenital heart disease. Nevertheless, it results in an abnormal hemodynamic state and a wide variety of late complications. Despite the clinical immediacy of these well-recognized problems, and the desire for systematic diagnostic and therapeutic approaches, three general barriers have hindered evidence-based approaches to patient management and the design of clinical trials to treat these complications. First, the data used to document the issues facing the Fontan patient are primarily observational, and have come from a wide variety of single-institution studies, small patient series, and case reports. Second, procedural and management differences between and within institutions make it difficult to reach generalizable conclusions from the available data. Third, there is little prospective information, especially from multi-center studies, addressing basic questions about the effect of various management strategies on outcomes such as overall health and functional status and ventricular performance in children after the Fontan procedure.

It is a high priority of the Pediatric Heart Network to use its multicenter clinical research infrastructure to overcome these barriers, and the Network Steering Committee initially set out to design a treatment trial in Fontan patients. After careful review of the literature and available preliminary studies, however, the Steering Committee was forced to conclude that the general lack of prospective, controlled data in the Fontan population makes it impossible to design clinical trials likely to answer the important management questions in these patients. The chief difficulty is the absence of prospectively collected outcome data that would 1) provide a better understanding of how measures of ventricular performance are related to overall health status and 2) permit hypotheses to be tested about specific endpoints in a treatment trial. The proposed protocol is designed to correct this limitation and to set the stage for a treatment trial to be conducted later in this grant period.

The protocol is a multi-center, cross-sectional, prospective study of the Fontan population with central interpretation and analysis of laboratory results, which will allow for the acquisition of reliable data on a large number of patients in a relatively short time period. The overall aim is to identify the laboratory parameters that are correlated with health status in Fontan patients from 6 to 18 years of age. The information gained from this study will not only provide important information in its own right, but also will serve the vital role of providing the basis for subsequent clinically relevant, randomized clinical trials of pharmacologic therapies in the Fontan population.

## B.3 Rationale for Selection of Outcome Measures

B.3.1 Measures of Health Status

B.3.1.a Child Health Questionnaire

The Child Health Questionnaire measures the physical and psychosocial (e.g., emotional, behavioral, and social) well-being of children five to eighteen years of age (19,20). The Parent Report form (CHQ-PF50) has 50 items and the Child Report form (CHQ-CF87), which has been validated only for children in the age range 10-18 years, has 87 items. The instrument provides two summary scores: 1) a measure of physical functional status and 2) a measure of psychosocial status. The CHQ can be reliably administered in a variety of formats including child- or parent-report, interview, and mail back. The CHQ User's Manual provides age- and gender-specific normative data for 379 children in the general United States population (Table 1), as well as for six clinical samples of children, including those with chronic illnesses (e.g., asthma and epilepsy) and psychiatric problems (20). Based on these data, five to ten point differences from the normative U.S. sample for either summary score (physical or psychosocial) represent true disease effects.

**Table 1. Normative Data for the CHQ: Mean and (Standard Deviation) By Summary Scale**

| Sample: | Physical | | Psychosocial | |
|---|---|---|---|---|
| U.S. Children | 53.0 | (8.8) | 51.2 | (9.1) |
| U.S. Boys | 52.4 | (10.3) | 50.7 | (9.4) |
| U.S. Girls | 54.9 | (6.0) | 51.9 | (8.7) |
| U.S. Children, ages 5-7 | 53.1 | (10.4) | 52.5 | (7.6) |
| U.S. Children, ages 8-10 | 52.7 | (9.1) | 52.0 | (8.3) |
| U.S. Children, ages 11-12 | 53.6 | (7.8) | 50.8 | (8.6) |
| U.S. Children, ages 13-15 | 53.0 | (8.8) | 50.0 | (8.3) |
| Attention Deficit Hyperactive Disorder | 57.6 | (47.7) | 36.9 | (10.9) |
| Asthma | 47.7 | (7.2) | 52.0 | (7.5) |
| Juvenile Rheumatoid Arthritis | 42.1 | (13.9) | 53.4 | (9.2) |
| Epilepsy | 47.7 | (13.9) | 46.5 | (11.7) |

The CHQ-PF has been used in two studies of children with congenital cardiac defects who underwent surgery during infancy. Williams et al. used the CHQ-PF28 (a shorter version Parent Form) to assess 106 children who had or were undergoing staged repair for classic hypoplastic left heart syndrome (HLHS) between February 1990-March 1999 at the College of Physicians and Surgeons, New York Presbyterian Hospital and Babies and Children's Hospital, New York (21). The CHQ-PF28 mean summary scores for physical and psychosocial health were 48.5±6.3 and 42.8±9.9 respectively, the latter of which was significantly lower than the mean score for normal children. The second study, by Dunbar-Masterson et al., was of children after the arterial switch procedure for transposition of the great arteries and who had been enrolled in the initial randomized clinical trial of children undergoing the arterial switch between April 1988 and February 1992 at Boston Children's Hospital (22). CHQ-PF50 questionnaires were completed for 155 of a total of 160 eligible subjects. The median age of the children was 8.1 years at the time the parents completed the CHQ-PF50. The mean physical health summary and psychosocial summary scores were 54.0±6.1 and 49.7±9.9, respectively. These scores are similar to those of normal subjects and appear to be better than those obtained in the study of children with HLHS. The children with HLHS scored significantly lower than normative controls in: role/social limitations due to emotional or behavior difficulty, behavioral, self-esteem, global health item, parental impact-emotional, family activities, and psychosocial summary score. However, the mean scores of the HLHS patients were not significantly different from the normal reference population in the following

scales: physical function, role/social limitations due to physical health, bodily pain, mental health, parental impact-time, family cohesion item, and physical summary score.

B.3.1.b Congenital Heart Adolescent and Teenager Questionnaire

The development of disease or condition-specific health status instruments has shown considerable growth in the pediatric population. Disease-specific measures tend to have a stronger relationship with measures of disease severity than do those from generic instruments. Disease-specific measures are much more likely to be sensitive to changes and provide greater discriminative validity. Disease-specific questionnaires often have fewer ceiling effects and show more variability in scores, thus allowing for greater sensitivity and responsiveness to change—a desirable feature when trying to assess the impact of different interventions on health status. Loonen et al. have recently reported that in the setting of pediatric inflammatory bowel disease, the disease-specific questionnaire showed a greater relationship with disease severity than did the generic instrument (23). They showed that while chronic disease had a significant disease impact as noted on the disease-specific questionnaire, this was without reduced health status as assessed using generic domains. The inclusion in our study of both the CHQ, which can be compared to normative data and results from other disease populations, and the (CHAT), which is a congenital heart disease-specific questionnaire for children aged ten to eighteen years, allows us to take advantage of the different measurement properties of each instrument in a population of children with congenital heart disease.

The preliminary content of the CHAT questionnaire was developed by Kendall et al. (24) who interviewed 37 adolescents aged eleven to eighteen years with congenital cardiac disease regarding health-related concerns and self-perceived health status. The interviews were analyzed to identify recurrent themes, and questions were developed to elicit information relevant to these specific domains. Based on this work, McCrindle and Veldtman restructured the questionnaire and piloted it in 40 adolescents aged ten to eighteen years attending the cardiology outpatient clinics. After receiving feedback from the respondents, the questionnaire was revised and administered to 162 cardiology outpatients (54% males; mean age 15.1 years, range 10.7 to 19 years) with various congenital cardiac defects, as well as to 20 adolescents who completed the questionnaire twice within a 3- to 6-week period to assess test-retest reliability. Concomitant medical information was obtained. Internal consistency was assessed

using Cronbach's alpha, and external validity was assessed by comparisons with the medical information obtained. Multi-item domains included symptom frequency (Cronbach alpha 0.79), symptom intensity (0.82), activity limitations (0.83), activity worries (0.71), impact on peer relationships (0.89), impact on future achievement (0.69), cardiac anxiety (0.81) and medication adverse effects. Single-item domains included self-perceived global health status, condition seriousness, feeling different and effect on social life. Self-perceived global health status and condition seriousness was significantly correlated to all domain scores.

More recently at the Hospital for Sick Children, 25 adolescents who underwent cardiopulmonary exercise testing have completed the CHAT questionnaire, and a cross-sectional study of adolescents post-Fontan is underway with planned comparisons between the CHQ, CHAT, and PedsQL questionnaires. This research will provide additional validation for the CHAT and pilot data that may be used in combination with the results from the proposed cross-sectional study in designing a therapeutic clinical trial. Based on the past and current research described here, the CHAT questionnaire will be used in the proposed study as a validated measure of health status in patients with congenital heart disease.

### B.3.2 Echocardiographic Indices of Diastolic Function

Ventricular diastolic function has been shown to be abnormal in patients following the Fontan procedure (11). The available data on diastolic function in patients after the Fontan operation are based on indices derived from Doppler samples of atrioventricular inflow, primarily:

- E:A ratio and
- Rate of deceleration of early inflow.

These indices are highly dependent on cardiac loading conditions (25), rendering their accuracy questionable in the Fontan circulation, which is known to be characterized by elevated systemic vascular resistance and reduced preload. Furthermore, enhanced chamber compliance, which is characteristic of volume-overloaded ventricles, is not distinguishable from impaired relaxation using this methodology (26). More recently, several promising alternative approaches have been reported (25) that may overcome these limitations, including:

- Duration of pulmonary vein flow reversal during atrial systole assessed using pulsed Doppler,

- Atrioventricular valve annulus velocity in early diastole assessed using tissue Doppler, and the
- Rate of ventricular flow propagation using M-mode color Doppler.

There are insufficient available data to establish which, if any, of these indices will prove more reliable and load-independent. Faced with this uncertainty, the ease of obtaining these indices during the echocardiogram, and the absence of additional expense to the study, we will obtain these three indices in addition to the two more conventional pulsed Doppler indices for comparison with previously published data.

### B.3.3 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) is a relatively new, non-invasive imaging modality, which uses a strong magnet (1.5 Tesla in clinical use) and radiofrequency pulses to image the cardiovascular system. The technique is used to visualize anatomy and to determine physiology and function including quantitative measures of localized blood flow. Importantly, MRI can also be used to determine ventricular volumes, mass and cardiac output with accuracy independent of geometric assumptions present in other techniques such as echocardiography or angiography. Fogel et al. have used cine cardiac MRI to measure cardiac output, ejection fraction, end-diastolic volume, and ventricular mass in patients with functional single ventricle throughout all 3 stages of Fontan reconstruction (27). Imaging was performed by obtaining contiguous off-axis sagittal slices throughout the ventricular mass and then summing the appropriate areas at end-systole and end-diastole and incorporating the heart rate during the study. The results indicate that, in patients following the Fontan procedure, ventricular mass remains significantly higher compared with normal left ventricular mass index. Furthermore, resting cardiac output and ejection fraction as measured by MRI are both lower than normal (27,28).

MRI has better precision than either echocardiography or exercise testing. Bellenger et al. have demonstrated the capability of MRI to detect as little as $\pm$17 gm ventricular mass using standard magnetic resonance techniques (29). Thus, if used as an outcome measure in a clinical trial, fewer subjects would be required to achieve a desired level of power. In this observational study, cardiac MRI will provide measures of:

- Ventricular mass,
- Ventricular end diastolic volume,
- Ventricular end systolic volume,
- Ventricular mass/volume ratio,
- Quantitative measures of localized blood flow, and
- Cardiac output.

B.3.4 Exercise Testing Measures of Ventricular Performance

Maximal exercise testing provides measures of cardiac output and oxygen consumption during exercise. It is very attractive as an outcome measure in a clinical trial designed to evaluate the impact of a therapeutic intervention on children with congenital heart disease because the exercise test itself approximates closely activities of daily living experienced by a child. The purpose of including exercise testing in this study is to test for a correlation between functional health status and:

- Maximal oxygen consumption,
- Oxygen pulse, and
- Anaerobic threshold.

Current studies of exercise performance in Fontan patients show that maximal exercise performance is abnormal and limited by an inability to appropriately increase cardiac stroke volume. Driscoll reported that maximal $VO_2$ achieved by Fontan patients was 65% of predicted value for healthy subjects (30). The reason for this impairment is a decrease in cardiac output during exercise. In 1990, Gewillig et al. showed that the inability to increase stroke volume during exercise in the Fontan patient resulted in an impaired rise in $VO_2$ during exercise (31).

Little information is available regarding the longitudinal changes in exercise performance in Fontan patients. Paridon has shown that the impairment in exercise capacity is progressive over time, particularly during adolescence and young adulthood (32). In a study by Reybrouck et al. (33), twelve subjects tested an average of two years apart showed a significant decrease in $VO_2$ measured at the aerobic threshold. Analysis of the individual data points of this study provided to us by these authors show a decline of approximately 2.0% per year in aerobic capacity. In a cross-sectional study of exercise performance in patients following Fontan,

Mahle (34) also has shown a strong negative linear relationship between percent of predicted maximal $VO_2$ and the age at testing with a slope of 2.2% per year, similar to that of Reybrouck.

### B.3.5 B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a neurohormone primarily secreted by the ventricular myocardium in response to volume expansion or pressure overload. Early studies demonstrated a correlation of the plasma BNP level with ventricular dilation in patients with dilated cardiomyopathy (35). The actions of this peptide include natriuresis, vasodilation, inhibition of the renin-angiotensin-aldosterone axis and inhibition of sympathetic nerve activity. Studies in adult patients found plasma BNP to be an accurate predictor of the presence of congestive heart failure. In patients with dyspnea, a BNP blood concentration of > 80 pg/ml had a 95% positive predictive value and a 98% negative predictive value for heart failure (36,37). The plasma BNP level has also been reported to provide predictive information for use in risk stratification in patients with acute coronary syndromes (38) and chronic heart failure (39).

Few studies have been performed measuring BNP levels in children with congenital heart disease (40,41). In a series of 30 patients with single ventricle who underwent a Fontan procedure, lower levels of BNP were seen in the early postoperative period compared to patients who had undergone repair of Tetralogy of Fallot (42). In contrast, higher levels of BNP were seen late after the Fontan procedure in children following the Fontan procedure or bidirectional Glenn shunt (43). No studies have correlated the plasma level of BNP with indices of ventricular performance or with health status in children with single ventricle disease.

## C. STUDY DESIGN AND METHODS

### C.1 Overview

This observational study will include children from 6 to 18 years of age who have undergone a Fontan procedure for palliation of a congenital cardiac defect that results in a functional single ventricle. Prospective data collection for each patient will occur within a single 3-month time window (ideally same-day data collection) and include health status questionnaires completed by parent and child (10 years and older), cardiac MRI, echocardiography, serology and maximal exercise testing. Patients who are unable to contribute the minimum required amount of data consisting of health status, echocardiographic results, and serology results within the 3-month time window will be excluded from the study. The primary goal is to determine the association

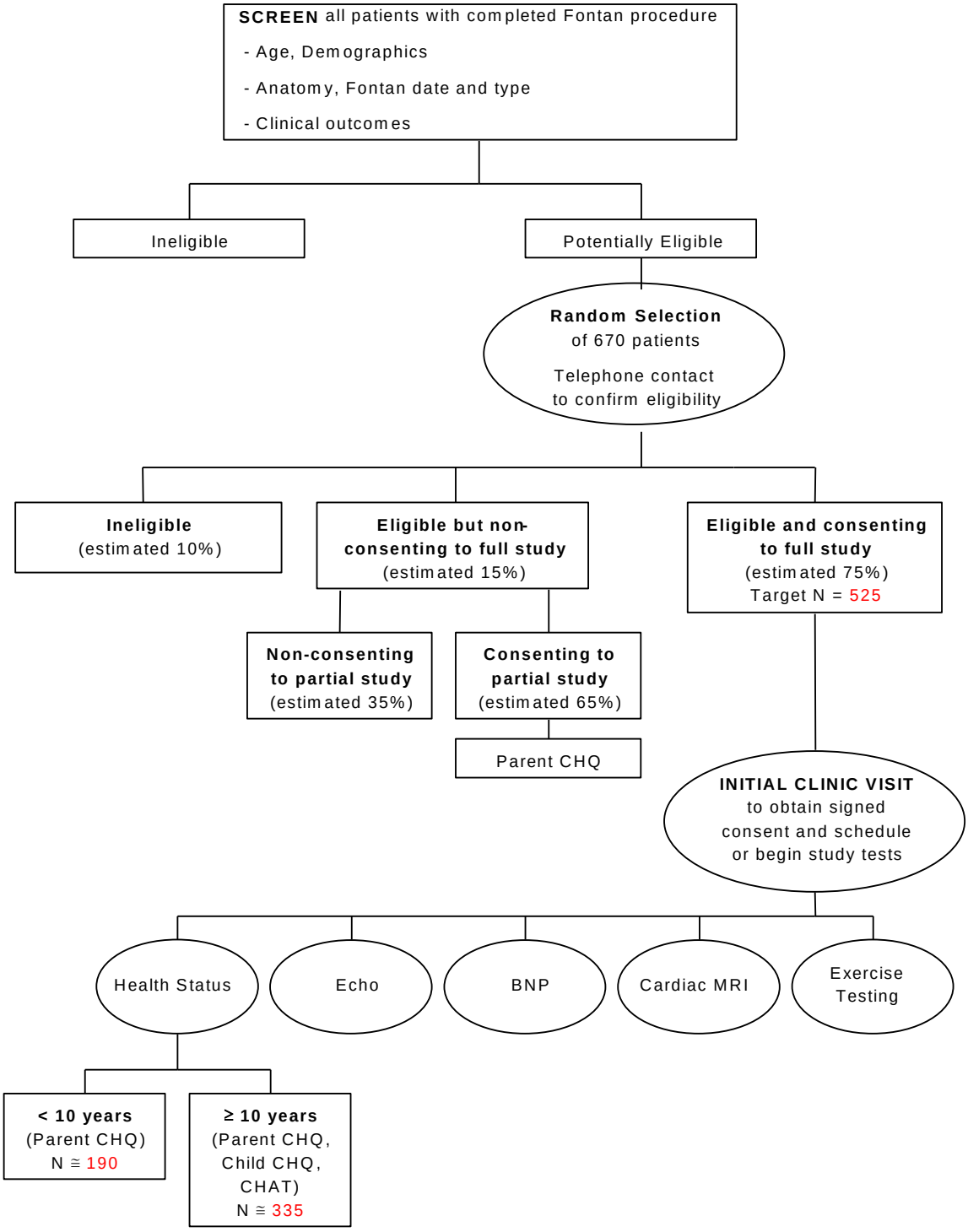
between health status and laboratory measures of ventricular state and performance, and secondarily to determine the interrelationships among laboratory measures of ventricular state and performance. Historical clinical and surgical information as well as ventricular morphology and the patient's current age will also be collected on each patient in order to address secondary aims, namely, to determine if differential associations exist between clinical and laboratory measures for patient subgroups and to determine the interrelationships between laboratory measures of ventricular state and performance. The screening period for a projected 2000 patients is two months and the data collection period for enrolled subjects is 10 months (50 per month, an average of 7 subjects per center per month). Cardiac MRI, echocardiographic, and serologic data will be centrally interpreted. Figure 1 displays the patient flow and key measurements for this study.

## C.2 Participants

### C.2.1 Inclusion Criteria

1. Age 6 through 18 years at the time of enrollment.
2. Fontan surgery of any type at least 6 months prior to the time of testing.
3. Agreement and ability to have all of the following testing completed:
   a. An echocardiogram at the study center,
   b. Parent health status questionnaire, and
   c. Blood testing.
4. Planned or ongoing cardiac care at the study center that will allow completion of study testing within 3 months of study enrollment.
5. Informed consent of a parent or guardian, and assent of the study participant if he/she is able to provide it, according to institutional guidelines.

## Figure 1. Patient Flow



### C.2.2 Exclusion Criteria

1. Non-cardiac medical or psychiatric disorder that would prevent successful completion of planned study testing or would invalidate the results of study testing.
2. Ongoing or planned participation in another research protocol that would either prevent successful completion of planned study testing or invalidate the results of study testing.
3. Lack of reading fluency by the primary caregiver in both English and Spanish, languages for which the parental report health status questionnaire has been validated.
4. Pregnancy at the time of enrollment or pregnancy planned prior to completion of study testing.

### C.2.3 Patient Availability

Estimates from the seven participating clinical sites indicate that approximately 3000 Fontan patients who have undergone a Fontan procedure are currently 18 years of age or younger. It is estimated that 35% of these patients (n=1050) are no longer followed at the sites. Of the patients currently followed (n=1950), it is estimated that 80% will be eligible (n=1560) and 70% of this cohort will give consent/assent to participate in the study. Thus, the estimated available study population is approximately 1100 patients. The required sample size to meet study aims is 525 patients and is described in Section C.6.1.

### C.2.4 Recruitment Protocol

The Data Coordinating Center (DCC) will provide each clinical site with a Screening Log to record basic identifying patient information (name, gender, date of birth, date of Fontan completion, medical record number) next to a set of pre-defined, eight-digit study identification numbers. The research coordinator at each site will review the clinic or hospital roster for all patients with a completed Fontan procedure who are believed to be alive and currently followed at the clinical site, and will record each of these patients on the Screening Log. The Screening Log will be kept on file at the clinical site and will be sent to the Data Coordinating Center after removal of the patient's name and medical record number. A Patient Screening Form will be completed for each patient by review of the patient's medical record. Completion of this form will require no contact with the patient. All screening forms will be entered into the web-based

data management system (ADEPT—Advanced Data Entry and Protocol Tracking). Upon complete entry of each form, ADEPT will determine if the patient is potentially eligible for participation in the study. Patients who do not meet criteria for age or Fontan surgery date, or who do not receive ongoing cardiac care at the clinical site, will not be included in the list of potentially eligible patients. When all screening is completed, the Data Coordinating Center will generate a list of potentially eligible patients from each clinic site. These lists comprise the sampling frame for the study.

C.2.5 Human Subjects Considerations

C.2.5.a Risk/Benefit Ratio

Participation in this study will involve minimal risk for all subjects. The majority of the prospective data collection involves procedures or testing that are part of routine care during follow-up of the Fontan patient.

C.2.5.b Reimbursement

Reimbursement for participation in this study will consist of a nominal compensation for the child/family's time, as well as payment of parking and travel costs for any trips required to conduct protocol-mandated testing.

C.2.5.c Gender and minority recruitment

Based on current rosters of Fontan patients at the Network sites, it is estimated that 40% of patients will be female and 15-30% of the patients to be of minority race/ethnicity, depending on geographic location of the clinical site.

## C.3 Study Enrollment

C.3.1 Sampling Scheme

The sampling frame described in Section C.2.4 will be the basis for selecting patients to be contacted and invited to participate in the study. If the required sample size for the study (N=525; see Section C.6.1) is smaller than the available number of patients across the seven clinical sites, random sampling (without replacement) of patients from each clinical site, in proportion to the number of patients contributed by each site to the Network total (proportion $p_i$, i=1,…7, calculated from the lists of potentially eligible patients), will occur. The Data Coordinating Center will generate a list of patients to be contacted by each clinic site. The

target enrollment for each site will be $N \times p_i$. The size of the list will be inflated to account for the estimated 30% of patients who will not provide consent or who cannot be contacted, expressed as $(N \times p_i)/0.7$. If the clinical site contacts all patients on the list and does not reach its target enrollment, then the Data Coordinating Center will generate a second list of randomly selected additional patients to contact from the pool of potentially eligible patients who were not already randomly selected. The size of the list will be determined by the remaining number of patients required to meet target enrollment.

If the consent rate amongst the eligible patients is higher than expected, then enrollment will stop when the overall target sample size of 525 is reached (see Section C.6.1), and analyses comparing the enrolled vs. the potentially eligible but unenrolled patients will be conducted (see Section C.6.2.b).

### C.3.2 Enrollment Process

The research coordinator at each clinical site will utilize the list of randomly selected, potentially eligible patients described in Section C.3.1 to make patient contacts. Initial patient contact will occur in one of two modes:

- Mailing to home followed up by a telephone call;
- Direct interview of the patient and parent(s) during a clinic visit.

A packet including: 1) a brochure describing the research study; 2) Parental consent form; and 3) Patient assent form will be mailed to the patient's home or presented to the family during the clinic visit. If mailed, the coordinator will contact the family by telephone approximately one week after the mailing. On this telephone call or during the in-person initial interview during a clinic visit, the research coordinator will determine eligibility of the patient, using a standardized interview script, with regard to criteria that cannot be determined using the medical record alone (i.e., reading fluency in either English or Spanish by the parent, willingness to undergo a blood draw, and intent of the patient to become pregnant or not). The remainder of the eligibility criteria will be assessed by medical record review prior to the patient contact. If the patient is medically eligible, the consent and assent (if applicable) forms (Appendix E) must be signed and dated in-person during a scheduled clinic visit for patients who are determined to be eligible as a result of the telephone screen. Upon completion of the consent form, a date will be scheduled for the patient to undergo study testing. All or some study testing may occur on the same day

that consent/assent is obtained. All study testing must be completed within 3 months of the date initial study testing occurs; measurements made outside the 3-month window will not be considered valid.

C.3.3 Non-Enrolled Patient Data Collection

On the initial phone contact, if it is determined by the study coordinator that the patient is eligible but does not wish to participate in the full study protocol, the parent will be asked if he/she is willing to complete a brief questionnaire (the 50-item Child Health Questionnaire Parent Report). These data will be used in conjunction with the screener information obtained by medical record review (see Section C.2.4) to assess whether the enrolled study subjects are representative of the non-enrolled Fontan patients. If the parent indicates a willingness to complete the questionnaire, an explanatory letter and questionnaire will be mailed to the parent following the telephone call. Consent in this substudy is implicit by return of a completed questionnaire by the parent. Completion of the child questionnaire will not be requested. If the questionnaire is not returned within 2 weeks of the mailing, then one telephone reminder will be made in order to request completion and return mailing of this information.

## C.4 Measurement

C.4.1 Schedule of Measurement

C.4.1.a. Overview (Table 2)

The clinical history of the patient will be reviewed via record abstraction and collected on standardized forms for research purposes as soon as consent is obtained. Prospective data collection will occur as soon as possible after consent is obtained. All prospective data will be collected in as short a time period as possible (ideally, one day), and must be completed within 3 months of the start of prospective data collection for each patient in order for the data to be considered valid.

**Table 2. Fontan Study Schedule of Measurement**

| **Measurement** | **Time of Measurement** | | |
|---|---|---|---|
| | Baseline | Month 1 to 3 | |
| | All Subjects | Age 6-9 | Age 10-18 |
| Clinical History | x | | |
| CHQ Child Report | | | X |
| CHQ Parent Report | | x | X |
| CHAT Questionnaire | | | X |
| Echocardiography | | x | X |
| Cardiac MRI | | x | X |
| Exercise Testing | | x | X |
| BNP Level | | x | X |

C.4.2 Outcome Variables (Table 3)

Two classes of measurements will be collected and analyzed in this study: clinical and laboratory. Because the primary aim of this study is to assess the association between these two classes of variables, both groups are considered of equal importance. Clinical measures include the Physical Function and Psychosocial Summary Scores of the CHQ and the overall CHAT questionnaire score. Summary scores for the health status questionnaires will be calculated and recorded by the DCC. The 13 laboratory measures of interest are included in Table 3. Data from MRI and echocardiogram studies will be forwarded to the appropriate core laboratory for analysis. Blood for measurement of BNP level will be shipped to the Serology Core Laboratory. Results from all tests performed by core laboratories will be forwarded to the DCC. Results of exercise testing will be determined and entered into the ADEPT data management system at each individual center. Effect modifiers to be collected include past clinical events, the patient's current age, ventricular morphology, and Fontan procedure characteristics.

**Table 3. Study Outcome Variables**

| Outcome Variable | Clinical Measure | Laboratory Measure |
|---|---|---|
| Parent CHQ<br>1) Physical Function Summary Score<br>2) Pyschosocial Summary Score | <br>X<br>X | |
| Child CHQ<br>1) Physical Function Summary Score<br>2) Pyschosocial Summary Score | <br>X<br>X | |
| CHAT Questionnaire Summary Score | X | |
| Echocardiogram<br>1) E:A ratio<br>2) Rate of deceleration of early inflow<br>3) Duration of pulmonary vein flow reversal during atrial systole using pulsed Doppler<br>4) Atrioventricular valve annulus velocity in early diastole assessed using tissue Doppler<br>5) Rate of ventricular flow propagation using M-mode color Doppler | <br><br><br><br><br><br><br><br><br> | <br>X<br>X<br><br><br>X<br><br><br>X<br><br><br>X |
| Cardiac MRI<br>1) Ventricular mass<br>2) Ventricular end diastolic volume<br>3) Ventricular end systolic volume<br>4) Ventricular mass/volume ratio | <br><br><br><br> | <br>X<br>X<br>X<br>X |
| Exercise Testing<br>1) Maximal oxygen consumption<br>2) Oxygen pulse<br>3) Anaerobic threshold | <br><br><br> | <br>X<br>X<br>X |
| BNP Level | | X |

C.4.3 Health Status

C.4.3.a Child Health Questionnaire

Health status assessment will be based on the CHQ that was officially released in 1996 and is included in the 1999 APA Handbook of Psychiatric Measures. The use of the CHQ requires purchase of the User Manual (22,23). Two CHQ formats will be used. For all subjects, a Parent Report form of the CHQ, the CHQ-PF50, which has 50 items,

will be used. In addition, for children ten years of age or older, the child will complete a CHQ-CF87. This is an 87-item, full-length instrument. In this study, the CHQ will be self-administered for both parents and children. Both forms of this instrument provide two summary scores: 1) physical function and 2) psychosocial. The parent and child (if $\geq$ 10 years) will complete the appropriate CHQ version before or on the day the child is undergoing imaging, for example, during a visit for echocardiographic or magnetic resonance imaging. If the visit for imaging is close in time to the visit at which consent is obtained, the questionnaire may be given to the parent and child (if applicable) at the initial visit. If not, then the questionnaire will be mailed to the parent prior to the visit. This will allow the family time to complete the questionnaire(s) before the imaging visit. If the questionnaire is misplaced, another one will be provided at the beginning of that day's clinic visit and will be completed during the visit. Every effort should be made to have the questionnaire completed before the patient has his/her office visit with the cardiologist. A trained interviewer will be available on that visit to assist the parent or caregiver with instructions for the questionnaire. The interviewer will collect the completed CHQ before the end of the visit. The completed CHQs will be centrally scored at the Data Coordinating Center.

C.4.3.b Congenital Heart Adolescent and Teenager Questionnaire

The CHAT questionnaire is a disease-specific instrument measuring cardiac health and functional status in children aged ten to eighteen years. It is self-administered and has been validated in children with congenital heart disease aged ten to eighteen. Multi-item domains include symptom frequency, symptom intensity, activity limitations, activity worries, impact on peer relationships, impact on future achievement, cardiac anxiety and medication adverse effects. Single-item domains include self-perceived global health status, condition seriousness, feeling different and effect on social life. The procedure for completion of the CHAT questionnaire will be identical to that described in Section C.4.3.a for the CHQ. For cross-validation purposes, every effort will be made to ensure that the CHQ and CHAT questionnaire are completed at the same time. A trained interviewer will be available on the visit during which the questionnaire is collected to assist the child with instructions for the questionnaire. The completed CHAT questionnaires will be centrally scored at the Data Coordinating Center.

### C.4.4 Echocardiogram

Subjects will not be sedated prior to acquisition of the echocardiogram for this research study. Echocardiograms of each patient will be recorded on a videotape or digital transfer medium, forwarded to the DCC for blinding, and distributed to the Echocardiographic Core Laboratory for interpretation. The echocardiogram will consist of a complete two-dimensional echocardiogram and Doppler evaluation. A complete assessment for valve dysfunction and intracardiac thrombi will be performed. Standard short and long axis views of the ventricle(s) will be recorded to assess regional wall motion. End-diastolic and end-systolic volumes, mass and ejection fraction will be obtained from two-dimensional images using a biplane modified Simpson's rule. Ventricular sphericity will be calculated as the ratio of short-axis area to long-axis dimension. Systolic, diastolic, and mean blood pressure will be measured using an automated vital signs monitor (such as the Dinamapp).

All measurements and derived indices for the study population will be expressed as z-scores relative to body surface area or to 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. Reporting the data as z-scores adjusts for the effects of variation in age and body size.

Cardiac output will be measured using standard Doppler methods (aortic trans-valvar time-velocity integral times the valve cross-sectional area). Systemic resistance is calculated as cardiac output divided by mean arterial pressure. The flow pattern in the superior mesenteric artery will be recorded as an index of mesenteric resistance.

Ventricular diastolic function will be assessed using several indices. Assessment of left ventricular diastolic filling will be performed using indices derived from pulsed Doppler interrogation of each of the atrioventricular valves (if present) and of the pulmonary veins. The atrioventricular valve early deceleration time and E/A ratio will be calculated. The duration of pulmonary vein flow reversal during atrial systole will be measured from pulmonary vein Doppler. The rate of diastolic flow propagation will be obtained using mitral valve inflow color Doppler M-mode. Atrioventricular valve early diastolic annular velocity will be assessed using tissue Doppler (see Appendix A).

### C.4.5 Cardiac Magnetic Resonance Imaging

Each subject will undergo an unsedated cardiac MRI. The study will last approximately 45 to no more than 60 minutes. Subjects who are unable to perform the study without sedation will not undergo this test. Intravenous contrast will not be used. Subjects will have continuous electrocardiogram (ECG), pulse oximetry and blood pressure monitoring throughout the study. Imaging protocols will be used which will allow offline calculation and determination of:

1) Ventricular mass, ventricular volume, ventricular mass/volume ratio, and stroke volume;
2) Measurement of localized blood flow including: inferior vena cava (IVC) or IVC/right atrial junction, superior vena cava, within the lateral tunnel or extracardiac conduit, right pulmonary artery, left pulmonary artery and ascending aorta; and
3) Optional measurement of evidence of localized Fontan pathway narrowing.

Digital data from each study will be forwarded to the Data Coordinating Center, where it will be logged and then forwarded to the MRI Core Laboratory for central interpretation (see Appendix B for full technical protocol). If a subject refuses to undergo the MRI on the day of testing, or the MRI is otherwise not successfully completed, the patient will remain in the study and complete all other required study tests.

### C.4.6 Exercise Testing

Each subject who is at least 115 cm tall and free of neurological or developmental defects that preclude exercise will undergo maximal exercise testing using a ramp bicycle protocol. Subjects will be fasted for two hours prior to exercising.

Resting pulmonary function consisting of inspiratory and expiratory flow volume loops and maximal voluntary ventilation will be performed prior to each exercise test. A 12-lead surface ECG will be obtained at rest in the supine, sitting and standing position. The rhythm will be monitored throughout the study and a 12-lead ECG obtained during every minute of exercise and the first ten minutes of recovery. Blood pressure will be measured at rest and during every three minutes of exercise and recovery. Oxygen saturation will be measured continually by oximetry.

The subject will be exercised to maximum exhaustion using an electronically- braked cyclo-ergonometer. The protocol will consist of sitting quietly for three minutes on the ergometer

followed by three minutes of unloaded pedaling. The work rate will then be increased using a ramp protocol with a slope chosen to achieve the subject's predicted maximal work rate in ten to twelve minutes of cycle time.

Minute oxygen consumption, minute carbon dioxide production ($VCO_2$), minute ventilation (VE), respiratory exchange rate ($VCO_2/VO_2$ - RER), tidal volume, respiratory rate, and $O_2$ pulse will be monitored continuously on a breath-by-breath basis using a metabolic cart during rest, exercise and the first two minutes of recovery. All subjects will be encouraged to exercise to exhaustion. A detailed exercise testing protocol is found in Appendix C.

C.4.7 12-Lead Electrocardiogram

For subjects who do not undergo exercise testing, standard 12-lead surface ECGs will be obtained in both the supine and standing postures.

C.4.8 Serology

A resting BNP level will be measured in plasma (see Appendix D). The sample for BNP will be drawn after the subject has been in a sitting/supine position in a quiet room for 30 minutes. A volume of no more than 5 cc of whole blood will be collected and placed into a pre-chilled lavender-topped EDTA tube. The tube will be inverted to mix thoroughly and immediately placed on ice. The Fontan Serology Core Laboratory will provide centrifugation method and timing instructions to the clinical sites. The resulting plasma will be dispensed into vials for storage and frozen immediately at –20° to –80° C. Each vial will have a label identifying the patient study number, protocol number, sample date, and study center. Samples will be batched and shipped to the Serology Core Laboratory on dry ice.

Although considered part of the minimal test set for an enrolled patient, if the patient or family has consented but refuses to allow blood to be drawn at the time of the visit, or if the blood draw attempt is unsuccessful, the patient will remain enrolled in the study for the remaining tests.

## C.5 Adverse Events

### C.5.1 Definition

An adverse event is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related symptoms or signs, or a single symptom or sign. Adverse events in this study should be rare. These may occur during blood drawing or during the performance of the individual studies including echocardiography, exercise testing, and MRI. Examples include bruising or bleeding at the site of blood drawing, anxiety during exercise testing or MRI, and tachycardia, syncope, and fall-induced trauma during exercise testing. The proposed testing procedures are well established in children and a minimal number of adverse events are expected.

### C.5.2 Classification

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

Possibly Related: The event follows a compatible temporal sequence from the time of study testing, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of study testing, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

### C.5.3 Severity

The severity of clinical adverse events and laboratory abnormalities will be assessed according to the following criteria:

1 = "Not Serious": Any event which:

(a) Results in minimal transient impairment of a body function or damage to a body structure; or

(b) Does not require any intervention other than monitoring.

2 = "Moderately Serious": Any event which:

(a) Results in moderate transient impairment of a body function or transient damage to a body structure; or

(b) Requires intervention, such as the administration of medication or a procedure, to prevent permanent impairment of a body function or damage to a body structure.

3 = "Serious": Any event which:

(a) Is fatal; or

(b) Is life-threatening (the patient 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) Requires hospital admission; or

(f) The Principal Investigator considers to be a serious adverse event.

### C.5.4 Data Collection Procedures for Adverse Events

Events will be recorded by the clinical center study coordinator, including the date and time of occurrence, severity, duration, treatment prescribed, and resolution. If classified as serious, this event information will be forwarded electronically within one working day to the Data Coordinating Center.

### C.5.5 Reporting Procedures

Reports of all serious adverse events must be recorded on study forms accompanied by a narrative document and submitted to the local Institutional Review Board (IRB) and to the DCC within one working day. The DCC will be responsible for reporting serious adverse events to the NHLBI as soon as possible and no later than seven calendar days after notification by the clinical site investigator. Minor, resolved adverse events must be recorded on study forms and submitted to the DCC at the end of study testing. Minor adverse events will be summarized by the DCC at the regularly scheduled DSMB meeting.

C.5.6 Post-Study Adverse Events

All unresolved adverse events at the completion of the patient's performance of the testing will be followed up by the site investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained or has stabilized. The site investigator will notify the local IRB and the DCC in writing of any death or clinically serious adverse event that may be related to the testing performed during the study. The DCC will then notify the NHLBI.

## C.6 Statistical Methods

C.6.1 Sample Size and Power

C.6.1.a. Primary Aims

*Step 1*: The required sample size to detect a correlation of R=0.3 between health status and any of the laboratory measures with 85% power using a two-tailed test and a Type I error rate of 0.05 is 100 (rounded up from 97). *Step 2*: Because the CHAT questionnaire is the only disease-specific instrument in this study, it is important to have sufficient power to detect correlations between CHAT scores and the laboratory parameters. Both the CHQ Child Report and the CHAT questionnaire require that the subject be at least ten years old in order to complete the instrument. Initial enrollments indicate that 64% of the subjects enrolled in this study will be at least ten years old. Therefore, 157 subjects (100/0.64) are required in order to detect R=0.3 with 85% power and obtain 100 subjects who are at least ten years old. *Step 3:* It is estimated that 30% of enrolled subjects will be able to successfully complete all testing required by the study protocol (which will enable a full multivariate model). Therefore, the target sample size for this study is 525 subjects.

C.6.1.b Secondary Aims

This study may not be powered to detect differential correlations between health status and laboratory measures by patient subgroup (e.g., fenestrated vs. non-fenestrated Fontan procedure; left vs. right ventricular dominance; presence or absence of clinical events), unless the correlations are large and the incidence of the clinical event or subgroup factor is not too rare. However, in order to understand the relative explanatory power of different laboratory and performance measures with regard to health status in the overall cohort, multiple linear regression will be utilized for each of the three health status measures. A sample of 100 subjects with all tests completed will provide 81%

and 94% power to detect a Model R = 0.35 and R = 0.40, respectively, using five predictors (44).

C.6.2 Analysis Plan

C.6.2.a Interim Analyses

Interim analyses will consist of: 1) periodic quality control reviews of the data; 2) monitoring of actual site- and age-specific group (< 10 years vs. ≥ 10 years) enrollment and 3) monitoring of the rate of completed tests in enrolled patients; and 4) correlations between health status and laboratory parameters for the entire cohort and pre-specified subgroups using data accrued by the time of the DSMB meeting. This meeting will occur at approximately the midpoint of patient accrual. The data management system will identify invalid values for growth and echocardiographic parameters at the time of data entry using age- and body surface area-specific validations. Exploratory graphics will be used to identify within-range values for other measurements that are inappropriate for an individual patient. Review of enrollment numbers within site and age group will determine whether selected sites will be requested to enroll over their target in order for overall targets to be attained. Examination of univariate correlations based on interim data will serve two purposes: 1) to identify better the data outliers, and 2) to provide interim estimates of correlations related to the specific aims of the study after resolution of questionable values.

C.6.2.b Final Primary Analyses

If the target sample size of 525 is reached before all potentially eligible patients are contacted, then a comparison of the confirmed eligible vs. potentially eligible patients will be made to assess the representativeness of the contacted patients. If there are identifiable systematic differences between the two groups, then the use of weights will be considered to report the profile of the enrolled sample.

The second analysis to be performed will compare the historical clinical outcome data and health status scores of the enrolled and eligible but not enrolled (in the full study) patient cohorts. If found to be similar, then the full study cohort will be considered representative of the target population. If the enrolled and eligible but not enrolled cohorts differ with respect to health status or clinical history, then these findings will aid in defining the narrower population to which the final study findings apply.

The CHQ and CHAT questionnaire will be scored centrally using programs at the Data Coordinating Center. There is no overall Summary Score for the CHQ. Three scores from the two questionnaires will be formed: 1) CHQ Physical Function Summary Score; 2) CHQ Psychosocial Summary Score; and the 3) CHAT questionnaire Summary Score. Selected multi-item domains that are related to physical function in the CHAT questionnaire will also be examined. All analyses will examine the three Summary Scores separately.

The distributions of all continuous health status and laboratory measures will be examined, and if appropriate, a normalizing transformation will be applied if one exists. The Pearson correlation coefficient will be used to estimate the association between each of the three summary scores and continuous, normally distributed laboratory measures or the appropriate transformation. If a laboratory measure is non-normally distributed and unable to be transformed, or the measure is not ordinal (not continuous), such as AV valve regurgitation grade, the Spearman correlation coefficient will be used to estimate association with health status. Nonparametric regression such as generalized additive modeling (45) will also be utilized to determine the most appropriate functional form for each laboratory measure of ventricular performance as a function of the CHQ and CHAT Summary Scores.

In order to address the primary aim of this study, univariate correlations between health status summary scores vs. laboratory measures will be estimated using all available data. Resulting analyses will be conducted on four cohorts of varying sample size:

1) All Ages, minimum test set for eligibility: Subjects with a completed CHQ parent report, echocardiogram, and BNP measurement;

2) All Ages, other tests: Subjects with a completed CHQ parent report, cardiac MRI and/or exercise test (in addition to echocardiogram and BNP);

3) Child age $\geq$ 10 years, minimum test set for eligibility: Subjects with a completed CHQ child report or CHAT questionnaire, echocardiogram, and BNP measurement;

4) Child age $\geq$ 10 years, other tests: Subjects with a completed CHQ child report or CHAT questionnaire, cardiac MRI and/or exercise test (in addition to echocardiogram and BNP).

The CHQ and CHAT Summary Scores will also be analyzed as categorical variables, defined by 1) a threshold (normal vs. abnormal) for the overall health and functional status of children without chronic disease, as well as 2) a threshold for good vs. poor health status within the Fontan population. In this setting, logistic regression will be used to assess the prognostic utility of the laboratory measures of ventricular performance.

C.6.2.c Final Secondary Analyses

Analyses to address the first secondary aim of the study, namely, intercorrelations between all of the laboratory measures collected, will be conducted using the univariate techniques described in Section C.6.2b (Pearson and Spearman correlation coefficients). Multivariate linear regression will be conducted to quantify which laboratory measures are independent correlates of health status. A separate multivariate regression for each of the three health status summary scores will be conducted using the laboratory measurements as predictors in order to determine what proportion of the variability observed in health status measures can be explained by the laboratory measures of ventricular state and performance, and the relative contributions of each. The multivariate modeling process will be conducted in stages, first identifying the independent predictors of health status within type of test (echocardiogram, MRI, exercise) and then by combining the independent predictors of health status from each type of test into a larger model. Stepwise regression methodology will also be employed to confirm the final multivariate model.

C.6.2.d Subgroup Analyses

The second secondary aim of this study focuses on two different types of subgroup analyses. The second secondary aim is to determine whether there is an association between health status and laboratory measures that differs as a function of patient age at the time of study enrollment, Fontan procedure type, ventricular morphology, presence of a fenestration (both surgical and fenestration created by a baffle leak) and history of clinical events. Correlations between clinical and laboratory parameters will be estimated using a regression model as described above, but with the addition of a main effect and interaction term for age group, Fontan procedure type, ventricular morphology and/or clinical history in order to determine if differential associations among parameters exist by subgroup.

C.6.2.e Intervening Variables

Detailed information on the pre-surgical (baseline) status of the Fontan patient will be collected. This information will be used to better understand how overall health status and laboratory measures of ventricular performance differ as a function of, for example, baseline variables such as anatomic diagnosis, pre-Fontan AV valve regurgitation and pulmonary artery pressure, and history of arrhythmias. Multiple linear and logistic regression will be used to examine the association between post-Fontan health status and laboratory outcomes and baseline patient characteristics. This cohort will be an important resource for identifying the set of pre-Fontan factors that impact a patient's later health status and ventricular performance. Modeling may also include time since the Fontan procedure and surgical characteristics that may alter the association between baseline patient characteristics and later state.

C.6.2.f Itemized CHAT Analysis

Because the CHAT questionnaire is a relatively new disease-specific instrument, this large study also provides the opportunity for further analysis of its properties. This analysis will include an examination of factors constructed from the individual CHAT items, in order to determine whether they can be separated into physical and psychosocial domains. Factors reflecting physical functioning will be considered as possible correlates of the protocol measures of ventricular state. In addition, principal components analysis of the CHAT questionnaire and cross-comparisons with selected domains from the Child CHQ will be used to determine if some of the currently defined CHAT domains based on small sets of items can be appropriately combined into a larger domain that defines overall physical functioning. Analyses of the association between this broader domain and the laboratory measures of ventricular performance will then be conducted.

## C.7 Data Management

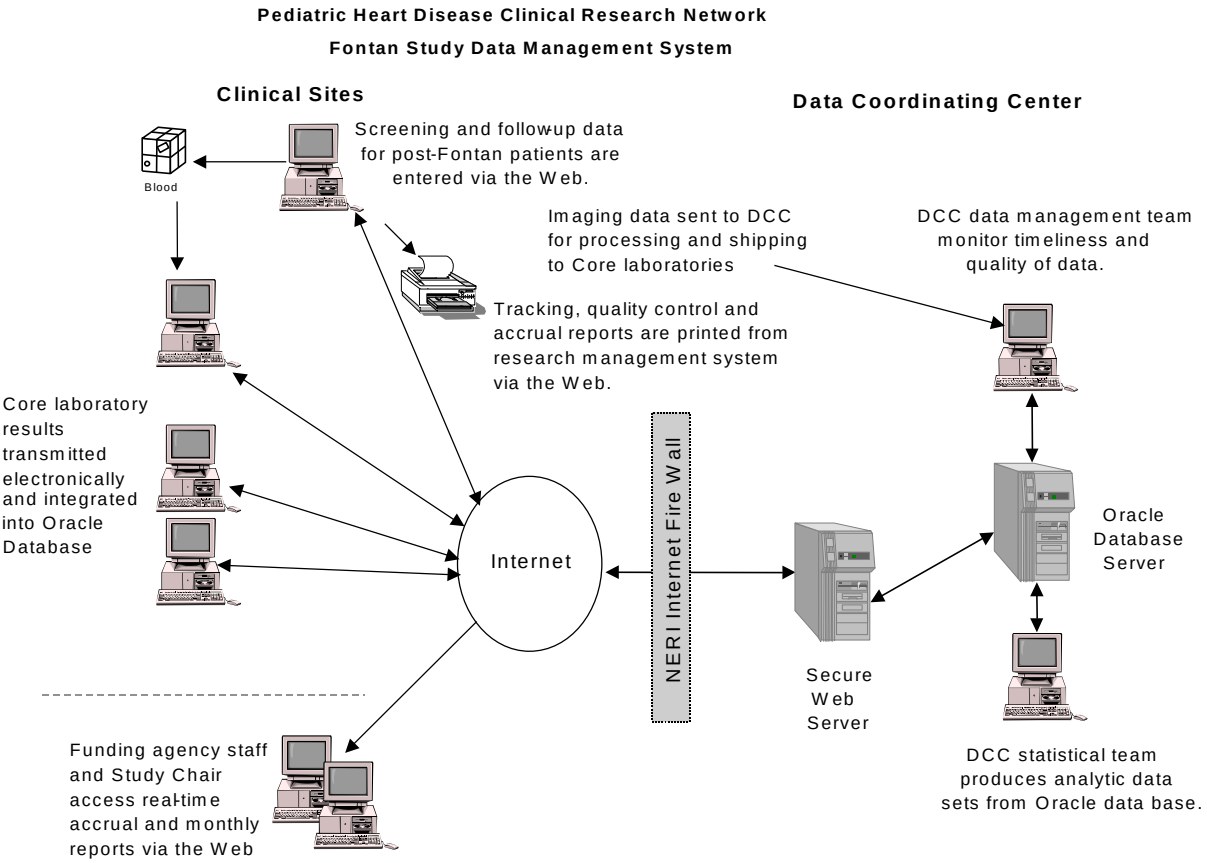
The DCC will provide a customized data management system for the study using NERI's Web-based Advanced Data Entry and Protocol Tracking (ADEPT) Data Management System (DMS). This system will integrate all aspects of study data collection including

- Data entry;
- Protocol management;
- Screening and enrollment of participants;
- Tracking of overdue forms and edits;
- Collection, processing, and tracking of laboratory specimens and echocardiography and MRI data; and
- Transfer of Core Laboratory test results to the DCC via the Web.

### C.7.1 Information Flow

Data will be received from several sources, including the clinical sites, and Serology (BNP), Echocardiography, and MRI Core Laboratories. The flow of data among the units in this study is illustrated below in Figure 2. The DCC will enter all hard-copy screening forms received from the clinical sites. After patient enrollment, clinical sites will enter data over the Internet via ADEPT's customized secure web application. Sites will send blood specimens directly to the Serology Core Laboratory for central processing. Imaging files from clinical sites may be transmitted to the DCC via the Web using NERI's PHN FTP site or submitted on other storage media, (such as digital echocardiographic images stored on CD-ROM). Results of studies performed by Core Laboratories will be directly uploaded to an Oracle database at the DCC, transmitted electronically, or centrally processed at the DCC after receipt of completed paper forms.

**Figure 2**




C.7.2 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 indexed by patient study ID number; names will not be linked with patient data in the database. Clinical sites will maintain records linking the patient name with the ID assigned for the study in locked files. 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 closely resemble 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.

Key capabilities of the ADEPT system are described below.

C.7.2.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 correct any data entry errors or resolve questions regarding out-of-range or questionable values. Edit reports will list the participant 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 who 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 member's error rate.

C.7.2.b Reporting

If required, the ADEPT system will generate 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, to the Study Chair, Program Officer, clinical site and Core Laboratory management 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;
- Patients with an overdue visit;
- Reimbursement information for sites and Core laboratories.

Other customized reports will be developed within the ADEPT system as needed.

C.7.2.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.

- 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 backup weekly;
- Backup files are stored off site in safety deposit box;
- Duplicate NT servers are available to replace the Oracle or Web Server;
- Primary identification is via Study ID-limited access to ID/Participant linkage;
- Access to electronic linkage limited by Oracle Database Administrator;
- Access to hard copies of linkage kept in locked cabinets by Clinical Site Coordinators;
- NERI firewall limits what 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 staff.

All study data will be stored on NERI's Microsoft Windows NT-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. Oracle archiving and backup system ensures minimal data loss, even in the most catastrophic system failure.

## C.8 Quality Control

This section describes the quality control program that will be implemented as part of the Fontan study to ensure standard implementation of the protocol, protocol compliance, and data integrity. The DCC will develop and update the Manual of Operations (MOO) in collaboration with study investigators and Core Laboratory directors. In addition, a Data Management 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.8.1 Clinical Center Coordinator Training

The PHN DCC, working closely with the Program Officer, Study Chair, and the Fontan Protocol Subcommittee, will provide central training of clinical site staff in the areas of protocol implementation, data collection and management, specimen collection and handling, collection and handling of imaging data, medical records abstraction, interview techniques, and quality control expectations. Training materials will be prepared which 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.8.2 Certification of Personnel

Echocardiography and MRI personnel at each center will undergo sessions on standardization of technique, and all studies will be read in a Core Laboratory. Poor quality echocardiograms or MRIs may necessitate site visits.

C.8.3 Data Monitoring/Site Visits

Representatives from the DCC and NHLBI will visit each clinical site once during the study period. The primary roles of the site visit team will be to evaluate general protocol compliance and adherence to IRB 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. 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 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 will 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 ORGANIZATION

The New England Research Institutes serves as the Data Coordinating Center for the Pediatric Heart Disease Clinical Research Network. The study described in this protocol, "The Relationship between Functional Health Status and Laboratory Parameters of Ventricular Performance after the Fontan Procedure" is a research component of this network. Participating clinical sites are: The Hospital for Sick Children, Toronto, Ontario; Children's Hospital Boston, Boston, MA; Children's Hospital of New York, New York, NY; Children's Hospital of Philadelphia, Philadelphia, PA; Duke University, Durham, NC; Medical University of South Carolina, Charleston, SC; and Primary Children's Medical Center, Salt Lake City, UT. The Network is chaired by Lynn Mahony, MD. The study will be chaired by Bernard. J. Clark, MD. Network committees include the Steering and Publications Committees. The Steering

Committee consists of the Network Chair, the DCC Principal Investigator (PI), each clinical site PI, and the NHLBI Project Officer, *ex officio*. The Steering Committee meets in person two to four times per year and by teleconference two times per month. The Publications, Presentations, and Ancillary Studies Committee meets once per year and as needed by conference call. The Data and Safety Monitoring Board meets twice per year either in person or by teleconference and consists of seven members including pediatric cardiologists, a statistician, an ethicist, and a layperson. Its function is to monitor study progress and accomplishment of study aims.

## E. STUDY LIMITATIONS

The generalizability of the findings of this study will be limited to children who have undergone the Fontan procedure and are between 6 and 18 years of age. The generalizability of results from maximal exercise testing are further restricted to those individuals who are capable of undergoing exercise testing and thus may not be applicable to children with moderate to serious neurological and developmental conditions.

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# THE RELATIONSHIP BETWEEN FUNCTIONAL HEALTH STATUS AND LABORATORY PARAMETERS OF VENTRICULAR PERFORMANCE AFTER THE FONTAN PROCEDURE

## APPENDICES

Appendix A. Echocardiography Core Laboratory Protocol

Appendix B. MRI Core Laboratory Protocol

Appendix C. Maximal Exercise Testing Protocol

Appendix D. Serology Core Laboratory Protocol

Appendix E. Consent/Assent Forms

- Sample Informed Consent Form
- Sample Informed Assent Form

## APPENDIX A

## ECHOCARDIOGRAPHY CORE LABORATORY PROTOCOL

Study Acquisition:

Subjects will not be sedated prior to acquisition of the echocardiogram for this research study. Echocardiographic examinations are performed using an echocardiographic imaging system equipped with transthoracic transducers appropriate to patient size, which implies that 7.5, 5.0, 3.5, and 2.5 MHz transducers or multifrequency transducers that cover this frequency range must be available. Studies are recorded in either sVHS format on standard 1/2" sVHS videotape or in any of the several full-motion digital formats in common use (MPEG-I, MPEG-II, MPEG-IV, motion JPEG, AVI). These recordings will be sent to the central digitizing facility for analysis. Original recording of analog recordings should be submitted to the central analysis facility. The central analysis facility will perform an analog to digital conversion of the analog data and return the original tape recording within 48 hours of receipt. To enable adequate quality digital conversion for electronic caliper measurements, sVHS format is required (VHS is not adequate). For all recordings, it is essential that the electrocardiographic signal be adjusted to provide unequivocal QRS detection in 2D, color Doppler, and spectral Doppler modes. In addition to complete orthogonal sweeps from subxyphoid, apical, parasternal, and suprasternal notch windows, the following information pertinent to derivation of the indices of ventricular function is required:

1. *Height and weight.*

Patient height in centimeters and weight in kilograms should be measured at the time of echocardiography. Reliance on prior charted values is unreliable since inpatients and patients with frequent admissions often have values from prior measurements carried forward rather than re-measured. The primary technical problem commonly encountered with the height and weight measurement relates to improper recording of units (pounds instead of kilograms, inches instead of centimeters) and failure to accurately measure length in small children.

2. *Recording of systolic, diastolic, and mean blood pressure.*

An automated blood pressure device (such as the Dinamapp) is used to record multiple right brachial blood pressures during echocardiographic assessment. At least four samples should be obtained, the first of which is discarded (since it is the least reliable) and the other samples

are averaged. The blood pressure should be recorded after the patient has been in a recumbent position for five to ten minutes, during or immediately after recording of ventricular images for function assessment. Ideally, the cuff is attached and the machine is allowed to obtain samples at one-minute intervals during the imaging of the ventricle. The primary technical problems commonly encountered with the blood pressure recording relate to i) patient movement, which interferes with accurate sampling, ii) failure to record during periods of steady state, iii) inadequate equipment maintenance and adjustment to standards.

3. *2-dimensional recording of the ventricular short axis.*

The short axis image is obtained at the position of the largest short axis cross-sectional area in a plane orthogonal to the long axis of the ventricle. Parasternal or subxyphoid images can be used, providing the correct orientation can be achieved. Sweeps through the ventricle should be recorded to permit the off-line reviewer to confirm correct positioning. Zoom mode is activated to provide maximum resolution and adjusted until the endocardium and epicardium of the ventricle are within the echocardiographic sector and visible throughout the cardiac cycle. The primary technical problems commonly encountered with recordings of this image relate to i) lateral endocardial dropout, ii) movement of lateral portions of the epicardial surface beyond the imaging sector during portions of the cardiac cycle, and iii) blurring of the posterior epicardial border due to excess gain. Adjustment of the time-gain compensation curve and lateral gain adjustment (on machines equipped with this feature) are used to maximize definition of these interfaces. For larger patients, second harmonic imaging (on machines with this feature) can sometimes be particularly helpful.

4. *Two-dimensional recording of the ventricular long axis.*

The long axis image is recorded in the plane transecting both atrioventricular valves (if both are present) and intersecting the true apex of the ventricle. The image can be recorded from either subxyphoid or apical positions, provided correct orientation can be achieved. Again, sweeps through the ventricle should be recorded to permit the off-line reviewer to confirm correct positioning. Zoom mode is activated to provide maximum resolution and adjusted until the plane of the atrioventricular valves, endocardium and epicardium of the ventricle are just within the echocardiographic sector and visible throughout the cardiac cycle. The primary technical problems commonly encountered with recordings of this image relate to i) foreshortening of the ventricle secondary to failure to position the transducer at the true apex, ii) lateral endocardial dropout, iii) movement of lateral portions of the epicardial surface beyond the imaging sector

during portions of the cardiac cycle, iv) inadequate definition of the apical epicardial and endocardial portions of the ventricle. Adjustment of the lateral gain control and use of second harmonic imaging (on machines with these features) can help with definition of the lateral endocardium and epicardium. Patient positioning can be helpful in bringing the apex into contact with the chest wall and avoiding foreshortening of the ventricle. For machines with dual focus transducers, apical endocardial resolution can be maximized by adjusting the position of the near-field focal zone over the apical endocardial surface.

5. *2-dimensional recording and measurement of the aortic valve annulus.*

Parasternal long axis images of the aortic root are recorded with zoom mode activated to maximize resolution of the aortic annulus. Although off-line measurement is possible, on-line inner-edge-to-inner-edge measurement in early systole at the aortic leaflet hinge-point is the preferred method.

6. *Color Doppler assessment of the severity of atrioventricular regurgitation.*

In subjects with atrioventricular regurgitation, color Doppler images of the proximal jet width are to be recorded from multiple views (1). For apical transverse and parasternal long-axis views, the scan plane is oriented to the plane that permits visualization of the proximal flow convergence zone, the point of flow passage through the leaflets, and the proximal regurgitant jet including the *vena contracta*. Zoom mode is activated to maximize resolution and the cross-sectional dimension of the proximal jet width is recorded and measured on-line in early systole from both views. From parasternal short axis views, the imaging plane is adjusted to obtain the minimum cross-sectional area of the regurgitant jet at the level of the leaflets and this jet area is planimetered in zoom mode. Following ascertainment of the proximal jet width, from apical views the color Doppler scale is adjusted until the distance between the plane of the anatomic flow orifice and a well defined alias within the proximal convergence zone is within 2 to 3 times the proximal jet width diameter. The primary technical problem commonly encountered with recordings of these images relate to a failure to orient the imaging plane to correspond to the plane of regurgitant jet passage through the valve.

7. *Spectral Doppler recording of the atrioventricular valve inflow jet.*

From apical views, 2D color Doppler mode is used to determine the position and direction of flow of the atrioventricular inflow jet. If two atrioventricular valves are present, the assessment is carried out on both. The transducer is moved to a position of maximum alignment with the direction of inflow at the atrioventricular leaflet tips and the pulsed Doppler sample is positioned in the center of the jet just proximal to the leaflet tips. The aortic valve closure is recorded using a phonocardiogram with the sensor placed at the left upper sternal border to enable calculation of isovolumic relaxation interval. At least ten to fifteen cardiac cycles should be recorded at the highest sweep speed setting (100 mm/sec). The primary technical problems commonly encountered with atrioventricular valve inflow samples relate to i) a failure to orient the imaging plane to correspond to the plane of the inflow jet and ii) sampling from an incorrect position within the inflow jet.

8. *Spectral Doppler recording of the pulmonary vein inflow jet.*

From subxyphoid, apical or parasternal views, color Doppler mode is used to determine the position and direction of flow of the inflow jet from a pulmonary vein. The transducer plane should be oriented such that the jet can be visualized both within the vein and as it opens into the atrium. The pulsed Doppler sample is positioned in the center of the jet within the pulmonary vein just proximal to the point at which the jet emerges within the left atrium. At least ten to fifteen cardiac cycles should be recorded at the highest sweep speed setting (100 mm/sec). The primary technical problem commonly encountered with pulmonary inflow samples relate to sampling from an incorrect position within the inflow jet (in the atrium and not in the vein).

9. *Spectral Doppler recording of the aortic outflow jet.*

From apical views, pulsed Doppler samples are recorded at the level of the aortic leaflet tips. Color Doppler is used to define the jet position and direction, transducer orientation is adjusted to maximize alignment parallel to this jet, and multiple samples (10-15 beats) are recorded at the highest sweep speed setting (100 mm/sec). The primary technical problems commonly encountered with aortic outflow samples relate to i) sampling from an incorrect position within the jet due to cardiac motion over the course of systole and ii) failure of adequate alignment of the plane of insonation parallel to the direction of flow.

10. *M-mode color-Doppler recording of the ventricular diastolic flow propagation velocity.*

From apical views, 2D color Doppler mode is used to determine the position and direction of flow of the atrioventricular inflow jet. The transducer is moved to a position of maximum alignment with the direction of inflow at the atrioventricular leaflet tips and M-mode color Doppler samples are recorded. At least ten to fifteen cardiac cycles should be recorded at the highest sweep speed setting (100 mm/sec). The primary technical problems commonly encountered with M-mode color Doppler atrioventricular valve inflow samples relate to i) a failure to orient the imaging plane to correspond to the plane of the inflow jet and ii) failure to position the transducer at the true apex.

11. *Spectral tissue Doppler recording of atrioventricular valve annular velocities.*

From apical views, 2D images are used to orient the transducer in the transverse plane transecting the plane of the two atrioventricular valves (if both are present). The pulsed sample volume is positioned within the myocardium just proximal to the valve annulus and adjusted until the sample volume remains within myocardium throughout the cardiac cycle. Tissue Doppler mode is activated and at least ten to fifteen cardiac cycles should be recorded, preferably using a strip chart recorder at maximum paper speed (100 mm/sec). This data acquisition is then repeated from the opposite ventricular free wall myocardium. The primary technical problems commonly encountered with spectral tissue Doppler samples relate to i) a failure to orient the imaging plane to correspond to the plane of the atrioventricular valves, ii) failure to sample from the true ventricular apex, and iii) excess myocardial motion resulting in the sample volume failing to record tissue Doppler throughout the cardiac cycle.

<u>Core Laboratory Data Analysis:</u>

The measured and derived parameters to be recorded on off-line review include the ventricular end-diastolic volume, end-systolic volume, ejection fraction, mass, eccentricity, mass:volume ratio, end-systolic wall stress, the severity of atrioventricular regurgitation, the presence of intracardiac thrombus and/or spontaneous cavitations, cardiac output, systemic resistance, velocity of flow propagation, early diastolic atrioventricular annulus velocity, duration of pulmonary vein flow reversal during atrial systole, early deceleration time from atrioventricular valve inflow Doppler, and the ratio of peak early to peak late diastolic atrioventricular valve inflow velocity.

Data primarily recorded on sVHS video tape will be converted to digital format using a video digital capture system at a temporal resolution of 30 frames per second (the same as recorded sVHS) and spatial resolution of 640 by 480 (higher than sVHS) avoiding any information loss in the data transfer. Video measurements will be performed on a microcomputer-based workstation custom programmed for electronic caliper overlay of captured digital images for recording of one- and two-dimensional data arrays.

The indices of ventricular size and function (end-diastolic volume, end-systolic volume, mass, mass:volume ratio, eccentricity, ejection fraction, and end-systolic wall stress) will be converted to age and body surface area adjusted norms, expressed in z-scores (normal deviates) relative to the distribution of each variable in the normal population to adjust for the effects of age and growth.

1. *Ventricular cavity size, shape, mass, and systolic function.*

After image conversion to digital format, end-diastolic and end-systolic frames are identified for analysis. End-diastole is taken as the frame at which atrioventricular valve closure occurs and end-systole is taken as the frame preceding atrioventricular valve opening. The endocardial and epicardial borders of the ventricle are manually traced using the electronic cursor on end-systolic and end-diastolic long and short axis images, excluding the papillary muscles. The long axis of the ventricle is automatically identified with the option of manual over-ride and the long axis dimension is obtained. The end-diastolic and end-systolic endocardial and epicardial volumes are then calculated using a modified Simpson's rule algorithm (2) to provide end-diastolic and end-systolic volumes, ejection fraction, ventricular mass, and mass:volume ratio. The shape of the ventricle is quantified as eccentricity from the end-diastolic long axis dimension (L) and short axis area (A) as:

$$\text{Eccentricity} = [L^2 - (4A/L)^2]^{0.5}/L$$

2. V*entricular peak and end-systolic wall stress.*

Peak systolic fiberstress is estimated from end-diastolic mass and volume and peak systolic pressure. This method is premised on the observation that peak wall stress is an early diastolic event, generally occurring prior to significant ventricular ejection. End-systolic fiberstress is calculated from end-systolic mass and volume, using mean arterial blood pressure as an estimate of end-systolic pressure (3). Volume-averaged fiber stress is obtained according to the method of Regen (4) from pressure (P), epicardial volume ($V_0$), and endocardial volume ($V_C$) as:

$$\text{Fiberstress} = [3P]/[2(\ln V_0 - \ln V_C)]$$

3. *Cardiac index and systemic resistance.*

Multiple cardiac cycles of the aortic outflow Doppler are digitized to obtain the aortic velocity-time integral ($VTI_{aortic}$). The measured aortic valve diameter is used to calculate flow area (FA), and stroke volume (SV) is obtained as SV = ($VTI_{aortic}$)(FA). Cardiac output (CO) is derived from SV and heart rate (HR) as CO = (SV)(HR), and cardiac index (CI) is calculated as CI = CO/BSA, where BSA = body surface area is calculated from height and weight according to the method of Haycock (5). Systemic resistance is calculated as (CO)/(mean arterial pressure).

4. *Doppler indices of diastolic function.*

At least three consecutive cardiac cycles will be digitized for atrioventricular valve and pulmonary vein inflow Doppler. Numerous derived variables have been reported from these tracings, but those, which have been identified as most important to date, include the ratio of peak early velocity ($E_P$) to peak atrial velocity ($A_P$), the early deceleration time, and the duration of the atrial contraction-related retrograde pulmonary vein Doppler signal (6).

5. *Diastolic ventricular flow propagation velocity.*

The color Doppler M-mode of ventricular inflow from at least three consecutive cardiac cycles will be analyzed to calculate the rate of diastolic flow propagation. The leading edge of the flow wave is digitized to provide the distance versus time relationship for the flow propagation (7). The curve is typically linear over the first 50-70% of the ventricular length with compliance-dependent non-linearity apparent at the ventricular apex (8). The slope of the early (linear)

portion of the curve is obtained by standard linear curve-fit and the magnitude of non-linearity is calculated as the exponent of the quadratic term of the best-fit second order polynomial.

6. *Tissue Doppler indices of diastolic function.*

Early diastolic tissue velocity will be averaged from at least three consecutive cardiac cycles for each of the sample sites (left and right ventricular free walls) (9).

7. *PISA calculation of atrioventricular regurgitant volume.*

An isovelocity hemisphere is identified within the proximal flow convergence zone positioned a distance of between 2 and 3 times the diameter of the *vena contracta* from the plane of the regurgitant orifice. The radius of the hemisphere is measured frame-by-frame over the course of systole and the per-frame regurgitant volume is calculated as the flow velocity at the hemisphere times the hemispheric surface area. The regurgitant volume is then obtained by integration over the cardiac cycle (10).

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## APPENDIX B
## MRI CORE LABORATORY PROTOCOL

**Introduction:**

The MRI outcomes of interest, which include ventricular mass, ventricular end diastolic and end systolic volume, mass to volume ratio and measures of localized flow and pathway patency, do not require the use of injection contrast. Injection contrast will not be used in patients participating in this study. The study is to last no longer than 60 minutes. If limited cooperation is anticipated from the subject, obtaining mass and volume measures is of primary importance. Subjects will have continuous electrocardiogram (ECG), pulse oximetry and blood pressure monitoring throughout the study.

The proposed protocol is designed for use with any modern MRI scanner equipped with cardiac software. The terminology used is generic to avoid vendor-specific jargon. Some imaging parameters, such as TE, flip angle, etc., are not specified because they vary by vendor, scanner model, and operating software version.

**Pre-scan localizing images:**

ECG (or VCG)-triggered breath-hold fast gradient echo sequence: “4-chamber” plane prescribed from the previous 2-chamber cine off the last image (end-diastole).

ECG (or VCG)-triggered breath-hold fast gradient echo sequence: short-axis plane; 12 slabs covering the systemic ventricle from the plane of the atrioventricular (AV) valve(s) to the cardiac apex.

The recommended sequence for assessment of ventricular function is either a segmented k-space fast spoiled gradient echo sequence or a steady-state free precession sequence. To ensure consistency and quality, specific imaging parameters will be determined by each participating center and the core laboratory prior to study commencement.

In patients who are unable to hold breath for 8-10 seconds at a time, image acquisition can be performed with free breathing. The number of signal averages (number of excitations) is increased to four.

**Variables to be analyzed:**

Group 1) End diastolic volume, end systolic volume, stroke volume, ejection fraction, mass, mass/volume ratio.

Group 2) Velocity mapping of localized blood flow in the inferior vena cava, lateral tunnel or extracardiac conduit, superior vena cava right pulmonary artery, left pulmonary artery, and ascending aorta.

Group 3) Optional measurement of anatomic detail of the Fontan pathway to determine the presence of pathway narrowing or obstruction.

## Reference List

Lorenz CH. The range of normal values of cardiovascular structures in infants, children, and adolescents measured by MRI. *Pediatr Cardiol*. 2000;21:37-46.

## APPENDIX C

## MAXIMAL EXERCISE TESTING PROTOCOL

All subjects who are at least 115 cm tall will undergo maximal exercise testing using a ramp cycle protocol. This height restriction was chosen to assure that all subjects undergoing exercise testing would have adequate leg length to properly perform cycle ergometry. All subjects will be asked to fast for approximately 2 hours prior to exercise testing. All subjects will be instructed to wear loose comfortable clothing appropriate for exercise testing (1).

**Pulmonary Testing:** Prior to exercise testing all subjects will undergo resting lung mechanics consisting of inspiratory and expiratory flow volume loops. The patients will be instructed in proper technique for performing pulmonary function maneuvers and be permitted to practice the technique prior to testing. They will be asked to perform at least three inspiratory and expiratory flow volume loops, which will be monitored graphically to insure proper technique and reproducibility of results.

Following completion of the flow volume loops, the patients will be asked to perform a maximal voluntary ventilation maneuver. This value will then be used to calculate breathing reserve during exercise (2).

**Exercise Protocol:** All subjects will be exercised to maximum volition using an electronically braked cycle ergometer. The protocol will consist of sitting quietly on the ergometer for 3 minutes followed by 3 minutes of unloaded pedaling. The work rate will then be increased using a ramp protocol with a slope chosen to achieve the subjects predicted maximal work rate in 10-to-12 minutes of total cycling time (1,3).

**Electrocardiographic Measurements:** A 12-lead electrocardiogram will be obtained at rest in the supine, sitting, and standing position. A 3-lead cardiac rhythm will be monitored continuously throughout this study using leads $V_1$, AVF, and $V_5$. A 12-lead ECG will be obtained during each minute of exercise, at peak exercise, and for the first 10 minutes of the recovery period.

**Blood Pressure Monitoring:** Blood pressure will be obtained at rest and every 3 minutes of exercise and recovery. Blood pressure will be measured by direct auscultation using either an

automatically cycled blood pressure cuff designed for exercise testing or direct auscultation using a sphygmomanometer (1).

**Oximetry:** Arterial oxygen saturation will be measured continuously throughout this study using either an ear or finger pulse oximeter.

**Metabolic Measurements:** Minute oxygen consumption ($VO_2$), minute carbon dioxide production ($VCO_2$), minute ventilation (VE) and respiratory exchange ratio (RER) will be monitored continuously on a breath-by-breath basis using commercially available metabolic carts. Tidal volume, respiratory rate and oxygen pulse ($VO_2$/HR) will also be monitored on a breath-by-breath basis. All metabolic measurements will be monitored through the pre-exercise resting phase, warm-up, exercise protocol, and the first 2 minutes of recovery. All subjects will be encouraged to exercise to their maximal capacities.

**Data Analysis:**

For purposes of data analysis, all breath-by-breath data will be averaged over 20 second intervals.

**Data Collection:**

1. **Maximal Work Rate**: This will be the maximal work rate obtained during the exercise test expressed in watts.
2. **$VO_2$**: Oxygen consumption will be expressed in ml/kg/min. Oxygen consumption will be recorded at rest. The maximal oxygen consumption will be defined as the highest oxygen consumption achieved during the exercise test when averaged over 20 second intervals and expressed as ml/kg/min.
3. **Ventilatory Anaerobic Threshold (VAT)**: VAT will be measured by the V slope method and confirmed using the ventilatory equivalent method (4). The data will be expressed as oxygen consumption in ml/kg/min at VAT and as the percent of maximal oxygen consumption ($VO_2$ at VAT/max $VO_2$) x 100.
4. **Oxygen Pulse**: Oxygen pulse will be measured at rest, at VAT and at maximal $VO_2$.
5. **Pulse Oximetry**: Pulse oximetry will be measured at rest, at VAT and at peak exercise.
6. **Heart Rate**: Heart rate will be measured at rest while sitting quietly on the cycle ergometer at VAT and at maximal exercise.
7. **Blood Pressure**: Blood pressure will be measured at rest and maximum exercise.

8. **Pulmonary Functions**: Minute ventilation, tidal volume and respiratory rate will be measured at rest at VAT and at maximal exercise. In order to measure ventilatory efficiency, the ventilatory equivalents of carbon dioxide ($VE/VCO_2$) will be measured at rest, VAT, and maximal exercise. Breathing reserve will be defined as (1-max VE/MVV) x 100 (4).

## Reference List


1. Paridon SM. Exercise testing. In: Garson A, Bricker JT, Fisher DJ, Neish SR, editors. The science and practice of pediatric cardiology, Second Edition. Philadelphia: Williams & Wilkins, 1998; Vol 1:40:875-888.

2. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R. Calculations, formulae, and examples. In: Principles of exercise testing and interpretation, Second Edition. Philadelphia: Lea and Febiger, 1994; 8:454-464.

3. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R. Protocols for exercise testing. In: Principles of exercise testing and interpretation, Second Edition. Philadelphia: Lea and Febiger, 1994; 5:95-111.

4. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R. Measurements during integrative cardiopulmonary exercise testing. Principles of exercise testing and interpretation, Second Edition. Philadelphia: Lea and Febiger, 1994; 3:52-79.

## APPENDIX D

## SEROLOGY CORE LABORATORY PROTOCOL

The Fontan Serology Core Laboratory will determine the type of fluorescence immunoassay (Shiniogi BNP-32 Human Assay versus Biosite Triage) which will be used to measure B-Type Natriuretic Peptide (BNP) levels in plasma.

Specimen Requirements: 1.0 mL frozen EDTA plasma. The sample must be spun down and plasma removed from the cells within 1-4 hours of draw. A minimum amount of 0.5 mL is required.

Reporting Results:

Results are reported up to 4 significant digits. If values are < 100, results will be reported with one decimal place. Values > 100 will be reported without decimals.

Units are pg/mL. The lower detection limit is 4 pg/mL and the upper detection limit is 1300 pg/mL.

# APPENDIX E

## CONSENT/ASSENT FORMS

Sample Informed Consent

Sample Informed Assent

Sample forms are included on the following pages. These forms may be modified by individual clinical sites to comply with local IRB regulations.

Form
M0345

***SAMPLE*** **INFORMED CONSENT FOR RESEARCH**

**CONSENT TO PARTICIPATE AS A SUBJECT**
**IN MEDICAL RESEARCH**
THE RELATIONSHIP BETWEEN FUNCTIONAL HEALTH STATUS AND
LABORATORY PARAMETERS OF VENTRICULAR PERFORMANCE
AFTER THE FONTAN PROCEDURE

PI:

IRB #

Purpose

**WE ARE ASKING YOU AND YOUR CHILD TO TAKE PART IN A RESEARCH STUDY BECAUSE YOUR CHILD HAS HAD A FONTAN OPERATION TO TREAT HIS/HER HEART ABNORMALITY. THIS STUDY IS BEING DONE TO FIND OUT WHAT TESTS ARE BEST USED TO DETERMINE HOW WELL YOUR CHILD'S HEART IS FUNCTIONING AFTER THIS OPERATION, AND TO COMPARE YOUR CHILD TO OTHER CHILDREN WHO HAVE HAD THE SAME SURGERY.**

***Description of the Study***
*In order for your child to participate in this study, he/she must meet certain specific criteria and you must sign this Consent Form. We will be reviewing and recording information from your child's medical chart to get background information about your child's heart problem, how it was treated, and what other medical problems your child has had. Your doctor will determine whether your child meets the criteria for the study based on his/her medical assessments. After your child has been evaluated and you have signed this consent, your child will be enrolled in the study. This study is designed so that your child will undergo a number of tests to evaluate how your child's heart is functioning. The tests must be scheduled and completed within three months after you sign the consent form. We hope that we can complete as many as of the tests as possible on one day or over a short time period for your convenience.*

As part of the study you will be asked to fill out part of a questionnaire that describes your child's health status. This questionnaire is called the Child Health Questionnaire (CHQ). It is used to measure the physical and emotional well-being of children. The study coordinator will explain the questionnaire to you and show you how to fill it out. You may ask him/her questions about how to complete the form, but he/she cannot help you decide what the answers are. The questionnaire is self-administered, and you can fill it out before your clinic appointment or during the time your child is at the center undergoing testing. Your answers should be based on how your child has felt for the last 4 weeks.

If your child is at least 10 years old, your child will also be asked to fill out part of the CHQ prior to or at the time of the scheduled clinic appointment. The study coordinator will go over the instructions with your child and show him/her how to fill it out, but he/she

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cannot provide your child with the answers or fill out the questionnaire for him/her. Your child's answers should be based on how he/she has felt during the last 4 weeks.

If your child is between 10 and 18 years of age, your child will also be asked to fill out another questionnaire called the Congenital Heart Adolescent and Teenage (CHAT) questionnaire. This questionnaire was developed by talking with teenagers who have heart problems to find out what things concerned them about their health and how their heart problem affected their lives. The purpose of the questionnaire is to find out if your child has any of these concerns that might affect his/her health and quality of life.

Your child will have blood drawn as part of this study. Blood levels of B-Type Naturietic Peptide (BNP) will be measured. BNP is a protein made by the heart that may be elevated in the blood of some patients. Prior to drawing a blood sample, your child will be asked to lie quietly for 30 minutes. Then a small needle will be placed into a vein in his/her arm and approximately 1 teaspoon (5 milliliters) of blood will be drawn from the needle.

As part of this research study your child will be scheduled for the following specific tests to evaluate how his/her heart is functioning:

Echocardiogram: An echocardiogram is a painless test using sound waves that takes a 2-dimensional picture of your child's heart. Your child will need to lie quietly on a table for about 30 minutes while the test is being done.

Cardiac Magnetic Resonance Imaging: Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. It will allow us to evaluate how your child's heart is functioning by showing us how large it is and also how hard it is pumping. The study involves entering a room in which a large magnet is present. Your child will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. Some children may experience anxiety or be nervous while lying in the tunnel. Your child will be asked to lie still for up to 60 minutes on this bed. Your child will hear a loud machine-like noise. Your child's heart rate and blood pressure may also be monitored during the test. A small band to monitor your child's pulse and blood oxygen content will be placed on a toe or finger. A loose strap will be placed around your child's chest to monitor breathing. Four EKG leads will be placed on your child's back. These monitoring devices will not harm your child. During the test, your child can have voice contact and physical contact with someone in attendance, if you desire. If your child does not want to do this test, the test will not be performed, but your child can remain in the study.

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Exercise testing:
If your child is at least 115 cm tall (about 52 inches), he/she will be asked to perform an exercise test. This test will look at how your child's heart functions while he/she is exercising. Your child will need to be fasting for at least 2 hours before the test. Pulmonary function tests will be done while your child is resting before the exercise portion of the test. Your child will be asked to breathe in and out of tubes, and the amount of air and pressure of air flowing will be measured. A standard ECG will be done and your child's blood pressure will be measured.

Then your child will get on a stationary bike and be asked to pedal as the wheels become harder to turn over a period of time. We will ask your child to pedal as long as he/she can. During this time various measurements of his/her breathing, heart rate and blood pressure will be taken. Your child will be monitored throughout the entire test, and he/she can stop at any time. However, it is important for your child to try as hard as he/she can for us to see how the heart functions during exercise.

We would like for all children who agree to be in the study to perform the exercise testing and have a cardiac MRI. The exercise testing and cardiac MRI are important parts of the study and will give us valuable information about how your child's heart functions. However, if you or your child do not wish to have the exercise testing or cardiac MRI, or your child has a limitation, which would not allow him/her to do the exercise testing or the cardiac MRI, you may still be in the study. We will attempt to schedule as many of these tests as possible on one day and coordinate it with a regular follow-up appointment. However, this may not always be possible, and two clinic visits to complete them may be necessary.

## Risks and Discomforts

Risks associated with drawing blood for the BNP level from a vein include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There are no risks associated with echocardiography.

Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to

the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal that may be in your child's body (this includes certain dyes found in tattoos). If there is any question about a potential hazard from metal within your child's body, this test will not be performed. During the study, the door to the MRI room will remain closed and monitored so that no one carrying metal objects can enter while your child is in the magnet. Some children may experience anxiety or be nervous while lying in the tunnel.

Exercise testing involves your child trying to exercise as hard as he/she can. A small number of children who have had a Fontan operation develop an abnormal heart rhythm with strenuous exercise. If this occurs in your child during this test, it will provide very important information for the future care of your child. Monitoring of your child's heart rhythm during the test will tell us whether this occurs and will help us learn what to do in caring for your child. A member of the exercise testing team will be present throughout the test to monitor continuously your child's heart rhythm and how your child is doing.

## Benefits

We will be able to determine how your child's heart is functioning through the use of the tests described above. Your child may receive no other direct benefit from the study tests. However, the information obtained from the study may prove useful to other children who have decreased heart function and require a surgical procedure to correct it. The results of all tests performed as part of the study will be made available to you through your child's cardiologist.

## Alternative Treatments

Since this study involves no direct treatments but is looking at what tests are helpful to evaluate your child's heart function after a Fontan operation, there is no specific alternative treatment that she/he would be eligible for in the study. Your child's doctor may use any treatment he/she thinks is necessary to help your child's heart function better while participating in the study.

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Study Participation/Withdrawal

Your decision to have your child participate in this study is completely voluntary. You may refuse to give permission to participate or you may withdraw your child from the study at any time. Refusal to participate or withdrawal from the study will not result in any penalty or loss of benefits to which you are otherwise entitled.

Your child's participation in this study can be stopped at any time if it is determined by your doctor to be in your child's best interest. You will be informed of any new findings that may affect your willingness to continue your child's participation in this study. A copy of this consent form will be provided to you for your records.

Confidentiality and Privacy of Information

You have a right to privacy and your child's participation in this research study will remain confidential. Your child's name will not be used in any report of this study or publication of information from this study. The tapes or disks with your child's echocardiogram and MRI studies will be sent to laboratories outside of _____ for reading. These tapes or disks, which may have your child's name on them, will be kept in locked files at these laboratories. Your child's name will not be recorded in any other records kept outside of _____. Information gathered during this study and your child's medical records may be inspected and verified by staff representatives of the study sponsor (the National Institutes of Health), _____ Institutional Review Board, or the Pediatric Heart Network Data Coordinating Center. Medical records for this study and medical records from other institutions that contain your child's identity will be treated as confidential by the National Institutes of Health and will be shared only with these agencies, or as required by law.

Costs

There will be no additional costs to you as a result of your child's participation in this study. Tests required by the study will be provided to you free of charge. You will be responsible for all other costs related to your child's medical care such as hospitalization, surgery, drugs, laboratory tests, diagnostic procedures and physician fees which are considered standard medical care for patients with your child's condition.

You will receive $100 for the time required by your family to participate in the study. The study will also pay for travel expenses and one meal for your child and two family

members/others on the days your child is scheduled for tests related to the study. If you live far away from the study center and an overnight stay is required to complete study testing, you will be reimbursed for one night's lodging and meals. You will receive this reimbursement after completing the final testing for the study.

Responsibility for Research-Related Risks

Immediate necessary medical care is available at _____ in the event that you are injured as a result of your participation in this research study. However, there is no commitment by _____, or your _____ physicians to provide monetary compensation or free medical care to you in the event of a study-related injury. Further information concerning this and your rights as a research subject can be obtained from the _____ Office of Risk Management at _____.

Contact Information

For information regarding your child's rights as a study subject you may contact:

_____

_____

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To obtain information about study procedures, report a research related injury or ask questions about this research study, you should contact:

| | | |
|---|---|---|
| Contact Name | Phone | Pager |
| Contact Name | Phone | Pager |

**Agreement to Participate in the Study**
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study with the understanding that I may withdraw at any time. I have been told that I will be given a signed copy of this consent form."

| | |
|---|---|
| Parent/Legal Guardian Signature | Date |
| Signature of Person Obtaining Consent | Date |
| Signature of subject if over 12 years of age | Date |

***SAMPLE*** **ASSENT FOR RESEARCH**

THE RELATIONSHIP BETWEEN FUNCTIONAL HEALTH STATUS AND
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Name_____
MR # _____

1. My name is _____.

2. We are asking you to take part in a research study because we are trying to learn more about how your heart is working after your Fontan operation.

3. If you agree to be in this study, we will review and record information from your medical chart, and you will be asked to fill out questionnaires about how you feel. We will ask you to have four tests done. The first one is an echocardiogram, which uses sound waves to see how your heart works and does not hurt at all to have done. You will have to lie still for the test for about 60 minutes. The second test is a heart magnetic resonance imaging (MRI) scan. The MRI uses magnetic energy to create pictures of how your heart works. It does not hurt to do, but you will hear loud noises as you lie on a small table inside a doughnut-shaped tube for about 45 minutes. The third is an exercise test. You will blow into some tubes to see how your lungs work and then pedal on a bike for several minutes until you are tired. This test doesn't hurt, but you will probably feel tired when you are done. The fourth and last test is a blood test to measure the level of a protein called BNP in your blood. A needle is used to take a small amount of blood (about a teaspoon) from a vein in your arm, so you will feel discomfort for a few seconds and a bruise could form where the blood was taken.

4. If you can't do the MRI or the exercise test, you can still be in the study.

5. This study may not help you, but it may help other children with heart problems who have had surgery like yours.

6. Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say “yes”, you can still decide not to do this.

7. If you don’t want to be in this study, you don’t have to participate. Remember, being in this study is up to you, and no one will be upset if you don’t want to participate or even if you change your mind later and want to stop. You can change your mind later, after saying yes to the study, so saying yes now does not mean you cannot remove yourself from the study later.

Name_____
MR # _____

8. You can and should ask any questions that you have about the study. If you have questions later that you didn't think of now, you can call:

_____

_____

or ask us next time. You may call us at any time to ask questions about your heart, the study or treatment.

9. Signing your name at the bottom means that you agree to be in this study. Your doctors will continue to treat you whether or not you participate in this study. You and your parents will be given a copy of this form after you have signed it.

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Obtaining Assent Date

_____ _____
Signature of Witness to Assent Date