BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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JACKSON HEART STUDY

National Heart Lung and Blood Institute

JACKSON HEART STUDY

VISIT 4

ECHOCARDIOGRAPHY
FIELD CENTER MANUAL OF OPERATIONS

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I. Introduction

The Reading Center in Boston, Massachusetts served as the Echocardiography Reading Center for the Jackson Heart Study (JHS) Visit 4. In 2023 the Reading Center transitioned to the University of Texas Southwestern Medical Center. This manual contains key information Field Centers need to perform high quality study echocardiograms.

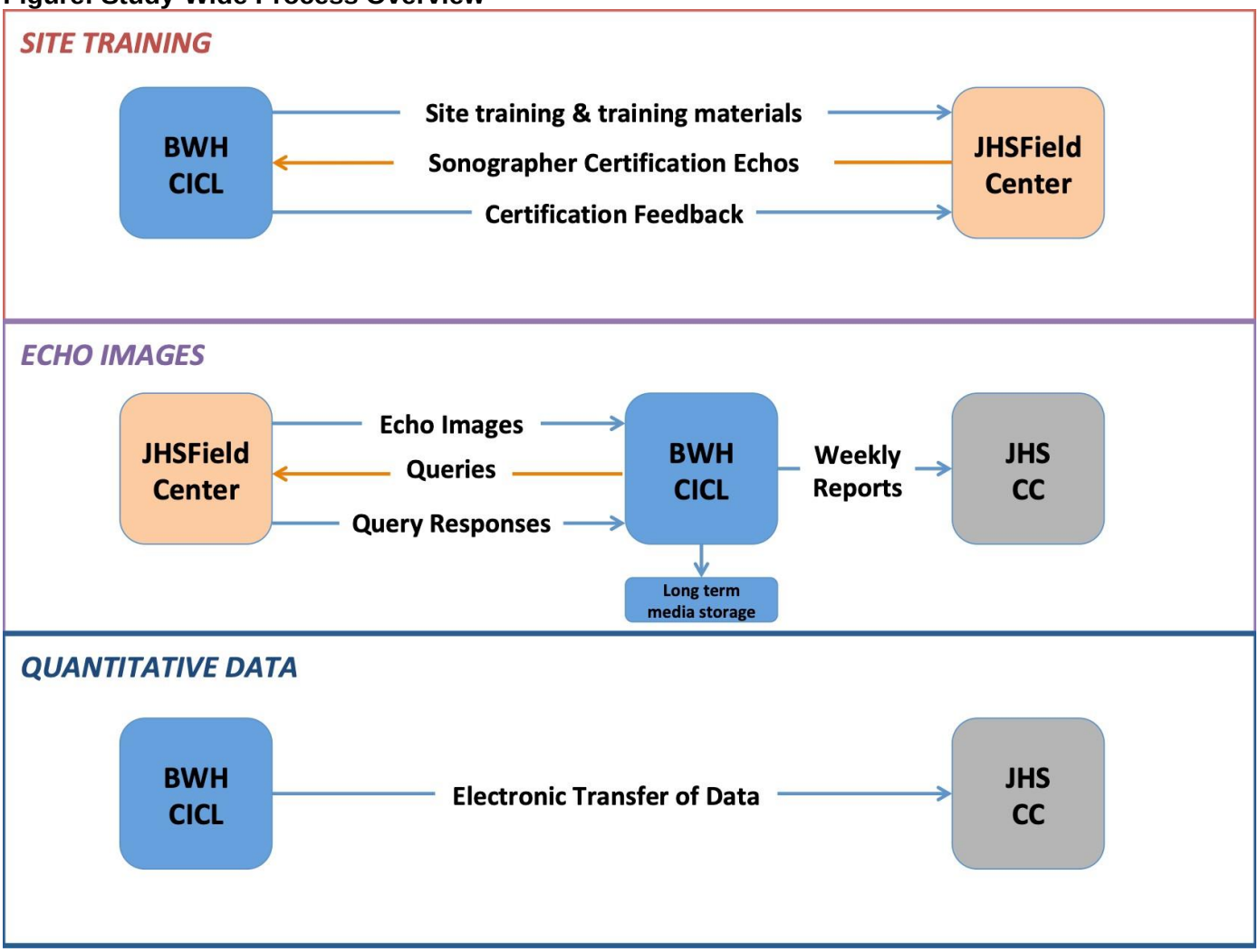
OBJECTIVES	
Cardiac Imaging Core Lab	• To provide high quality reproducible quantitative analysis of study echocardiograms
Site Instruction Manual	• To instruct field centers on how to perform and send study echos to the Reading Center.

ROLES AND RESPONSIBILITIES	
Field Centers Sonographers	• Perform highest-quality study echocardiograms per the protocol contained in this document • Participate in monthly JHS Echocardiography Sonographer calls
Field Center Sonographers, Study Coordinators, and PIs	• Ensure that the Reading Center stays informed of study-wide changes and updates as the study progresses. • Serve as the primary liaison between the Reading Center and field centers for study deficiencies, chronic poor-quality studies and other issues related to overall site performance. • Provide oversight and support, as required, for the entire process
Cardiac Imaging Core Lab	• Receive, review and analyze study echos. • Train and certify each field center sonographer. • Provide field centers feedback on poor quality echos, and queries for technical/process improvement. • Serve as a resource for sites for all echo-related questions.

II. Study-Wide Process Overview

The Field center will electronically transmit echos directly to the Reading Center. Below is a basic diagram

Figure: Study-Wide Process Overview



III. Echocardiogram Protocol: Required Views

A. Brachial Blood pressure	♦ Ensure that BP obtained within 30 min of the echo examination
B. Parasternal Position	
❒ *Parasternal long axis*	♦ 2D imaging (at deep depth) ♦ 2D imaging (at shallow depth) ♦ Color Doppler of the mitral and aortic valves
❒ *Parasternal RV inflow view*	♦ 2D imaging of TV ♦ Color Doppler of TV ♦ CW of TV regurgitation
❒ *Parasternal RV outflow view*	♦ 2D imaging of RVOT and PV ♦ Color Doppler of PV ♦ PW of RVOT ♦ CW Doppler of PV, being sure to include full PR envelope
❒ *Parasternal short axis – Aortic valve level*	♦ 2D imaging of AV ♦ Color Doppler of AV ♦ 2D imaging of TV ♦ Color Doppler of TV ♦ CW Doppler of tricuspid regurgitation ♦ 2D imaging of right ventricular outflow tract ♦ Color Doppler of right ventricular outflow tract and PV ♦ PW Doppler of the RVOT ♦ CW Doppler of PV, being sure to include full PR envelope
❒ *Parasternal short axis – Mitral valve level*	♦ 2D imaging
❒ *Parasternal short axis – Papillary muscle level*	♦ 2D imaging
❒ *Parasternal short axis – LV apex*	♦ 2D imaging
C. Apical Position	
❒ *Apical 4 chamber view*	♦ 2D imaging ♦ 2D imaging, focused on LV ♦ 2D imaging, zoomed on LA ♦ Color Doppler of mitral valve/LA ♦ PW Doppler of mitral flow at leaflet tips ♦ PW Doppler of mitral flow at mitral annulus ♦ CW Doppler of mitral inflow ♦ TDI color and PW of lateral mitral annulus ♦ TDI color and PW of septal mitral annulus
❒ *Apical 4 chamber – focused on the RV*	♦ 2D imaging ♦ Color Doppler of tricuspid valve/RA ♦ PW Doppler of tricuspid inflow flow at tricuspid annulus ♦ CW Doppler of tricuspid regurgitation ♦ M-Mode of lateral tricuspid annulus ♦ TDI of lateral tricuspid annulus

❒ *Apical 5 chamber view*	♦ 2D imaging ♦ Color Doppler of LV, including MV and AV ♦ Color Doppler of left ventricular outflow tract and AV ♦ Pulse wave of LVOT flow ♦ CW of transaortic flow
❒ *Apical 2 chamber view*	♦ 2D imaging ♦ 2D imaging focused on LV ♦ 2D imaging zoomed on LA ♦ Color Doppler MV/LA
❒ *Apical 3 chamber view*	♦ 2D imaging ♦ color Doppler LVOT/AV
D. Subcostal View	
❒ *Inferior vena cava*	♦ 2D imaging (5 second acquisition)
❒ *4 chamber view*	♦ 2D imaging
E. 3D Imaging (pause protocol)	
❒ *Apical Position*	♦ 3D full volume acquisition of LV ♦ 3D full volume acquisition of RV
❒ *Parasternal Position*	♦ 3D full volume acquisition of MV and TV

IV. Site Training

Sonographers at each Field Center will undergo two days of on-site Jackson Heart Study Visit 4 echocardiography-specific training performed by ERC PI (Dr Amil Shah) and the Reading Center Chief Sonographer. Training will focus on the JHS Visit 4 imaging protocol (including live supervised scanning on models), electronic image transfer, procedures for handling potential clinical alerts based on echocardiographic findings.

Following on-site training, and prior to submission of certification echocardiograms (section IV below), Field Center sonographers will be required to perform the complete JHS Visit 4 imaging protocol on 4 volunteers, and to transmit these studies to the Reading Center.

V. Sonographer Certification

The purpose of certification is to ensure consistency in how echocardiograms are performed study-wide and to ensure performance of the highest quality echocardiograms. Any sonographer who will be performing study echocardiograms must first submit two certification studies performed in accordance with the protocol described in this manual and transferred electronically to the Reading Center for review and certification.

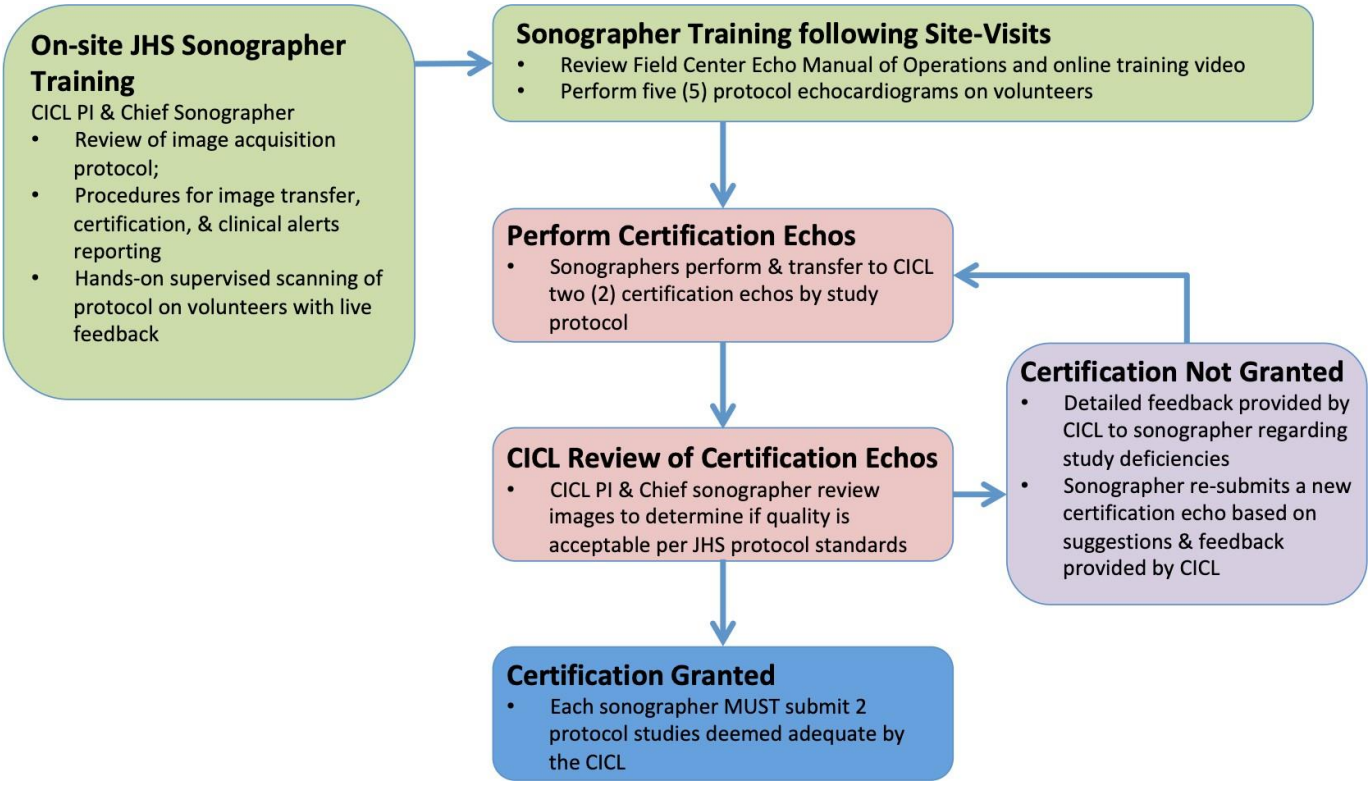
Studies will be scrutinized for adherence to protocol, acquisition of all required views, and image quality. Itemized direct written feedback and suggestions from the technical project manager will be provided for each study submitted. This is intended to address any individual equipment or operator dependent problems that may arise. Sonographers will have the opportunity to re-submit a sample protocol study should the initial submission be inadequate. Following submission of an adequate sample study, the sonographer will be officially certified and will receive feedback documenting this.

New Field Center sonographers starting during the study period will be required undergo the certification process outlined above by submitting 2 sample protocol studies in order to demonstrate the ability to perform a technically adequate protocol study and the knowledge to successfully transmit this data to the Reading Center.

A general outline of the process is outlined below. Prior to performing and submitting a sample study for certification, the following steps are recommended:

1. Read and review this Site Manual of Operations and refer to the JHS Visit 4 Echo Pocket Guide during performance of the echocardiogram. The instructional video available on the JHS Visit 4 Echocardiography Reading Center website is an additional resource. This is considered supplemental and is not a requirement to receive certification.
2. Contact the Reading Center for any questions before performing and submitting the certification echo to the Reading Center.
3. Send the certification echo to the Reading Center – per the instructions provided in this manual.

Figure: Sonographer Training and Certification Process



VI. Submission of Studies from the Field Center to the Reading Center

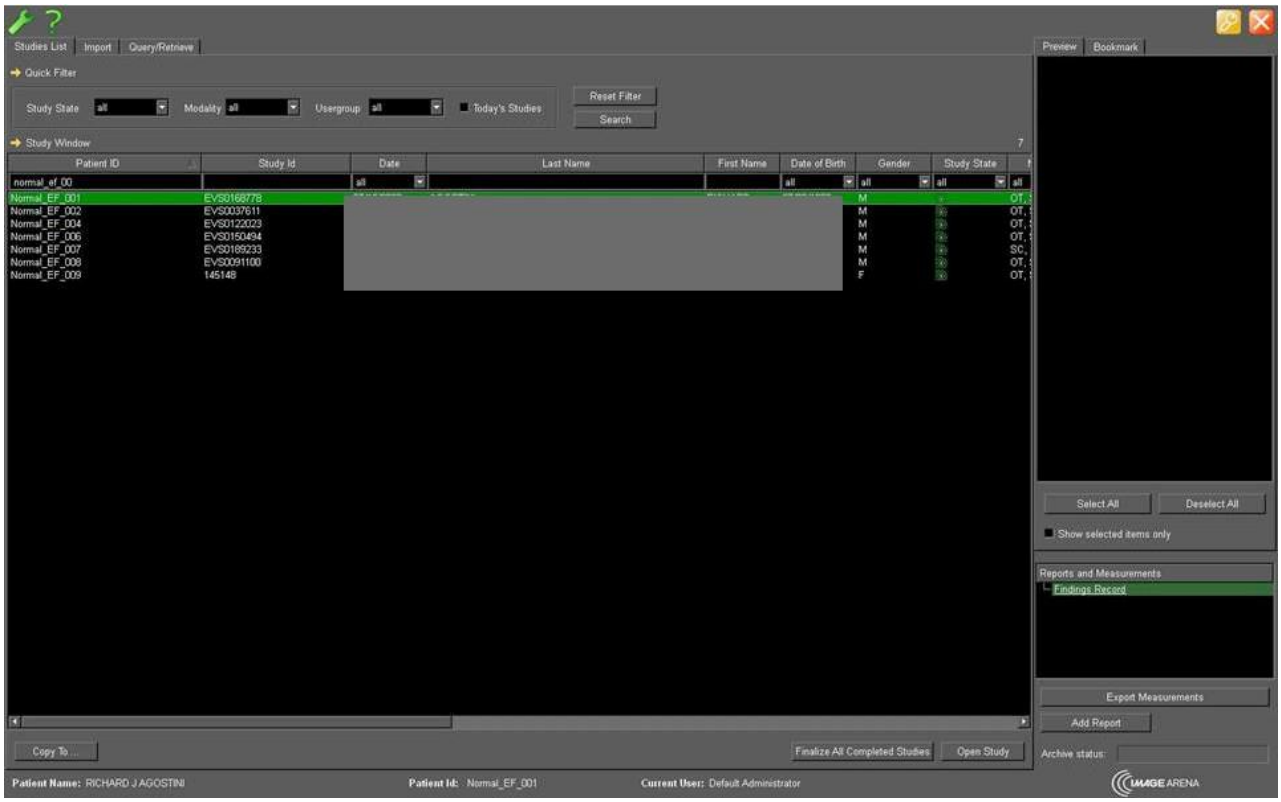
All JHS Visit 4 echocardiograms will be transmitted electronically from Field Centers to the Echocardiography Reading Center via a secure web transfer system as detailed below. Field center staff will receive electronic confirmation (by email) upon successful receipt of each echocardiogram by the Reading Center.

VI.a. Instructions for Electronic Transfer of Studies to the Reading Center

Echocardiograms will be transferred from the Field Center to the Reading Center electronically via direct VPN tunnel from the field center to the reading center server. Transfer of completed studies to the Reading Center has **2** components:

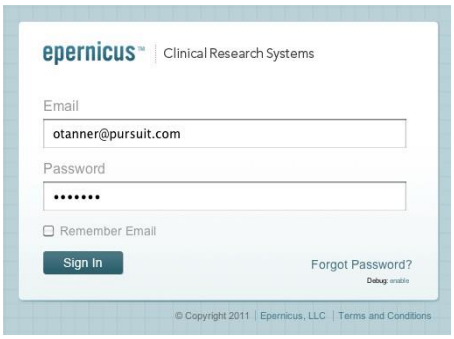
(1) Transfer of Image Files

Upon finalizing and closing a study on the iE33 and EPIQ machines, studies will be automatically transferred to the Field Center PC which houses the Tomtec Image Arena software. This will act as a local temporary PACs for recent studies performed at the Field Center. Image Arena will be configured such that studies will automatically transfer to the RC server. If the Field Center prefers, studies may alternatively be manually selected for transfer by site sonographer from Image Arena to the RC server. The user interface for the Tomtec Image Arena software is demonstrated in the figure below.



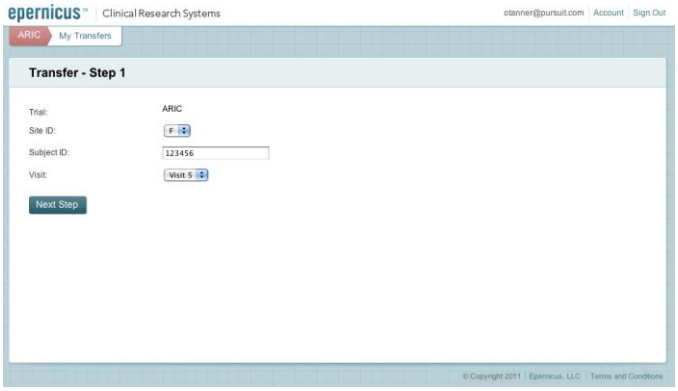
(2) Transfer of the Echocardiogram Electronic Transfer Form (ETF)
For each Echocardiogram study performed and transmitted to the Reading Center, the sonographer must also ***separately*** submit an Electronic Transfer Form (ETF) to the Reading Center as outlined below. This form provides a notification for the Reading Center to expect the study images and provides important demographic and physiologic (heart rate, blood pressure) information necessary in analyzing the echo studies.

1. Sign in: Navigate to https://Reading Center.clinicalresearchsystems.com and sign in with your email address and password (provided to you by the Reading Center)

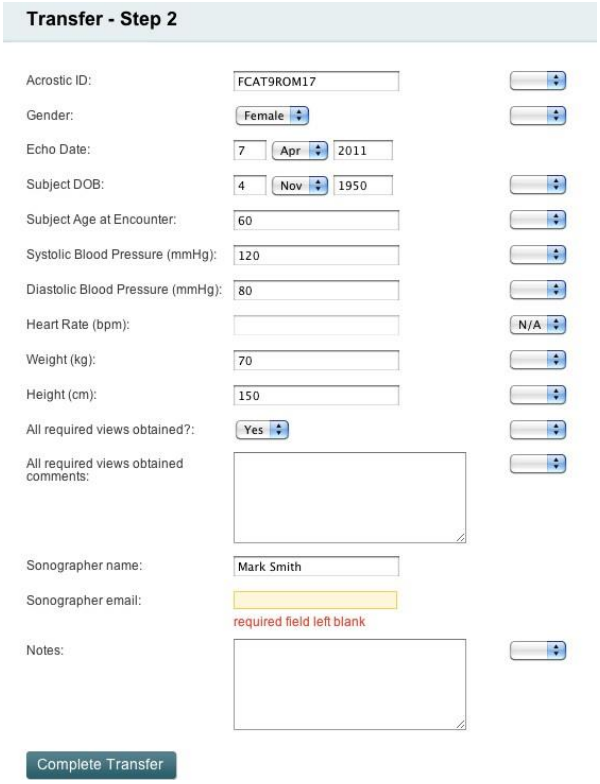


2. Initiate new ETF: Click on “New Transfer” to begin process

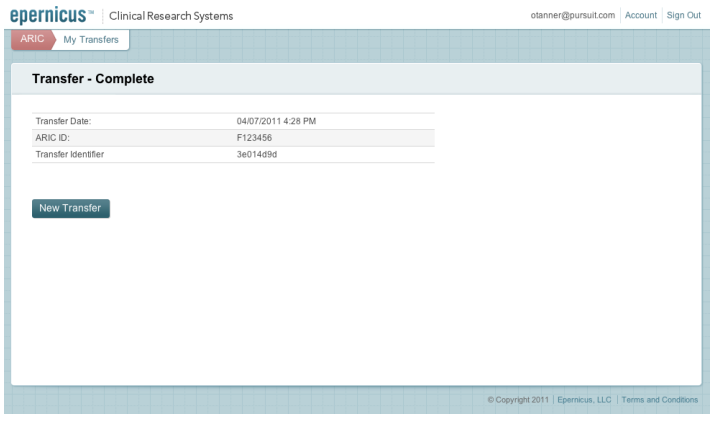
1. Enter participant JHS ID
    - Enter the 6digit Subject ID. Visit will default to the only available option (‘Visit 4’)



2. Enter required data
    - All fields are required, and are validated according to type. If certain fields are unavailable, you can select ‘N/A’ from the menu to the right side of that field to indicate that it is intentionally left blank.



3. Complete transfer by clicking the ‘Complete Transfer’ button
4. ‘Transfer compete’ confirmation screen
    - You can initiate another transfer, click on “My Transfers” to view your transfer history



For questions regarding either study performance or submission, the Reading Center has an established “hot line” channel of communication, which is listed within the Field Center Manual of Operations.

VII. Reading Center Feedback to Field Centers

The Reading Center will continuously monitor the adequacy and quality of all studies received according to the criteria outlined in the table below:

Criteria for Evaluating Image Quality		
View	**Score**	**Criteria**
Parasternal long axis view	2 points	• Image is on axis and endocardial border well visualized in all anatomic segments of the main structures imaged (e.g. all 4 segments of the LV)
	1 point	• Image is not completely on axis (e.g. low parasternal view), or the endocardial border is well visualized in most but not all anatomic segments of the main structures imaged (e.g. only 3/4 anatomic segments of the LV)
	0 points	• Image is completely off axis, or endocardial border not well visualized >25% of anatomic segments of the main structures imaged
Parasternal short axis, mid-ventricular level	2 points	• Image is on axis and endocardial border well visualized in all anatomic segments of the main structures imaged (e.g. all 6 segments of the LV)
	1 point	• Image is not completely on axis, or endocardial border is well visualized in most but not all anatomic segments of the main structures imaged (e.g. only 5/6 anatomic segments of the LV)
	0 points	• Image is completely off axis or endocardial border not well visualized >15% of anatomic segments of the main structures imaged (e.g. there is dropout of ≥2 (of 6) anatomic segments of the LV)
Apical 4 chamber view	2 points	• Image is on axis and endocardial border well visualized in all anatomic segments of the main structures imaged (e.g. all 6 segments of the LV)
	1 point	• Image is not completely on axis, or endocardial border is well visualized in most but not all anatomic segments of the main structures imaged (e.g. only 5/6 anatomic segments of the LV)
	0 points	• Image is completely off axis, or endocardial border not well visualized >15% of anatomic segments of the main structures imaged (e.g. there is dropout of ≥2 (of 6) anatomic segments of the LV)
Apical 2 chamber view	2 points	• Image is on axis and endocardial border well visualized in all anatomic segments of the main structures imaged (e.g. all 6 segments of the LV)
	1 point	• Image is not completely on axis, or endocardial border is well visualized in most but not all anatomic segments of the main structures imaged (e.g. only 5/6 anatomic segments of the LV)
	0 points	• Image is completely off axis or endocardial border not well visualized >15% of anatomic segments of the main structures imaged (e.g. there is dropout of ≥2 (of 6) anatomic segments of the LV)
Doppler views	2 points	• Clear signals captured over at least 3 cardiac cycles for all Doppler measures
	1 point	• Clear signals captured over at least 2 cardiac cycles for most Doppler measures
	0 points	• Absent or unclear signals captured for most Doppler measures

Scoring Criteria	
Grading	**Total Points**
Good quality	9-10 points
Acceptable quality	6-8 points
Fair quality	4-5 points
Poor quality	≤3 points

For each echocardiogram received by the Reading Center, quality feedback will be provided via email to the performing sonographer, in addition to the appropriate Field Center Coordinator. Quality feedback will include the quality score – defined as above – in addition to directed feedback regarding parasternal and apical view

foreshortening, endocardial border definition, missing views, spectral and Tissue Doppler quality, and quality of 3D image acquisitions.

In situations where concerns arise regarding the quality of a study submitted by the Field Center, this feedback will include technical instructions for quality improvement. Additionally, if any queries arise at the Reading Center regarding images submitted, the Field Center coordinator and sonographer will receive a Reading Center- Query via email. The query email will contain easy to follow instructions for the Field Center on how to resolve the query. Field Center should respond to queries as soon as possible but latest within 10 business days. The Field Center should contact the Reading Center with questions related to queries received.

A pattern of inadequate or poor-quality studies will prompt directed discussion by Reading Center staff with the Field Center PI and/or sonographer and, possibly, retraining. The Reading Center will also hold monthly teleconferences with study sonographers to review common or persistent quality issues with study echocardiograms, and receive feedback from sonographers.

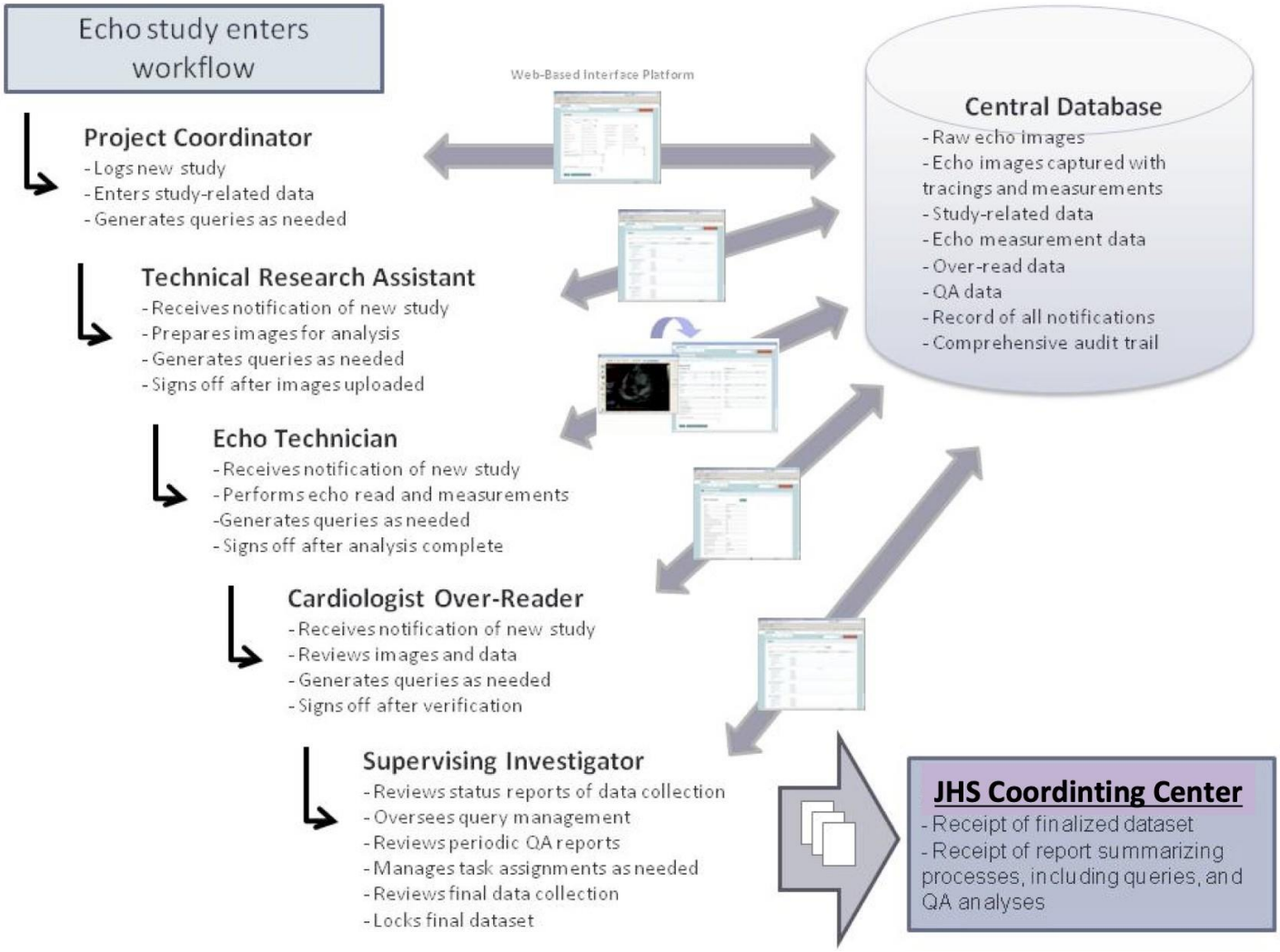
VIII. Reading Center Data Management Processes

All echocardiographic studies will be transferred from Field Centers to the Reading Center electronically using a secure web-based application. The Field Center will be automatically notified upon successful receipt of the submitted studies.

The Reading Center uses a custom designed comprehensive workflow and database platform for study tracking, query generation, capture of echocardiogram analysis data, management of analysis data, and management of study workflow (Clinical Research Systems, Newton, MA). All image acquisition and image analysis data that is captured and managed by the CRS platform is housed in a secure, industrial strength SQL relational database system that includes robust data replication and backup systems. Front-end interfaces to the platform reside on all Project Coordinator workstations, Echo Technician workstations, and Over-Reader workstations. Front-end interfaces to the platform are password-protected for use only by authorized personnel and allow role-specific (Administrative, Technical, Over-Read) access to data entry, review, edit, and management features. This custom database also provides the features of 21CFR11 compliance, including role-based access control and a built-in audit trail of all changes to administrative and technical data that is automatically generated from the point of initial data entry.

For analysis of established parameters of cardiac structure and function, the Reading Center utilizes commercially available and custom-designed and validated analysis software which allow for standard echocardiographic analysis from digital (DICOM) echocardiograms. The software is capable of making all standard echocardiographic measures, including ventricular volumes and LVEF via modified Simpson's method, wall thickness radially around the circumference of the LV base using the Wyatt convention, and full Doppler measurements. This combination of software has been extensively utilized for echocardiographic studies analyzed in the READING CENTER since 1998. All 2D speckle- tracking measurements will be performed using the Tomtec® software. TomTec 2D and 3D Cardiac Performance Analysis (2D CPA) is a vendor independent solution dedicated for strain, strain rate and velocity analysis based on speckle tracking. VVI data are extracted into a spreadsheet for the generation of time velocity and strain curves from apical or parasternal views.

Analyses will be formally over-read Cardiovascular Imaging staff affiliated with the Reading Center. Over-readers will be assessing study echocardiograms for critical abnormalities that may require clinical attention and impact study subject care and for standard clinically reportable measurements that will be used to generate clinical alerts. Over-readers will not be re-measuring values but reviewing both images and measurements to ensure appropriateness of reported measures.


Echo study enters workflow
Project Coordinator
- Logs new study
- Enters study-related data
- Generates queries as needed
Technical Research Assistant
- Receives notification of new study
- Prepares images for analysis
- Generates queries as needed
- Signs off after images uploaded
Echo Technician
- Receives notification of new study
- Performs echo read and measurements
-Generates queries as needed
- Signs off after analysis complete
Cardiologist Over-Reader
- Receives notification of new study
- Reviews images and data
- Generates queries as needed
- Signs off after verification
Supervising Investigator
- Reviews status reports of data collection
- Oversees query management
- Reviews periodic QA reports
- Manages task assignments as needed
- Reviews final data collection
- Locks final dataset
Web-Based Interface Platform
Central Database
- Raw echo images
- Echo images captured with tracings and measurements
- Study-related data
- Echo measurement data
- Over-read data
- QA data
- Record of all notifications
- Comprehensive audit trail
JHS Coordinting Center
- Receipt of finalized dataset
- Receipt of report summarizing processes, including queries, and QA analyses

IX. Quantitative Echocardiographic Measurements by the Reading Center

The following echocardiographic assessments will be performed at the Echo Reading Center:

LV Structure

- Left Ventricular End-Diastolic Dimension (LVEDD)
- Left Ventricular End-Systolic Dimension (LVESD)
- Interventricular Septum thickness (IVST)
- Posterior Wall Thickness (PWT)
- Left Ventricular End-Systolic Dimension (LVEDV)
- Left Ventricular End-Diastolic Volume (LVEDV)
- Left Ventricular End-Systolic Volume (LVESV)
- LV mass (derived)
- Relative Wall Thickness (RWT) (derived)
- Left Ventricular Outflow Tract (LVOT) diameter

LV Systolic Function

- LVEF (2D) (derived)
- LVFS (2D) (derived)
- Stroke volume (SV) (derived)
- Tissue Doppler Imaging (TDI S_{prime}) (septal, lateral)
- Global longitudinal strain (GLS)
- Global circumferential strain (GCS)
- LVOT Velocity Time Integral (LVOT VTI)

LV diastolic Function

- E wave velocity
- E Wave VTI
- A wave velocity
- A wave VTI
- Deceleration time
- E/A ratio (derived)
- Mitral Inflow VTI
- TDI eprime (septal, lateral)
- E/e' ratio (septal, lateral; derived)
- TDI s' wave

LA size and function

- LA diameter
- LA area
- LA volume (derived)

RV size and function

- Right Ventricular End-Diastolic Area (RVEDA)
- Right Ventricular End-Systolic Area (RVESA)

- Right Ventricular Fractional Area Change (RVFAC)
- Tricuspid Annular Plane Systolic Excursion (TAPSE)
- Tricuspid Annular Systolic Velocity (TA Sprime)
- RVOT Velocity Time Integral (RVOT VTI)
- RV MPI (RV Myocardial performance Index) (derived)
- RA end diastolic volume (RAEDV)

Pulmonic vascular assessment

- TR velocity
- TR mean gradient
- TR VTI

Valvular Assessment

- MRJA/LAA ratio
- Peak AV Velocity
- TRJA/RAA ratio

IX.A. Assessment of Global Left Ventricular Size and Function

The reported values will be the average of the raw data.

From the parasternal long or short axis view below the tips of the mitral valve, the end-diastolic dimensions as well as the interventricular septum thickness and posterior wall thickness of the left ventricle will be measured according to the recommendations of the American Society of Echocardiography.

From the 4-chamber and 2-chamber apical views, the endocardial borders will be traced in both end-diastole and end-systole to obtain left ventricular areas.

Left ventricular volumes will be obtained utilizing the Simpson's rule algorithm and average of four chamber and two chamber single plane volumes.

Parasternal long axis view:

- End-diastolic left ventricular diameter (cm)
- End-diastolic interventricular septum thickness (cm)
- End-diastolic posterior wall thickness (cm)
- End-systolic left ventricular diameter (cm)
- End-systolic posterior wall thickness (cm)
- LVOT diameter (cm)
- Aortic Root Diameter (cm)

Parasternal short axis papillary view:

- LV average circumferential strain (%)

Apical 4 Chamber View

- Endocardial area end-diastole (cm^2)
- Endocardial area end-systole (cm^2)
- End-diastolic volume (ml)
- End-systolic volume (ml)
- LV average longitudinal strain (%)

Apical 5 Chamber View

- LVOT velocity (cm/sec)
- LVOT VTI (cm)
- AV velocity (cm/sec)
- AV VTI (cm)
- AV pre-ejection time (sec)
- AV total ejection time (sec)

Apical 2 Chamber View

- Endocardial area end-diastole (cm^2)
- Endocardial area end-systole (cm^2)
- End-diastolic volume (ml)
- End-systolic volume (ml)
- LV average longitudinal strain (%)

IX.B. Assessment of Left Ventricular Diastolic function

All measurements will be made in triplicate (in patients with atrial fibrillation measurements will be repeated five times). The reported values will be the average of the raw data.
The peak velocities of the early rapid filling wave (E wave), and the peak velocity of the late filling wave (A wave) will be measured. The deceleration time of the E wave will be measured as the interval from the peak E wave to its extrapolation to the baseline.

Mitral annular velocities (for tissue Doppler imaging) will be recorded in systole and diastole at the lateral and septal annulus in 4-chamber view. Early diastolic myocardial velocity (E_m) and late diastolic myocardial velocity (A_m) will be measured at the lateral and septal annulus.

Apical 4 Chamber View

Mitral Inflow Doppler at the tips of the mitral leaflets

- Peak E wave velocity (cm/sec)
- E wave VTI (cm)
- Peak A wave velocity (cm/sec)
- A wave VTI (cm)
- Deceleration time (sec)

Tissue Doppler Imaging

- Lateral early diastolic myocardial velocity ($E_{prime\ lateral}$) (cm/sec)

- Lateral late diastolic myocardial velocity ($A_{prime\ lateral}$) (cm/sec
- Lateral systolic myocardial velocity ($S_{prime\ lateral}$) (cm/sec)
- Septal early diastolic myocardial velocity ($E_{prime\ septal}$) (cm/sec)
- Septal late diastolic myocardial velocity ($A_{prime\ septal}$) (cm/sec)
- Septal systolic myocardial velocity ($S_{prime\ septal}$) (cm/sec)

IX.C. Assessment of Left Atrial Size

All measurements will be made in triplicate (in patients with atrial fibrillation measurements will be repeated five times). The reported values will be the average of the raw data.
From the parasternal long axis view, the maximal left atrial diameter will be measured according to the recommendations of the American Society of Echocardiography.
From the apical 4-chamber view left atrial endocardial borders will be traced, and a straight line will be extrapolated connecting the attachment points of the mitral leaflets to the valve ring.
The measurements will be made at the ventricular end-systole, defined as the frame immediately preceding mitral valve opening.

Parasternal long axis view

- Maximal left atrial diameter (cm)

Apical 4 Chamber View

- Left atrial endocardial area at ventricular end-systole (cm^2)
- Left atrial volume at ventricular end systole (ml)
- Mitral regurgitation jet area on color flow Doppler (cm^2)

Apical 2 chamber View

- Left atrial endocardial area at ventricular end-systole (cm^2)
- Left atrial volume at ventricular end systole (ml)
- Mitral regurgitation jet area on color flow Doppler (cm^2)

IX.D. Assessment of Global Right Ventricular Size and Function

The reported values will be the average of the raw data.
From dedicated 4-chamber apical views focusing on the right ventricle, RV endocardial borders will be traced at both end-diastole and end-systole to obtain right ventricular areas. From RV areas right ventricular fractional area change (RVFAC) will be derived.
M-mode assessment of lateral tricuspid annular motion will be recorded at a sweep speed of 100 mm/sec with measurement of tricuspid annular plane systolic excursion towards the apex (TAPSE).

Tissue Doppler imaging of the lateral tricuspid annular systolic displacement will be recorded at a sweep speed of 100 mm/sec with measurement of the tricuspid annular systolic contraction velocity (TA S').

From dedicated 4-chamber apical views focusing on the right ventricle, RV endocardial borders will be traced at end-diastole and using a strain-specific software (Tomtec) the endocardial border will be followed during the whole cardiac cycle to derived RV free wall longitudinal strain (FWLS).
From the parasternal short axis view at the level of the aortic valve, pulse wave Doppler recording at the right ventricular outflow tract (RVOT) will be performed with measurement of the RVOT

velocity time integral (VTI), a visual assessment of the presence of systolic notching in the RVOT PW flow, and RV ejection time (RV ET) defined as the interval time between the onset and cessation of the pulmonary valve outflow

Peak tricuspid regurgitation (m/sec) velocity defined as the peak velocity of the tricuspid regurgitation envelope and tricuspid inflow duration defined, as the interval time between onset and cessation of the tricuspid inflow will be measured from the better-quality view among the recorded views for tricuspid regurgitation jet using continuous wave Doppler through the tricuspid valve looking for the maximum velocity peak among all the views recorded for tricuspid regurgitation. Tricuspid valve closure to opening time will recorded on CW tricuspid regurgitation Doppler.

The subcostal view of the inferior vena cava (IVC) the maximal width of the IVC and degree of inspiratory collapse will be measured.

Parasternal Short axis Aortic view

- RVOT Diameter
- RVOT velocity (cm/sec)
- RV ejection time (sec)
- RVOT VTI (cm)
- Pulmonic Acceleration time (sec)
- Pulmonic regurgitation early diastolic velocity (cm/sec)
- Pulmonic regurgitation end-diastolic velocity (cm/sec)
- Tricuspid regurgitation velocity (cm/sec)
- Tricuspid regurgitation VTI (cm)

Apical 4 Chamber View (RV Focused)

- RV endocardial area end-diastole (cm^2)
- RV endocardial area end-systole (cm^2)
- Tricuspid annular plane systolic excursion by M-mode (cm)
- Peak systolic tricuspid annular velocity (by tissue Doppler imaging) at lateral annulus (cm/sec)
- RA volume (ml)
- RA area (cm2)

Apical 4 Chamber View (RV focused)

- Peak tricuspid regurgitation velocity by CW Doppler (m/sec)
- Tricuspid regurgitation VTI (cm)
- Tricuspid regurgitation area (cm^2)

Sub-costal view

- RV free wall thickness
- Maximal IVC diameter (cm)
- Minimal IVC diameter (cm)

IX.E. Assessment of Ventricular-Vascular Coupling

From the apical 4-chamber view, the time from the peak of the R wave to onset of LVOT systolic flow (R→onset) and the time from the peak of the R wave to the end of aortic ejection (R→end) will be measured from LVOT pulsed wave Doppler.

Ejection fraction will be derived from the apical 4 and 2 chamber end-diastolic and end-systolic volumes. Stroke volume will be derived from LVOT VTI from the apical 5 chamber view and LVOT diameter from the parasternal long axis view.

Apical 4 Chamber View

Pulsed wave Doppler

- R→onset, R→end

IX.F. Derived Measurements

- Stroke volume (SV) (ml)
  Π x $LVOT^2$ /2 x LVOT VTI

- SV/ SVI derived from LV volumes

- Cardiac output (CO) (ml/min)
  SV x HR

- Ejection Fraction (%)
  $EF = 100*(LVEDV_{mean}-LVESV_{mean})/LVEDV_{mean}$

- Average LV wall thickness (cm)
  $lvwt_{mean} = (lvpw_{mean} + lvs_{mean})/2$

- LV mass and LV mass Index (gm/m^2)
  $LV\ mass\ (g) = = 0.8*\{1.04*[(LVIDd+IVSTd+PWTd)^3 - (LVIDd)^3]\}+0.6$

- LA volume and LA volume Index (ml/m^2)

- LV Fractional shortening (%)
  $FS = 100*(LVEDD_{mean}-LVESD_{mean})/LVEDD_{mean}$

- LV relative wall thickness (RWT)
  $(2 \times PWT_d)/LVID_d$

- Mean LV wall thickness (cm) = (PWT+ASWT)/2

- LV End systolic Elastance (E_{ES}) - Using Time from R to onset of aortic ejection (R→onset), Time from R to end of aortic ejection (R→end), SBP, DBP.

$$E_{ES} = [DBP - (E_{Nd(est)} \times SBP \times 0.9)]/[SV \times E_{Nd(est)}]$$

Where:

$$E_{Nd(est)} = 0.0275 - 0.165 \times EF + 0.3656 \times (DBP/SBP) + 0.515 \times E_{Nd(avg)}$$

$$E_{Nd(avg)} = \sum a_i \times t_{Nd}^{\ i}$$

where t_{Nd} = R→onset/R→end

and a_i are (0.35695, -7.2266, 74.249, -307.39, 684.54, -856.92, 571.95, -159.1)

for i = 0 to 7

- Arterial Elastance (E_A)
  (E_A) = (SBP x 0.9)/SV
- EA/EES
- Mitral regurgitation area/LA area ratio (MRJA/LAA Ratio)
- Tricuspid regurgitation area/RA area ratio (TRJA/RAA Ratio)
- RV fractional area change = (RVEDA – RVESA)/RVEDA
- RV MPI (Tei index) = (TV Closure time – RV ejection time)/RV ejection time
- Pulmonary vascular resistance (PVR) =
  Peak TR velocity (m/sec)/RVOT VTI (cm) x 10 + 0.16 (Woods units)
- RV systolic pressure = 4 x (peak TR velocity)^2 + right atrial pressure (estimated from IVC width) (mmHg)
- E/A ratio: Peak E wave velocity/ Peak A wave velocity
- E/$E_{prime\ lateral}$: Peak E wave velocity/ Lateral early diastolic myocardial velocity

IX.G. Assessment of Left Ventricular Deformation (LV strain analysis)

From the 4-chamber and 2-chamber apical views, the endocardial borders will be traced for measurement of longitudinal strain.

From the parasternal short axis at the level of the mid-papillary muscle, endocardial and epicardial borders will be traced for measurement of radial strain and circumferential strain.

Parasternal short axis view (mitral level, mid-papillary level, apex):

- Average peak circumferential strain
- Standard deviation in time to peak circumferential strain (msec)

Apical 4 Chamber View

- Average peak longitudinal strain
- Standard deviation in time to peak longitudinal strain (msec)

Apical 2 Chamber View

- Average peak longitudinal strain
- Standard deviation in time to peak longitudinal strain (msec)

IX.H. 3D Echocardiography analysis: is performed using TOMTEC version 4.6 build 3.9.

- Left Ventricular End-Diastolic Volume (LVEDV)
- Left Ventricular End-Systolic Volume (LVESV)
- Left Ventricular Ejection Fraction (LVEF)
- Right Ventricular End-Diastolic Volume (RVEDV)
- Right Ventricular End-Systolic Volume (RVESV)
- Right Ventricular Ejection Fraction (RVEF)

X. Over-reading

All echocardiograms will be over-read by a Board-Certified cardiologist with either COCATS Level 3 advanced training in echocardiography and/or American Society of Echocardiography Board Certification in Comprehensive Adult Echocardiography. Over-readers will be presented with the following key quantitative measurements made by technicians: left ventricular (LV) end-diastolic dimension, LV wall thickness, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, left atrial volume index, right ventricular fractional area change, mitral regurgitation jet area-to left atrial area ratio, aortic valve peak antegrade velocity, and tricuspid regurgitation velocity. Over-readers will review echocardiograms to confirm the accuracy of these measurements and to identify clinically important findings not otherwise represented by the technical measurements. Such clinically important findings include significant aortic insufficiency, mitral stenosis, pulmonary hypertension, or right ventricular enlargement or 'critical abnormalities' including but not limited to: a) tamponade, b) aortic dissection, c) thrombosed or frankly dysfunctional prosthetic valve, d) pseudoaneurysm, e) intracardiac abscess or obvious vegetation, f) intracardiac thrombus. If a critical abnormality is identified, over-readers will report such critical findings directly to the Data Coordinating Center at the time of study review via a web-based data entry form (please refer to section VII for further details). Over-readers must approve analysis for each study prior to study data being finalized for transfer to the Coordinating Center.

XI. Reporting of Findings to Field Center

Echocardiography will be performed to assess cardiac structure and function. All exams will be performed by qualified sonographers specifically trained in performing a JHS protocol study. The imaging protocol will consist of the sub-set of the views obtained in a standard clinical echocardiogram as recommended by the American Society of Echocardiography. Studies will be acquired digitally and transferred electronically to the JHS Echocardiography Reading Center. All quantitative measures of cardiac structure and function will be performed off-site at the Echocardiography Reading Center, typically within several weeks of study performance. Reporting of findings to participants or site investigators may occur at multiple points:

1. Sonographers performing echocardiographic studies will occasionally identify abnormalities that they consider important and will alert site investigators directly. These findings will include, but are not limited to, tamponade, aortic dissection, thrombosed or frankly dysfunctional prosthetic valve, pseudoaneurysm, intracardiac abscess or obvious vegetation, and intracardiac thrombus. The Echocardiography Reading Center will also be informed to facilitate an expedited analysis of the study. Site investigators will be responsible for handling alert findings (either as alerts requiring emergency/immediate referral, urgent referral, or routine referral as they deem appropriate), including relaying findings to study participant and, where consent has been provided, to the participant's treating provider.

2. Overreading cardiologists at the Echocardiography Reading Center may identify critical abnormalities that would require emergent notification and arrangements for care. Such findings will be reported within 24 hours of review by the Reading Center to the Data Coordinating Center and will be communicated to the field center as an Immediate Alert Notification. Abnormalities that would trigger a critical result include, but are not limited to a) tamponade, b) aortic dissection, c) thrombosed or frankly dysfunctional prosthetic valve, d) pseudoaneurysm, e) intracardiac abscess or obvious vegetation, f) intracardiac thrombus. Each field center should have a plan for handling these types of alerts, including relaying findings to study participant and, where consent has been provided, to the participant's treating provider.

3. Overreading cardiologists at the Echocardiography Reading Center may identify specific non-critical abnormalities that would be important for a patient and physician to be aware of, but that don't necessarily require emergent care. These findings will be incorporated into the routine data transfers from the Echocardiography Reading Center to the Data Coordinating Center. Such findings include: a) moderate or greater mitral regurgitation, b) moderate or greater mitral stenosis, c) moderate or greater obstructive lesions of left ventricular outflow, including aortic stenosis and dynamic left ventricular outflow tract obstruction, d) moderate or greater aortic regurgitation, e) moderate to severe pulmonary hypertension, f) severe right ventricular enlargement.

4. Limited quantitative data will be included in the routine reporting letter generated by the Data Coordinating Center for all participants. This will include three commonly used measures of cardiac structure and function: a) left ventricular ejection fraction, b) left ventricular diastolic diameter, c) left ventricular wall thickness. These data will be presented in a table with reference values (see example below). Values that exceed the reference thresholds would represent routine referrals as defined in the section title 'Study Results Reporting Schedule' of this document. All other study measurements, i.e. those not routinely reported to participants and/or her/his health care provider, are considered to be of research value only. If a participant requests them in writing, these values are provided on an ad hoc basis.

Routine Reporting example:

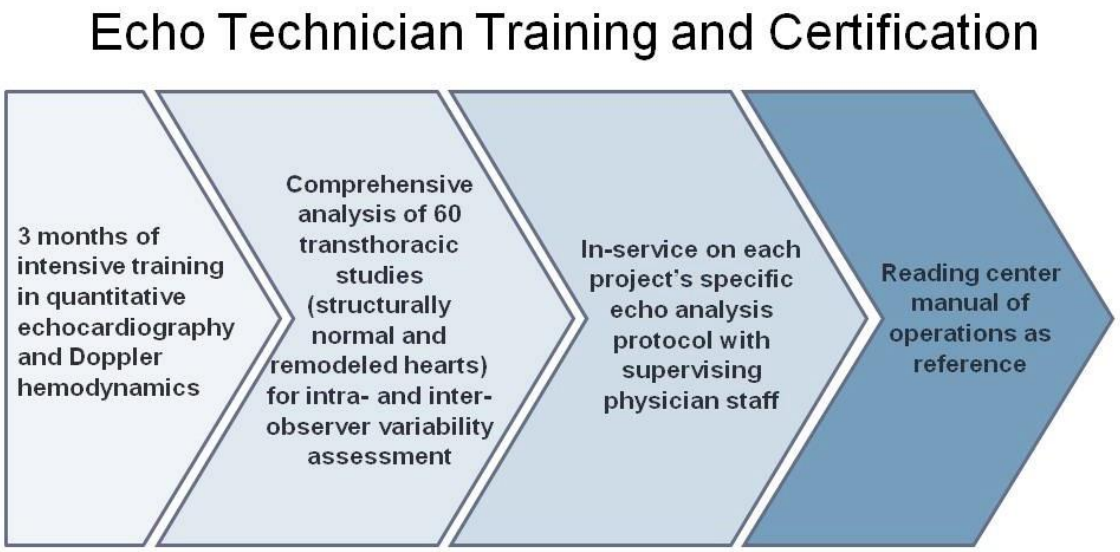
The echocardiogram that you had performed was for research purposes only, is not as extensive as a clinical echocardiogram, was analyzed in the absence of any clinical information regarding you/your patient, and is not meant to substitute for a clinical echocardiogram. The assessments below of cardiac structure and function are being provided as a courtesy, along with reference ranges. These findings could be further evaluated with a clinical echocardiogram if clinically indicated.

Parameter	Value		Low Normal	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
LV ejection fraction (%)	**[VALUE]**	**Both**	**50 – 54**	**45 – 49**	**30 – 44**	**<30**
LV diastolic diameter (cm)	**[VALUE]**	**Men** **Women**		**6.0-6.3** **5.4-5.7**	**6.4-6.8** **5.8-6.1**	**≥6.9** **≥6.2**
LV wall thickness (cm)	**[VALUE]**	**Men** **Women**		**1.1-1.3** **1.0-1.2**	**1.4-1.6** **1.3-1.5**	**≥1.7** **≥1.6**

If specific triggered abnormalities were detected by the reading cardiologist (see #3 above), an additional sentence(s) will be added.
Your echocardiogram displayed evidence of [moderate/severe] [xxxxxxxxxx]. These findings should be discussed with your physician and follow-up studies may be warranted.
Example:
Your echocardiogram displayed evidence of moderate aortic stenosis. These findings, if not already known, should be discussed with your physician and follow-up studies may be warranted.

XII. Reading Center Echo Technician Training and Certification

All echo technicians undergo a minimum of 3 months of intensive training in quantitative echocardiography, including cardiac anatomy, transthoracic echocardiographic views, standard echocardiographic measures, and Doppler hemodynamics. This is accomplished through a combination of didactic talks by READING CENTER physician staff and review of reference material. During this period, technical staff performs comprehensive analysis on 60 transthoracic studies, which are assessed for intra- and inter-observer reproducibility. Technical staff involved in the JHS project will undergo an additional in-service to thoroughly familiarize them with the analysis protocol. Technical staff involved in the 2D speckle-tracking strain and strain rate analysis will have to demonstrate acceptable intra- and inter-observer reproducibility of average longitudinal and circumferential strain measures.



XIII. Quality Assurance Plan

Echocardiography Reading Center technician intra- and interobserver reproducibility

Purpose: The Reading Center will employ a modular analysis model, whereby each Reading Center technician will be responsible for specific quantitative measures for each echocardiogram. As a result, each quantitative measure will be performed by a single technician for all JHS Visit 4 echocardiograms, minimizing interobserver variability. The focus of the Reading Center quality assurance procedures therefore will be to quantify and minimize intra-observer variability and temporal drift.

The purpose of the Reading Center quality assurance procedures are to: (1) quantify intra-observer reproducibility, (2) quantify inter-observer reproducibility, and (3) quantify and mitigate temporal drift in echocardiographic analysis over the study period.

Intra- and interobserver variability – For the assessment of intra-observer variability, the primary study technician repeats study analysis in a blinded fashion. Each technician will perform duplicate blind re-reads of approximately 40 studies every 4 months. For the assessment of interobserver variability, each technician will also perform analysis of the views for which s/he is not primarily responsible. Of the 40 studies analyzed, 20 studies will be the same studies throughout the visit period (to allow for assessment of temporal drift – see below). The remaining 20 studies will be randomly selected from each 4-month period for re-analysis. Technicians will be blinded as to original study ID. Interobserver variability will be documented prior to any transitions in technicians performing measurements.

Temporal drift – To assess for temporal drift for both established and 2D speckle-tracking measures, each technician will be required to perform blind re-reads on same set of 20 studies at 4-month intervals. Reproducibility of the above key measures will be assessed for each technician using the Bland-Altman method to compare repeated measures, with the coefficient of variation and bias reported as described above.

IX.iii. Reporting of QA Assessments

Data on *intra-observer variability* for key echocardiographic measures will be reported to the Coordinating Center every 4 months. Data regarding *temporal drift* will be reported to the Coordinating Center every 4 months. Reproducibility results will be reported primarily as the coefficient of variation, bias, and limits of agreement.