

**VARIABILITY OF ECHOCARDIOGRAPHIC LEFT VENTRICULAR
MASS, VOLUME AND EJECTION FRACTION IN PEDIATRIC
PATIENTS WITH CONGESTIVE (DILATED) CARDIOMYOPATHY**

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TABLE OF CONTENTS

PROTOCOL OVERVIEW (ABSTRACT)	1
A. SPECIFIC AIMS	2
A.1 Primary Aim.....	2
A.2 Secondary Aim.....	2
A.3 Secondary Aim.....	2
A.4 Secondary Aim.....	3
B. BACKGROUND	3
B.1 Significance.....	3
B.2 Preliminary Studies.....	5
C. STUDY DESIGN AND METHODS	7
C.1 Overview.....	7
Figure 1: Study Flow.....	9
C.2 Participants	10
C.2.1 Inclusion Criteria	10
C.2.2 Exclusion Criteria	10
C.2.3 Human Subjects Considerations	11
C.2.4 Subject Availability	12
C.3 Study Enrollment	12
C.3.1 Recruitment Protocol.....	12
C.3.2 Indications for Withdrawal from Study	13
C.4 Treatment	13
C.5 Measurements.....	13
C.5.1 Schedule of Measurement.....	13
C.5.2 Outcome Variables.....	14

C.5.3 Clinical Data Collection	14
C.5.4 Local Echocardiographic Image Acquisition	14
C.5.5 Local Echocardiographic Measurement Requirements.....	16
C.5.6 Core Laboratory Procedure	17
C.6 Adverse Events	18
C.6.1 Definition	18
C.6.2 Classification of Adverse Events	18
C.6.3 Data Collection Procedures for Adverse Events	21
C.6.4 Reporting Procedures	20
C.6.5 Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials	21
C.6.6 Post-Study Procedures for Adverse Events.....	22
C.7 Statistical Methods	22
C.7.1 Sample Size and Power	22
C.7.2 Analysis Plan.....	23
Table 1. Dataset Comparisons.....	23
C.8 Data Management	25
C.8.1 Information Flow.....	26
Figure 2. Data Management System and Information Flow	26
C.8.2 Overview of Data Management System	26
C.9 Quality Control	27
 D. STUDY LIMITATIONS	 27
 E. ORGANIZATION	 27
E.1 Time Line	27
E.2 Study Organization	28
 F. REFERENCES	 29
 G. APPENDICES.....	 30
Appendix A. Informed Consent Template for Study	31

OVERVIEW (ABSTRACT)

Cardiomyopathy is an important cause of chronic disability and death in pediatric patients and currently accounts for approximately 50% of cardiac transplants performed during childhood. Recent progress in therapies for patients with congestive (dilated) cardiomyopathy has an evidence base that is primarily limited to the adult population. The pediatric experience is often limited to uncontrolled studies providing safety data and experience interpreted as suggestive of efficacy. The limited availability of quantitative longitudinal data concerning indices of ventricular function in this patient population is a major impediment to controlled trials of therapy for ventricular dysfunction in children. Knowledge of the longitudinal variation in these indices is essential for study endpoint selection, sample size calculations, and determining study feasibility. This observational study will provide these data and will also quantitatively evaluate the relative contribution of several potentially controllable sources of intra- and interstudy variability.

Patients with suspected or documented chronic dilated cardiomyopathy who are undergoing routine echocardiographic evaluation of ventricular function will be recruited for the study. Eligible, consenting patients will be evaluated at enrollment and, if confirmed to have dilated cardiomyopathy, will be re-evaluated again at the time of each clinically indicated echocardiogram over the following 3 to 13 months. Data (image) acquisition will be performed by two observers, and measurements will be performed by one local and two core laboratory observers. We will evaluate inter-observer variability of data acquisition and both intra- and inter-observer variability in data measurement as well as local versus core lab reproducibility. The primary aim is to quantify interstudy variability (that is, the variance of change in measurements over time) in echocardiographically-determined left ventricular end-diastolic volume z-score, mass z-score, and ejection fraction z-score. Secondary aims include evaluation of interstudy variability of other echocardiographic indices of ventricular function and quantification of the relative contribution of definable sources of interstudy variability. The total sample size target is 120 subjects with qualifying baseline echocardiograms (to ensure that 86 of these have paired interpretable echocardiograms performed under similar conditions).

A. SPECIFIC AIMS

A.1 Primary Aim

To determine the interstudy variability of echocardiographically-derived LV end-diastolic volume z-score, mass z-score, and ejection fraction z-score in pediatric patients with dilated cardiomyopathy; more specifically, the variance at a single point in time as well as the variance of change in measurements over time.

Hypothesis: Longitudinal variation in LV size and function in chronic pediatric dilated cardiomyopathy is sufficiently narrow to permit design of clinical trials with an achievable sample size.

Outcomes: Single point variance and variance of change of two-dimensional echocardiographically determined LV end-diastolic volume z-score, LV mass z-score, and LV ejection fraction z-score.

A.2 Secondary Aim

To determine the relative magnitude of the various sources of variability in echocardiographic outcomes in order to optimize operational procedures that can minimize variance.

Hypothesis: Certain sources of variance in echocardiographic assessment of LV function contribute significantly more than others to the overall variability.

Outcomes: Interobserver variability of image acquisition within centers, interobserver variability of image measurement between the center and the core laboratory, and both interobserver and intraobserver variability of image measurement at the core laboratory.

A.3 Secondary Aim

To determine the interstudy variability of echocardiographically-derived indices of LV systolic and diastolic function derived from m-mode, spectral Doppler, and tissue Doppler techniques used in pediatric patients with dilated cardiomyopathy.

Hypothesis: Echocardiographic methods of assessment of ventricular function provide useful endpoints in clinical trials in pediatric cardiomyopathy because of high reproducibility and few technical obstacles.

Outcomes: Interstudy variability of echocardiographic parameters of LV systolic and diastolic function derived from m-mode, spectral Doppler, tissue Doppler, and m-mode color Doppler.

A.4 Secondary Aim

To determine the relationship of clinical status, including treatment, to the interstudy variability and repeatability of echocardiographic measurements.

Hypothesis: Interstudy variability and repeatability of echocardiographic measurements will relate to clinical status and concurrent therapy

Outcomes: Relation of clinical status (Ross heart failure score or New York Heart Association congestive heart failure class) and treatment (medical management) to the echocardiographic variables listed in the foregoing.

B. BACKGROUND

B.1 Significance

Left ventricular size and function are important independent predictors of outcome in numerous forms of cardiovascular disease, and echocardiography is the primary modality used to assess ventricular function in children. Similarly, echocardiographically-derived measurements are commonly used as endpoints in pediatric clinical trials. Knowledge of the limits of reproducibility of echocardiography is essential for both these purposes. Although there is extensive experience with this technology, there are few quantitative data concerning reproducibility of these measurements, particularly in children. This issue is particularly problematic because of the range of factors that are known to affect this reproducibility. Patient age and body habitus are known to be important, as is disease status. Less commonly appreciated is the evolution of technology over time, which requires that this issue be addressed anew with each new generation of echocardiographic equipment.

Reproducibility of the measurements of LV size and function is of particular interest with regard to patients with dilated cardiomyopathy. Meaningful clinical or research use of these measurements requires knowledge of their reproducibility in the specific population. Due to the striking changes in LV morphology, shape, and position induced

by the cardiomyopathic state, it is unreasonable to assume that data collected in other populations are relevant to this group of patients. The purpose of this study is to evaluate the amount and source of variability in echocardiographic assessment of LV size and function in pediatric patients with dilated cardiomyopathy.

The sources of variability in echocardiographic measurements include:

- 1) Interpatient variability: differences between patients related to numerous patient-specific factors such as age, body size, variation in cardiac output, physical training, etc., and disease-specific factors such as severity of disease and treatment status;
- 2) Interstudy variability: longitudinal variation within an individual due to physiologic factors, variation in treatment, and change in disease status;
- 3) Intrastudy variability: short term (beat-to-beat) variations in the same patient secondary to respiratory effects or change in position and minute to minute variation related to factors such as change in emotional state;
- 4) Measurement variability modulating each of the foregoing:
 - a) Variability due to differences in echocardiographic and image analysis equipment;
 - b) Intra- and interobserver variability in data (image) acquisition;
 - c) Intra- and interobserver variability in data analysis (measurements), including frame selection and structure identification.

Some sources of variability are nearly impossible to quantify, such as variance secondary to differences between machines, transducers, and machine settings, due to the nearly infinite number of ways in which these factors can be combined. In clinical trials, some of the other sources of variability can be minimized, though not eliminated, by protocol-driven study design and core laboratory review. However, estimation of the number of patients that must be enrolled in a clinical trial requires knowledge of the inpatient variability, and these data must therefore be available during the design phase. Assessment of inpatient variability requires assessment of longitudinal data. Although relevant data can often be obtained from review of existing records rather than prospective data collection, there has been sufficient evolution in equipment, methods, and clinical practice that retrospective analysis would fail to reflect current practice.

Intra- and interobserver variability in frame selection and measurement can also be determined from retrospective analysis, but variability due to image acquisition cannot.

B.2 Preliminary Studies

Many clinical trials in cardiology employ indices of ventricular size and function as surrogate outcome study endpoints.¹⁻³ In particular, temporal changes in end-diastolic volume, end-systolic volume, and ejection fraction are common clinical endpoints. Although data concerning temporal variability in these indices exist for adult patients with various forms of heart disease, this issue has not been addressed in pediatric patients with dilated cardiomyopathy and other forms of ventricular dysfunction. Available adult data indicate that despite the recognized clinical utility of these methods, the magnitude of the technique-related variance imposes a significant penalty in terms of sample size requirements for studies based on these endpoints. For example, echocardiographic assessment of LV mass is reported to have intra-sonographer variance of 10%, inter-sonographer variance of 10%, intra-reader variance of 10% that increases to 16% when the same reader repeats the interpretation 5 years later, inter-reader variance of 14%, and a frequency of non-measurable echocardiograms of 33%.⁴ Not only was the intra-reader variance higher when the second measurement was repeated 5 years later, a systematic longitudinal drift toward lower LV mass values was observed on the repeat analysis performed 5 years later. This phenomenon could have an important impact on study design because it implies that all echocardiograms on a particular patient should undergo measurement in close temporal proximity in order to avoid the potential confounding effect of this longitudinal reader drift. The reliability of the measurements is inversely related to age and body mass index, predicting a potentially better performance of the technology in children. Although studies comparing core laboratory versus clinical center interpretation of echocardiograms in children are available,⁵ studies examining the various sources of variance have not been performed in children.

As an alternative to directly assessing the variance of derived parameters, it is possible to directly calculate the propagation of error. For example, if the standard deviation for end-diastolic volume (EDV) and end-systolic (ESV) volume are SDD and SDS, respectively, then the standard deviation for EDV-ESV = stroke volume (SV) is $SDSV = ((SDS)^2 + (SDD)^2)^{0.5}$. Similarly, error propagation of ejection fraction (EF) = SV/EDV can be calculated as $SDEF = MEF * ((SDSV/MSV)^2 + (SDD/MD)^2)^{0.5}$, where MEF, MSV,

and MD are the mean values for ejection fraction, stroke volume, and end-diastolic volume, respectively. However, this calculation assumes that the variance of EDV and ESV are independent, when in fact these volumes are closely correlated. Due to the positive correlation, the variances of stroke volume and ejection fraction are usually less than these calculations would predict. Because of these confounders, the approach taken in this study will be to directly assess the variance of derived parameters.

In general, the interstudy (longitudinal) variability that is of interest is that related to “natural history”. Significant interventions or changes in management may affect ventricular size, shape, and function. The stage of the disease may also be relevant. For example, studies of interventions for acute myocarditis require data concerning the interstudy variability in ventricular size, shape, and function over the time interval immediately after presentation, and this variability will generally be very large. In contrast, interventions for patients with chronic congestive heart failure generally target populations that have relatively stable disease. Determination of appropriate variance requires availability of appropriate disease-process information. The data collection process must therefore include information about clinical status and treatment.

Serial evaluation of cardiovascular parameters is subject to the confounding effects of growth and age. For example, in a study evaluating the change in LV end-diastolic volume over a 12 month period, it is necessary to account for the amount of change that is due to somatic growth. Use of “indexed” variables calculated by simple division by body surface area (BSA) has been widely recognized to be flawed⁶ and there has been a general acceptance within the pediatric cardiology community of adjusting for these effects through the use of z-scores calculated relative to normative data.⁷ The z-score of a variable is the position, expressed in standard deviations, of the observed case relative to the mean of the population distribution. For cardiovascular structures, the calculation of z-scores is performed relative to the distribution of the structure in the normal population in order to adjust for the effect of body size or age. The position of a data point within the normal distribution for a given BSA is determined as the number of standard deviations from the normal population mean. Mathematically, for a patient who has an observed body surface area = BSA_O , and an observed value (V) = V_O , the normative data are used to determine the mean value (V_N) of the parameter that would be expected for that body size in the normal population and the standard deviation (SD_N)

of the parameter that would be expected for that BSA. The z-score is then calculated as $(V_O - V_N) / SD_N$. The interpretation of z-scores is straightforward. A z-score of zero represents a value at the normal population mean. A z-score of 2 or -2 represents a value that is 2 standard deviations above or below the normal mean, which are commonly taken as the upper and lower limits of normal. The z-scores are quite similar to the more familiar percentiles that are used clinically to express age-adjusted height and weight percentiles with respect to the normal population. In the case of height and weight, calculation of percentiles adjusts for the normally expected age-related change in height or weight, permitting comparison of subjects at varying ages. Calculation of percentiles for height and weight therefore serves the same purpose as calculation of z-scores for the size of cardiovascular structures and z-scores can be readily converted to percentiles. Z-scores are truly a “normalized” variable insofar as they are dimensionless and have a mean of zero and a standard deviation of one in the normal population.

Acquisition of these data, based on currently available echocardiographic technology and methods, is needed to enable the design of clinical trials in this important patient population. It is the intent of this study to perform a multicenter, serial echocardiographic assessment of ventricular size and function in pediatric patients with ventricular dysfunction secondary to dilated cardiomyopathy. Because these patients undergo repeat clinically indicated echocardiographic assessment at frequent intervals, it is possible to accumulate these data in a reasonably short period of time. Furthermore, the Pediatric Heart Disease Clinical Research Network has an established cooperative arrangement and an existing core laboratory structure that will facilitate this multicenter data compilation.

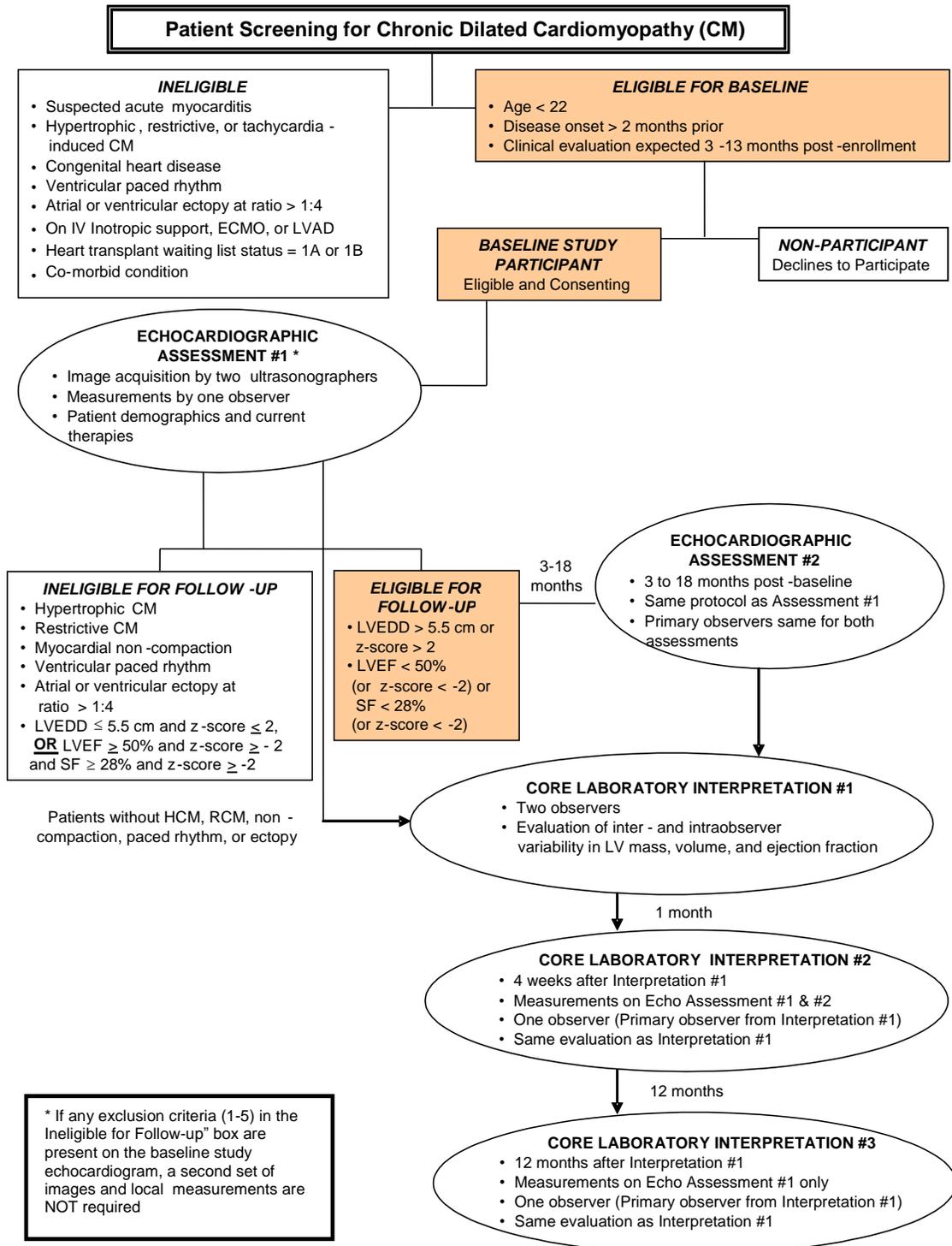
C. STUDY DESIGN AND METHODS

C.1 Overview

We will prospectively evaluate pediatric patients with dilated cardiomyopathy who are undergoing clinically-indicated echocardiographic evaluation of LV function. All clinical centers will follow the same protocol for image acquisition. Patients with known or suspected dilated cardiomyopathy will be recruited. Those confirmed to have dilated cardiomyopathy and who undergo at least two echocardiograms 3 to 13 months apart will have their primary image acquisition performed by the same ultrasonographer

whenever possible. The allowable window for inclusion of the one-year follow-up echo in analysis is 18 months. This ultrasonographer will also measure each of the parameters of ventricular function, either on-line or off-line. In addition, for each echocardiogram, an independent recording of the required images will be performed by a second individual. At the time of each echocardiogram, data concerning clinical status and treatment will be collected from the patient and the chart. For each echocardiogram, the clinical site will submit two sets of de-identified image data, one set of measurements, and data concerning clinical status at the time of the echocardiograms to the Data Coordinating Center. The data center will transfer the image data to the echocardiographic core laboratory for central measurement of all echocardiographic variables by each of 2 experienced observers. The primary core laboratory observer will repeat measurements on the first image acquisition approximately 1 month later for all study echocardiograms and also 12 months later for the baseline echocardiogram only. This process will result in six and five sets of core laboratory measurements for the baseline and follow-up echocardiogram, respectively. Two pairs of core laboratory observers (one pair for all LV dimension and volume measurements and one pair for all Doppler and time interval measurements) will be used for the duration of this observational study. The study flow for two study echocardiograms is shown in Figure 1. Interpretation of echocardiogram studies 3-5, if done, will be same as for Assessment #2.

Figure 1. Study Flow



C.2 Participants

C.2.1 Inclusion Criteria

In order for a patient to be eligible for the inclusion of serial echocardiograms, all of the following criteria must be met:

- 1) Aged < 22 years, of either gender and any race
- 2) Diagnosis of dilated cardiomyopathy
- 3) LVEDD >5.5 cm (or z-score for BSA >2) on the primary image acquisition from the first study echocardiogram
- 4) LV ejection fraction <50% (or z-score for age <-2) or shortening fraction <28% (or z-score for age <-2), as measured on the primary image acquisition from the first study echocardiogram
- 5) Disease onset greater than 2 months prior to screening
- 6) Anticipated to undergo repeat evaluation at the same institution at least 3 months but not more than 13 months later
- 7) Informed consent of parent(s) or legal guardian and assent of subject if required.

C.2.2 Exclusion Criteria

A patient is ineligible for the study if any (one or more) of the following criteria are met:

- 1) Hypertrophic cardiomyopathy
- 2) Restrictive cardiomyopathy
- 3) Myocardial non-compaction (LV hypertrabeculation) - The patient is eligible for the study as long as the echocardiogram performed at the time of screening has no evidence of myocardial non-compaction.
- 4) Ventricular paced rhythm
- 5) Atrial or ventricular ectopy at ratio greater than 1:4
- 6) Suspected acute myocarditis
- 7) Tachycardia-induced cardiomyopathy
- 8) Congenital heart disease (repaired or unrepaired)
- 9) Currently on intravenous inotropic support
- 10) Current left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO)
- 11) Heart transplant waiting list status of 1A or 1B

12) Co-morbid condition that precludes the ability to successfully obtain an echocardiogram according to the specifications of the study protocol.

It should be noted that echocardiographic inclusion criteria #3 and #4 require that the patient consents to be in the study and undergo the baseline echocardiogram. For patients who meet all of the non-echocardiographic inclusion criteria and none of the exclusion criteria based on medical record review, exclusion criteria #1 through #5 will also be re-evaluated from the baseline echocardiogram. The results of this initial study echocardiogram may render the patient ineligible for further study:

- If any of the exclusion criteria are met, the echocardiogram will not be sent for core lab review.
- If any of the inclusion criteria are not met or any of the exclusion criteria are met on the first echocardiogram, no subsequent echocardiograms will be requested for that patient.

C.2.3 Human Subjects Considerations

C.2.3.a Risks to Subjects

Because evaluations are performed during clinically indicated echocardiograms and each of these measurements is part of standard clinical practice, the only potential risks or discomforts relate to the repeat data recording by a second observer. This non-invasive method has no known risks. The secondary data collection will prolong the echocardiographic exam by about 10 minutes and this portion of the protocol will be limited to cooperative and comfortable patients. For patients who require sedation for their echocardiogram, standard doses will be used per local practice, no additional sedation will be provided, and the secondary evaluation will be performed after the clinically indicated data are obtained to prevent any interference with clinical care.

C.2.3.b Potential Benefits to Subjects

Patients are not expected to derive any direct benefit from participation in this study.

C.2.3.c Gender and Minority Recruitment

Gender distribution in children with dilated cardiomyopathy is approximately 60% male and 40% female.⁸ The incidence in blacks is approximately twice that in whites and in Hispanics is approximately 1.5 times that in whites.⁸ These data

indicate that 40% of the subjects will be members of underrepresented racial or ethnic groups.

C.2.3.d Subject Confidentiality

Each subject will be assigned a unique study identification (I.D.) number so that study information will be confidential. The link between subject name and I.D. number will be stored only at the site where the subject received his/her clinical care.

C.2.4 Subject Availability

This study requires enrollment of children with dilated cardiomyopathy. A recent survey conducted by the PHN indicated that approximately 190 children with dilated cardiomyopathy, who are within the age range 6-17 years, are currently seen at the 7 PHN centers. It is likely that the majority of these children will be eligible. Because the highest incidence of dilated cardiomyopathy is within the first year of life, the number of available patients is expected to be higher than 190 since the study will include all patients under the age of 18 years, not just the 6-17 year-old age group. It is estimated that the target of 120 subjects with a qualifying baseline echocardiogram will be recruited in less than 2 years.

C.3 Study Enrollment

C.3.1 Recruitment Protocol

The nurse or study coordinator at the local clinical center will identify all potentially eligible patients by chart review or based on a new referral for known or suspected dilated cardiomyopathy. A screening form will be completed on all potentially eligible patients. However, a maximum of 40 patients with adriamycin-associated cardiomyopathy will be enrolled. Adriamycin-associated cardiomyopathy is generally more slowly progressive than other types of cardiomyopathy. To prevent bias due to inclusion of an excess number of these patients, center-specific enrollment limits for this subpopulation will be determined, and screening forms on additional patients in this subgroup will not be completed once this limit is reached. A patient who meets all initial inclusion criteria and none of the study exclusion criteria (Section C.2.2) is defined as potentially study eligible. Every potentially eligible patient will be approached for participation in the study, and if consenting, the patient will undergo a clinically indicated echocardiogram that will follow study protocol both to confirm study eligibility as well as

provide baseline study data. If the baseline echocardiogram does not confirm eligibility the subject will be withdrawn from further participation (see Section C.3.2). The consent process will involve consent by the parent or legal guardian, consent by the patient if of legal age, and assent by the patient, where applicable according to local guidelines.

C.3.2 Indications for Withdrawal from Study

A subject will be withdrawn from the study (i.e., will not undergo study-related data collection on subsequent echocardiograms) if any of the following conditions are met:

- Baseline echocardiogram does not confirm study eligibility
- Death
- Cardiac transplantation or LV reduction surgery
- Use of ECMO or other LV assist device
- Patient or physician preference

The reason for withdrawal will be documented for all subjects withdrawn from the study. The initiation of inotrope use after the baseline echocardiogram does not constitute an indication for withdrawal from the study.

C.4 Treatment

This study involves secondary analysis of clinically obtained echocardiographic data acquired in the course of routine medical care. No change in treatment or diagnosis will result from participation in this study.

C.5 Measurements

C.5.1 Schedule of Measurement

Recording of echocardiographic images for study purposes will be obtained at the time of all clinically indicated exams separated by at least 3 months, with an acceptable window of 3 to 18 months. The decision to perform study-related data acquisition in conjunction with clinically indicated echocardiograms was made to minimize the burden of study participation and to maximize patient enrollment and compliance. Ideally, echocardiograms obtained approximately one year apart will be available in all patients. However, due to the anticipated variation in the timing of clinically indicated echocardiograms and the significant potential for termination of study participation due to transplantation or death, it is likely that some subjects will not achieve a 12 month follow-up evaluation. In order to maximize acquisition of serial data, all echocardiograms

performed at least 3 months apart over the 13-month window will be included in the study, study participation will end if a follow-up echocardiogram at greater than 11 months from enrollment has been obtained, and the allowable window for acquisition of at least one usable follow-up echocardiogram is 18 months.

C.5.2 Outcome Variables

Primary outcome: The variance of change in left-ventricular BSA-adjusted end-diastolic volume z-score, BSA-adjusted mass z-score, and age-adjusted ejection fraction z-score.

Secondary outcomes:

- 1) Longitudinal variance for each of the other echocardiographically derived parameters of systolic and diastolic function (see Sections C.5.5 and C.5.6)
- 2) Magnitude of the contribution of inter-beat, inter-observer, and intra-observer variability to the overall interstudy variability of each parameter
- 3) Relationship of clinical status including treatment to the longitudinal variance and repeatability of the echocardiographic measurements.

C.5.3 Clinical Data Collection

The clinical record of the subject will be reviewed to document diagnosis; age at diagnosis; age, weight, and height, and medical therapy at the time of each of the echocardiograms. Procedures, interventions, and changes in therapy during the 6 months (or since the time of diagnosis if less than 6 months) preceding the first echocardiogram, and during the interval until the second echocardiogram will be recorded.

C.5.4 Local Echocardiographic Image Acquisition

Primary image acquisition on successive echocardiograms within subject will be performed by the same primary ultrasonographer who performed the primary image acquisition for the initial echocardiogram, insofar as that is possible within the clinical structure of the laboratory. In addition, for laboratories that are able to schedule their clinical exams to accommodate technician availability, the same technician will be the primary ultrasonographer performing these exams for all enrolled patients. The secondary image acquisition at successive echocardiograms need not be performed by

the same secondary ultrasonographer who performed the secondary image acquisition at the time of the initial echocardiogram.

Repeat, independent image acquisition by a second observer (secondary image acquisition) will be performed when possible. Availability of personnel and potential interference with clinical care may preclude repeat image acquisition in some subjects, but based on prior experience the secondary image acquisition should be possible in 70-80% of studies.

During the echocardiographic exam, the following standard images will be acquired by the primary ultrasonographers (primary image acquisition). For each image, at least 6 measurable cardiac cycles must be recorded.

- a) 2-dimensionally directed m-mode of the LV short axis from parasternal windows for measurement of LV dimension and wall thickness
- b) 2-dimensionally directed m-mode of aortic valve and mitral valve motion from parasternal windows for measurement of systolic ejection time and the time interval from mitral valve closure to mitral valve opening
- c) 2-dimensional parasternal long-axis images of the aortic root for measurement of aortic annulus diameter
- d) 2-dimensional images of the LV short axis from parasternal view for measurement of LV mass, volume, and eccentricity
- e) 2-dimensional images of the LV long axis from apical view for measurement of LV mass, volume, and eccentricity
- f) 2-dimensionally-directed apical window spectral Doppler samples of aortic outflow for measurement of aortic trans-valvar time-velocity integral and systolic ejection time
- g) 2-dimensionally-directed apical window spectral Doppler samples of right lower pulmonary vein inflow velocity for measurement of duration of atrial flow reversal
- h) 2-dimensionally-directed apical window spectral Doppler samples of mitral inflow at the leaflet tips for measurement of peak A wave, peak E wave, early deceleration time, A wave duration, and the time interval from mitral valve closure to mitral valve opening

- i) 2-dimensionally-directed apical window continuous wave Doppler recording of mitral regurgitant jet (in patients with mitral regurgitation) for measurement of dp/dt
- j) 2-dimensionally-directed apical window LV color Doppler m-mode for measurement of flow propagation velocity
- k) 2-dimensionally-directed apical window tissue Doppler samples of the lateral and septal mitral annular velocities for measurement of peak systolic, peak early diastolic, and peak late diastolic velocity and isovolumic acceleration
- l) Quaduplicate recording of systolic, diastolic, and mean brachial blood pressure using an automated blood pressure device

C.5.5 Local Echocardiographic Measurement Requirements

The following image measurements will be performed by one observer at the clinical site. Whenever possible, this observer should be the same individual for the subject's first and second echocardiogram. Measurement of the derived variables described below is not required for the secondary image acquisition. The measurements may be performed either on-line or off-line (whichever is the customary practice at that center), on three successive cardiac cycles:

- a) Systolic and diastolic dimensions and wall thicknesses from m-mode
- b) LV ejection time from the aortic valve m-mode
- c) Time from mitral valve closure to mitral valve opening from the mitral valve m-mode
- d) Aortic annulus diameter from aortic root images
- e) Peak, mean, and time-velocity aortic outflow velocities, and ejection time from the aortic spectral Doppler recording
- f) LV short axis systolic and diastolic endocardial and epicardial diameters and areas
- g) LV long axis systolic and diastolic endocardial and epicardial dimensions
- h) Pulmonary vein a-wave duration
- i) Peak early and atrial mitral velocities, early deceleration time, duration of atrial flow, time interval from mitral valve closure to mitral valve opening
- j) Calculation of dp/dt from mitral regurgitant jet⁹

- k) Tissue Doppler-derived peak systolic and peak early and late diastolic lateral and septal mitral annular velocities, isovolumic acceleration, systolic and diastolic time intervals, isovolumic contraction and relaxation time intervals
- l) LV color Doppler m-mode derived flow propagation rate

Echocardiograms will undergo analog-to-digital conversion with de-identification (an echocardiogram I.D. number will be imposed on the image, rather than the subject I.D. number) prior to submission to the Data Coordinating Center for forwarding to the core laboratory.

C.5.6 Core Laboratory Procedure

- 1) The echocardiographic core laboratory measurement package will consist of each of the echocardiographic measurements detailed in Section C.5.5 in addition to derived parameters to include: Tei index from aortic and mitral m-mode, pulsed and tissue Doppler; stroke volume and cardiac output from aortic Doppler; fractional shortening; velocity of circumferential fiber shortening; area change fraction; LV mass, end-systolic volume, end-diastolic volume, ejection fraction, stroke volume, and cardiac output obtained using both $\frac{5}{6} \times \text{Area} \times \text{Length}$ algorithm and biplane Simpson's rule algorithm employing parasternal short axis images and apical transverse long axis systolic and diastolic images; LV end-systolic wall stress; and LV end-systolic fiber stress.
- 2) For each echocardiogram, a complete set of measurements will consist of all measurements performed on three successive cardiac cycles.
- 3) The primary core laboratory observer will perform a complete set of measurements for both the primary and secondary data acquisitions (when both are present) for each echocardiogram.
- 4) The secondary core laboratory observer will independently perform a complete set of measurements for both the primary and secondary image acquisitions (when both are present) for each echocardiogram.
- 5) The primary core laboratory observer will repeat the full set of measurements on the primary image acquisition of each study echocardiogram at a target of one month after the initial set of core laboratory measurements.
- 6) The primary core laboratory observer will repeat a complete set of measurements for the primary data acquisition on the first echocardiogram only

for each subject 12-14 months after the initial set of core laboratory measurements.

The core laboratory will be blinded to the clinical status and treatment of participating patients, and will not have knowledge of the paired status of the echocardiograms within subject.

C.6 Adverse Events

C.6.1 Definition

An adverse event is any untoward medical occurrence experienced by a subject that occurs in temporal association with the use of an administered investigational intervention, whether considered intervention-related or not. An event can be any sign, symptom, laboratory abnormality, or disease. This observational study does not place patients at additional risk and no adverse events are anticipated. However, any event that is a change in the patient's clinical condition for the 24 hours following the echocardiogram will be reported.

C.6.2 Classification of Adverse Events

C.6.2.a Relationship

The relationship between the echocardiogram and any adverse event will be determined by the investigator, medical monitor, and DSMB using the following criteria:

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

C.6.2.b Severity

The severity of adverse events will be assessed according to the following criteria:

1 = "Not Serious": Any event which:

- (a) Results in transient impairment of a body function or damage to a body structure that does not interfere with the patient's usual activity; 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 minor 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 subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred); or
- (c) Is severely or permanently disabling; or
- (d) Necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or
- (e) Necessitates or prolongs hospital admission; or
- (f) Increases the level of care; or
- (g) Involves a drug overdose; or
- (h) The Principal Investigator, medical monitor, or DSMB considers to be a serious adverse event.

C.6.2.c Expectedness of the Event

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

1 = "Expected": An event is considered expected if it is known to be associated with the underlying cardiovascular abnormality. An event may

be expected despite the study subject's clinical state immediately prior to the event. For this protocol, expected events include:

- (a) Sudden cardiac death
- (b) Worsening congestive heart failure
- (c) Arrhythmias
- (d) Failure to thrive
- (e) Respiratory distress
- (f) Pericardial effusion

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

C.6.2.d Treatment or Action Taken

AEs and SAEs will result in:

- (a) Intervention: Surgery or procedure
- (b) Other Treatment: Medication initiation, change, or discontinuation
- (c) None: No action is taken

C.6.2.e Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

- (a) Death
- (b) Recovered: the patient returned to baseline status
- (c) Symptoms continue

C.6.3 Data Collection Procedures for Adverse Events

Events will be recorded according to the date and time of first occurrence, severity, and their duration, as well as any treatment prescribed. After the echocardiogram, all new or continuing adverse events that were not present prior to the echocardiogram and take place within 24 hours will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, worsening of a medical condition that was present at the

initial visit will be considered a new adverse event and reported. Serious adverse events will be reviewed by the NHLBI-appointed medical monitor as well as by the DSMB and NHLBI staff. Differences of opinion as to the causality, classification, or expectedness of events will be adjudicated by the medical monitor and the DSMB.

C.6.4 Reporting Procedures

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

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

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

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

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

- A statement that if safety concerns are identified, the Program Officer will communicate these promptly to the investigators.

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

C.6.6 Post-Study Procedures for Adverse Events

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

C.7 Statistical Methods

C.7.1 Sample Size and Power

The required sample size to estimate the population standard deviation to within a prespecified tolerance is $n = z^2_{1-\alpha/2} / (2d^2)$, where d = allowed fractional deviation from σ , the population sample standard deviation¹⁰. To construct a two-sided 95% confidence interval for σ that deviates no more than 15% from the true value requires $n = 86$. It is estimated that 25-30% of subjects may withdraw for reasons indicated in Section C.3.2, have echocardiograms conducted under differing sedation conditions, or incomplete baseline-follow-up echocardiogram pairs for other reasons. Therefore, the target sample size is 120 patients with qualifying baseline echocardiograms to ensure that 86 of these have paired interpretable echocardiograms (a total of 172 echocardiograms) performed under similar conditions. This sample size requires 19-20 patients from the 4 largest PHN centers and 13-14 patients each from the 3 smaller PHN centers. A maximum of 40 patients with dilated cardiomyopathy associated with adriamycin treatment will be enrolled in the study, with center-specific limits for this subpopulation.

C.7.2 Analysis Plan

Table 1 displays the sequence of measurements to be obtained in this study. For simplicity in this table, it is assumed that a) the second image acquisition of each echocardiogram is by the same local ultrasonographer denoted as A_2 and b) there are two echocardiograms per subject. Available data for echocardiograms at baseline and at follow-up will include image acquisition by a primary ultrasonographer (A_1) who will perform the primary image acquisition on all exams for the subject and a second ultrasonographer (A_2), who need not be the same on successive exams. Image measurements will be performed by the primary clinical center ultrasonographer (A_1) and by two core lab observers (CL_1 and CL_2). Image measurements by the first core lab observer (CL_1) on all echocardiograms performed by the primary ultrasonographer A_1 will be performed three times (CL_1 , CL_1 early repeat, and CL_1 late repeat) with the early repeat set of measurements performed in close time proximity to the initial core lab image measurements and the late repeat image measurements performed at about 12 months following the initial core lab image measurements. Therefore, for any given echocardiographic parameter, if 120 subjects are enrolled and undergo 2 echocardiograms, there will be a total of 1560 observations. Each set of measurements will comprise a data set, with the overall list of data sets as follows:

Table 1. Dataset Comparisons

	ACQUISITION			
MEASURER	Baseline		Follow-Up	
	A_1	A_2	A_1	A_2
A_1	Data set B.1.1		Data set F.1.1	
CL_1	Data set B.1.2	Data set B.2.1	Data set F.1.2	Data set F.2.1
CL_2	Data set B.1.3	Data set B.2.2	Data set F.1.3	Data set F.2.2
CL_1 (early repeat)	Data set B.1.4		Data set F.1.4	
CL_1 (12 mo. later)	Data set B.1.5			

All 13 sets of data will have measurements of 3 sequential cardiac cycles for each derived parameter. Beat-to-beat variability will be calculated for each parameter both for all observers and as a comparison between observers. For each of the 13 data sets, the average of the 3 cardiac cycles will be calculated to provide the 3-beat mean value for each parameter. The values for the first analyzed beat and the 3-beat mean value will

then be used for all subsequent analyses of each echocardiographic parameter to allow us to determine whether beat averaging improves reproducibility.

The analyses of these data sets include the following comparisons of interest to assess: **Changes over time in cardiac function holding acquisition observer and measurer constant:**

- 1) *Images acquired by the same observer and measured by the same observer:*
Comparison of data sets B.1.1 versus F.1.1, B.1.2 versus F.1.2, B.1.3 versus F.1.3, and B.1.4 versus F.1.4

Interacquisition observer variability:

- 2) *Images acquired by different observers and measured by the same observer:*
Comparison of data sets B.1.2 versus B.2.1 and F.1.2 versus F.2.1

Intraobserver Variability:

- 3) *Same set of images measured twice by the same person close in time:*
Comparison of data sets B.1.2 versus B.1.4 and F.1.2 versus F.1.4
- 4) *Same set of images measured twice by the same person spaced by 12 months:*
Comparison of data sets B.1.2 versus B.1.5

Interobserver Variability:

- 5) *Same set of images, measurements by one core lab observer versus measurements by second core lab observer:* Comparison of data sets B.1.2 versus B.1.3 and F.1.2 versus F.1.3
- 6) *Same set of images, measurements by core lab versus measurements by study site:* Comparison of data sets B.1.1 versus B.1.2, B.1.1 versus B.1.3, F.1.1 versus F.1.2, and F.1.1 versus F.1.3

The first stage of analyses will examine the hypothesis that there is beat-to-beat variation in echocardiographic measurements, with beat incorporated as a random effect in the model. This will provide important information about the conditions under which the practice of averaging across measures is appropriate. Subsequent analyses will be conducted twice: once using single beat data and once using a 3-beat average.

The second stage of analyses will utilize the data points derived from averaging across beats. The first set of models will utilize the design factors only. Using a mixed modeling approach, the interstudy variability of ventricular volume, mass, and ejection fraction will be determined, using fixed effects for time and random effects for the acquisition observer and the measurement observers (both local and core laboratory).

Since all subjects will not have the follow-up echocardiogram at precisely the same time point, time will also be modeled as a continuous covariate and not solely as an indicator of baseline vs. follow-up. Because the study design is essentially a fractional factorial with several goals (see above), the data will be partitioned into different analyses consistent with the Dataset Comparisons listed above (displayed in Table 1). The second set of models will utilize design factors as well as clinical information. The contribution of intra- and inter-observer variability, disease etiology, age, use of sedation, and interstudy time interval will be evaluated using mixed models with variance component estimation.

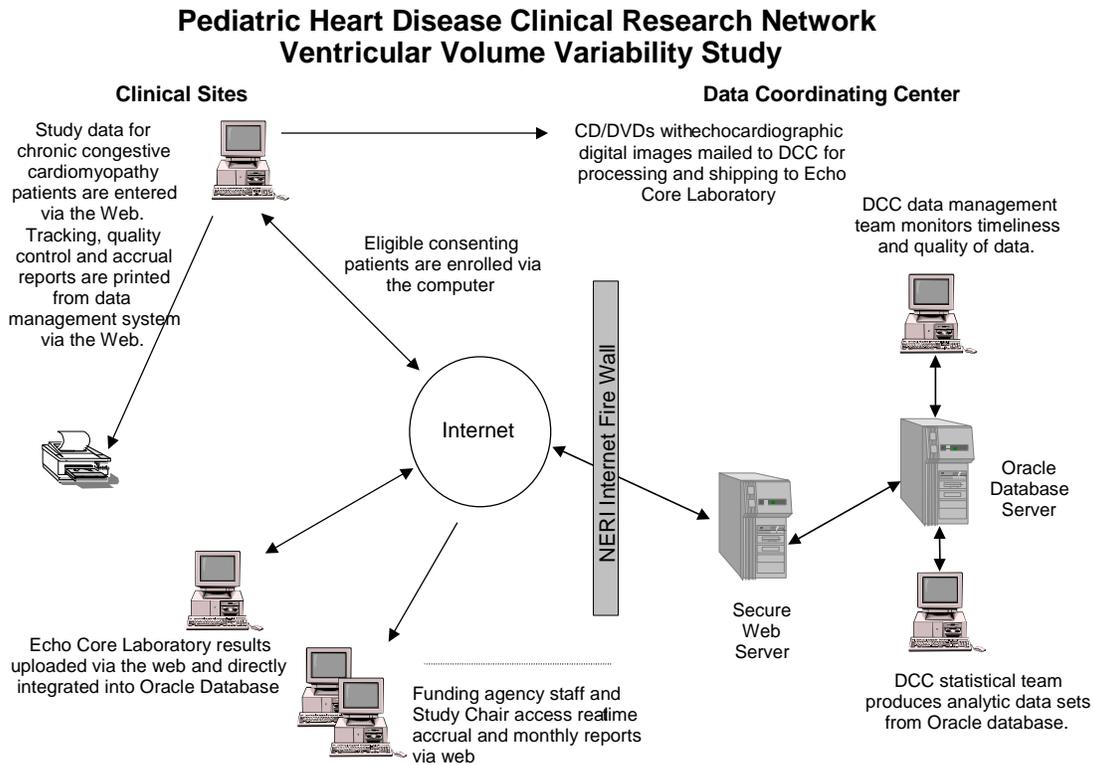
The third stage of analyses will be conducted if sufficient serial data are collected. A repeated measures model will be utilized to examine changes over time in cardiac size and function, and to assess changes in correlation between measurements over time within subject. This will provide important information about the primary endpoint (variance of change) in terms of understanding how time intervals affect the required sample size for a proposed trial.

C.8 Data Management

The clinical sites will submit the clinical data, locally-determined echocardiographic measurements, and electronically recorded (DVD or CDROM) echocardiographic image data to the Data Coordinating Center at New England Research Institutes (NERI). NERI will forward the DVD or CDROM recordings of echocardiographic images to the echocardiographic core laboratory for analysis.

C.8.1 Information Flow

Figure 2. Data Management System and Information Flow



C.8.2 Overview of Data Management System

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at NERI, and then stores these data centrally at the DCC. Information entered into the data entry system will be by patient study I.D. number; names will not be linked with patient data in the database. Clinical sites will maintain records linking the patient name with the I.D. 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.

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.9 Quality Control

All echocardiograms will be obtained based on a standardized protocol that will be detailed in the study Procedure Manual along with CDROM-based examples of each of the recordings and measurements. Each of the measurements is currently being obtained in conjunction with existing Pediatric Heart Network protocols and therefore all participating centers have prior experience with these methods. All LV dimension and volume measurements will be performed by the same 2 core laboratory individuals and all Doppler and time interval measurements will be performed by the same 2 core laboratory individuals throughout the study to eliminate the confounding effects of additional observers.

D. STUDY LIMITATIONS

The progression of dilated cardiomyopathy is highly variable and, for the purposes of this observational study, no attempt will be made to impose uniform treatment strategies across clinical sites. We therefore recognize that it will be impossible to fully differentiate the contribution these factors have on the interstudy variance of the obtained parameters of LV function. Nevertheless, the data we obtain will be relevant to the "real world" limitations that are important for planning a clinical trial in this patient population.

E. ORGANIZATION

E.1 Time Line

Development of the manual of operations and data collection forms, system testing, and IRB approvals is estimated to require 4 months. Recruitment is anticipated to require up to 2 years. Participation of individual patients will be up to 18 months, depending on

when their clinically indicated follow-up visits occur. Data analysis will require approximately 6 months after the study is closed, so a total study duration of 4 years is expected.

E.2 Study Organization

The study is organized under the auspices of the Pediatric Heart Network, a multicenter network funded by the NIH and the NHLBI to plan and perform clinical studies in children with heart disease. The network is comprised of the NHLBI, a Study Chair, 7 clinical centers, and a Data Coordinating Center who jointly hold frequent Steering Committee meetings and conference calls to design, organize, and conduct these studies. Other internal network committees include the Publications and Presentations Committee, Ancillary Studies Committee and the Core Laboratory Selection Committee. Additional resources available to the network include an independent Protocol Review Committee that reviews protocols and advises during the study design phase and a Data and Safety Monitoring Board that monitors study conduct, patient safety, and study findings of all network studies.

F. REFERENCES

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Appendix A.

Informed Consent Template for Study

INFORMED CONSENT TEMPLATE

CONSENT TO PARTICIPATE AS A SUBJECT IN MEDICAL RESEARCH

VARIABILITY OF ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS, VOLUME AND EJECTION FRACTION IN PEDIATRIC PATIENTS WITH CONGESTIVE (DILATED) CARDIOMYOPATHY

PI:

IRB#

DESCRIPTION AND EXPLANATION OF PROCEDURE:

Echocardiography (ultrasound of the heart) is the primary method used clinically to evaluate the size of the heart and how well it works. These measurements are used to detect abnormalities such as heart muscle disease and to evaluate changes in how well the heart works over time. At present, we do not know how reproducible some of the echocardiography measurements are in children or what factors affect the accuracy of these measurements. This research study is designed to help us understand the sources of error in these measurements and the true change in values over time.

You/your child are being asked to participate in this research study because you/your child have or are suspected of having a cardiomyopathy (heart muscle disease). Children with cardiomyopathy typically need repeat echocardiograms to evaluate their heart function. If you/your child decide(s) to participate in this study, we will record the measurements obtained during your/your child's next echocardiogram performed in the cardiology clinic to use in our study. In addition, at the end of the echocardiogram, another person who does echocardiograms will take a second set of echo pictures. These additional pictures will add about 10-20 minutes to the time it usually takes for an echocardiogram. The measurements collected during this study will become part of the permanent echocardiographic record. Finally, a nurse or physician will review your/your child's medical record for diagnosis, clinical status, and medications.

By comparing the measurements made from the two different echocardiograms, we will be better able to tell whether differences are due to variations in making the measurements or getting the pictures or from the real changes in your/your child's heart. If the echocardiogram shows you have/your child has heart-muscle disease, we will also take an extra set of pictures at the end of each echocardiogram you have/your child has over the next 12-18 months (if there are at least 3 months between each test). Study participation will end if a usable follow-up echocardiogram at greater than 11 months from enrollment has been obtained.

Up to 160 patients from up to 10 different hospitals will participate in this study, including <#> from <institution>.

INFORMED CONSENT TEMPLATE

CONSENT TO PARTICIPATE AS A SUBJECT IN MEDICAL RESEARCH

VARIABILITY OF ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS, VOLUME AND EJECTION FRACTION IN PEDIATRIC PATIENTS WITH CONGESTIVE (DILATED) CARDIOMYOPATHY

PI:

IRB#

EXPENSES/COMPENSATION/REIMBURSEMENT

There are no additional costs associated with participating in this research. Since the echocardiogram is being done as part of your/your child's regular care for the heart condition, the cost of the echocardiograms and any co-payments will be your responsibility and will be billed to you or your insurance. You will be given \$xx.xx per study echocardiogram to cover the cost of transportation, parking, and meals. You will not receive additional reimbursement or compensation.

RISKS AND DISCOMFORTS

There are no foreseeable risks associated with participation in this research. The only discomfort is the additional 10-20 minutes needed to get a second set of pictures of your child's heart. There is always some risk of breach of confidentiality, but the chance of this is quite remote because we go to great lengths to protect the privacy and confidentiality of all our patients. The exact methods we use are discussed in more detail below in the Confidentiality section.

POTENTIAL BENEFITS

There is unlikely to be any direct benefit to you/your child from participating in this research. However, the results of this study will be beneficial to the care of children with cardiomyopathy because it will improve our ability to perform and interpret the measurements of cardiac function.

CONFIDENTIALITY

Protecting the privacy of patients who agree to participate in this research study is very important to us. We will never use your/your child's name or other personal information for this research. We protect the identities of our patients by assigning them a unique ID number and sometimes a few letters from the first and last name in place of their name.

Information contained in your/your child's medical record cannot be given to anyone unaffiliated with <institution> in a way that could identify you/your child without written consent, except as required or permitted by law. Information that is collected during this study will be stored in a separate research file available only to the research personnel conducting this study. These personnel are responsible for maintaining the confidentiality and security of these records.

INFORMED CONSENT TEMPLATE

CONSENT TO PARTICIPATE AS A SUBJECT IN MEDICAL RESEARCH

VARIABILITY OF ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS, VOLUME AND EJECTION FRACTION IN PEDIATRIC PATIENTS WITH CONGESTIVE (DILATED) CARDIOMYOPATHY

PI:

IRB#

The tapes or disks with your child's echocardiogram will be sent to the Pediatric Heart Network Data Coordinating Center (New England Research Institutes, in Watertown, Massachusetts) for submission to a central laboratory outside of _____ for reading. Although the standard procedure will be to remove your/your child's name from all echocardiogram pictures on the tapes or disks sent to the Data Coordinating Center, there is a possibility that your/your child's name may appear on a tape or disk. However, all tapes, disks, and electronic images will be kept in a secure location at this laboratory. 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. The results of this study may be published for all the subjects as a group, but will not identify your child individually.

If you/your child withdraw from this research study, your/your child's privacy and confidentiality will continue to be protected, but the information that has already been collected will remain part of the research data.

ALTERNATIVES

Participation in this research is voluntary. If you choose to participate, you are free to withdraw at any time. If you decide not to participate, your/your child's care will not be affected in any way.

CONSENT

By signing this form, I agree that:

1. The study has been explained to me. All my questions were answered.
2. The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
3. I know about the alternatives to participating/having my child take part in this study. I understand that I have the right to refuse to participate and

Pediatric Heart Network

Ventricular Volume Variability Study Protocol – Appendix A
10/30/06

