

## CICL Reading Center Manual of Operations



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# Hispanic Community Health Study – Study of Latinos

## HCHS/SOL Cohort – Visit 2

### Echocardiography Reading Center Manual of Operations

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## I. Introduction

The National Heart, Lung and Blood Institute (NHLBI) initiated the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) in 2006, with the recruitment of approximately 16,000 Hispanic/Latino adults from 4 communities across the country. In addition to being disproportionately affected by diabetes, and the component conditions of the metabolic syndrome, Hispanics remain unfavorably affected by health care disparities that predispose to all major adverse events. Therefore, Hispanics represent a population that is particularly vulnerable to cardiovascular outcomes, including heart failure (HF). The performance of echocardiography at the HCHS/SOL Visit 2 examination offers the opportunity to identify the manifestations of cardiac dysfunction that precede overt HF in the at-risk, understudied population of Hispanic/Latino Americans. Whereas prior and predominantly cross-sectional studies have investigated the demographic, social/culture, and clinical factors associated with HF in Hispanics/Latinos, echocardiography in HCHS/SOL will be the first to provide comprehensive, detailed phenotyping of pre-clinical cardiac disease in a large sample of Hispanics/Latinos with representation across age, sex, ethnic/cultural subgroups, and geographic regions.

The Brigham and Women's Hospital CICL will serve as the Echocardiography Reading Center for HCHS/SOL Visit 2. This document outlines the CICL procedures for:

1. Field Center sonographer training and certification
2. Reading Center technical staff training and evaluation
3. Processing and analysis of Field Center echocardiograms
4. Reporting of abnormal measures made on echocardiograms to Field Centers for communication to subjects' local physicians

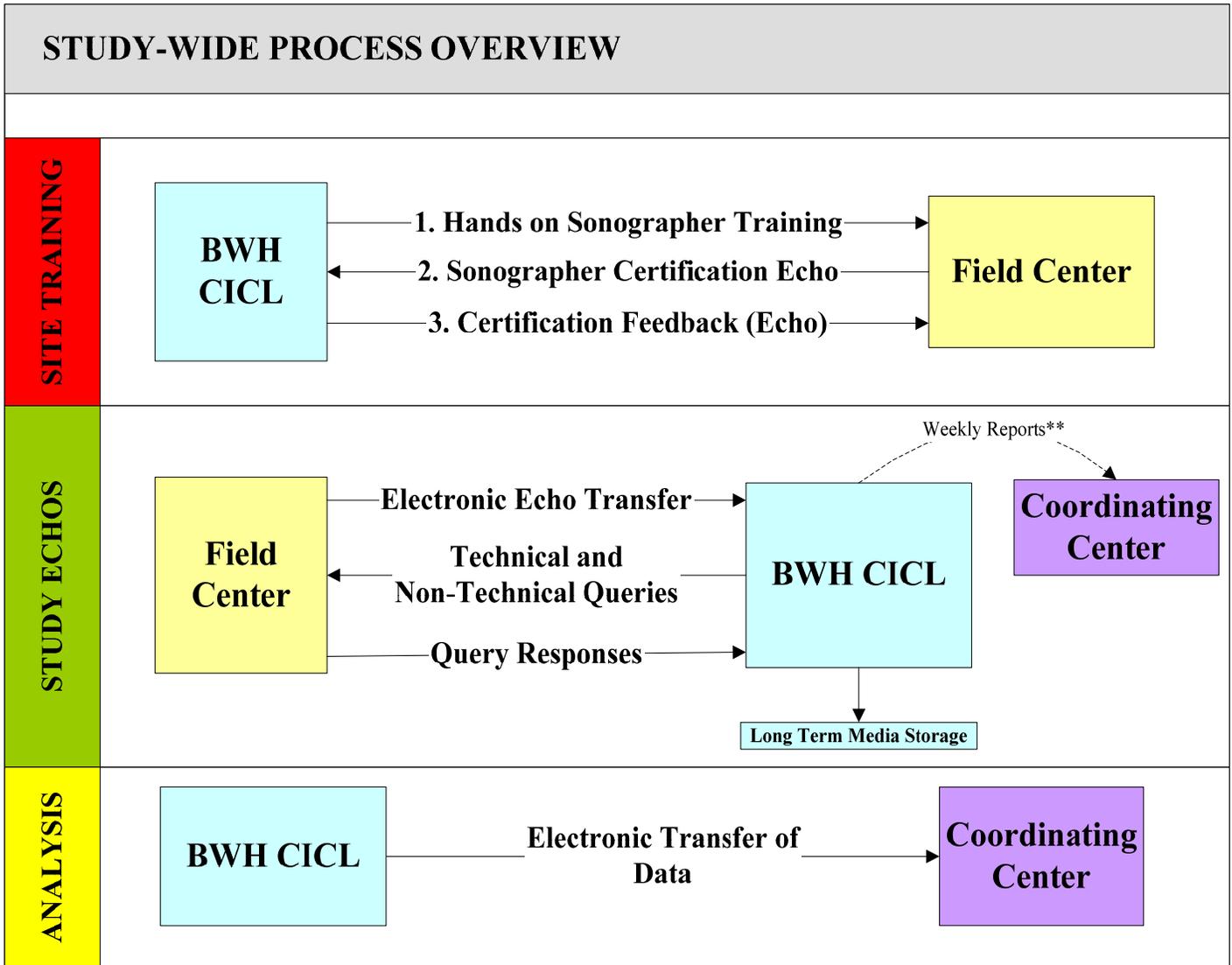
## II. Overall Study Aims and Processes

OBJECTIVES	
<b>Echocardiography</b>	<ul style="list-style-type: none"><li>▪ Echocardiographic examinations will be performed to estimate myocardial structure and performance including but not limited to: left and right ventricular systolic function, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular mass, left atrial size, LV diastolic function, mitral inflow pulsed wave Doppler (E wave, A wave), isovolumic relaxation time (IVRT), tricuspid regurgitation (TR) velocity.</li></ul>
<b>Cardiac Imaging Core Lab</b>	<ul style="list-style-type: none"><li>▪ To provide high quality reproducible quantitative analysis of study echocardiograms</li></ul>
<b>Field Center Manual of Operations</b>	<ul style="list-style-type: none"><li>▪ To instruct field centers on how to perform and send study echos to the Cardiac Imaging Core Lab (CICL).</li></ul>

ROLES AND RESPONSIBILITIES	
<b>Field Centers</b>	<ul style="list-style-type: none"><li>▪ Perform high-quality study echocardiograms per the protocol contained in this document</li></ul>
<b>Cardiac Imaging Core Lab</b>	<ul style="list-style-type: none"><li>▪ Receive, review and analyze study echos.</li><li>▪ Train and certify each field center sonographer.</li><li>▪ Provide field centers quality feedback on echos.</li><li>▪ Serve as a resource for sites for all echo-related questions.</li></ul>

## Study-Wide Process Overview

Field centers will electronically transmit echos directly to the Cardiac Imaging Core Lab (CICL). Below is a basic diagram to describe the study wide process that will occur.



### III. Echocardiogram Protocol: Required Views

**Required Study Views** – The following subset of views from a standard transthoracic echocardiogram examination is necessary for the proposed measurements of cardiac structure and function:

<b>Blood pressure</b>	
Brachial blood pressure	Measure BP at the beginning of echo examination
<b>Echocardiographic View</b>	<b>Measurement</b>
<b>Parasternal Position</b>	
Parasternal long axis	2D imaging Color Doppler of the mitral valve Color Doppler of the aortic valve 2D focused imaging of the ascending aorta
Parasternal short axis – Aortic valve level	2D imaging PW and CW Doppler of the RVOT
Parasternal short axis – LV base	2D imaging
Parasternal short axis – Papillary muscle	2D imaging
Parasternal short axis – LV apex	M-mode 2D imaging
<b>Apical Position</b>	
Apical 4 chamber view	2D imaging (including LA) Color Doppler of mitral valve/LA Spectral Doppler (pulse wave and continuous wave) mitral flow TDI of septal and lateral mitral annulus
Apical 4 chamber – focused on the RV	2D imaging (including RA) Color Doppler of tricuspid valve/RA Continuous wave Doppler of tricuspid regurgitation TDI of lateral tricuspid annulus TAPSE of lateral tricuspid annulus
Apical 5 chamber view	2D imaging Pulse wave of LVOT flow Continuous wave of transaortic flow
Apical 2 chamber view	2D imaging (including LA) Color Doppler MV/LA
Apical 3 chamber view	2D imaging
<b>Subcostal View</b>	
Inferior vena cava	2D imaging for 5-10 cardiac cycles M-mode with sniff

## IV. Field Center Sonographer Training and Certification

### *Sonographer training*

Sonographer training is a multilayer process and includes the following components:

**Live training session** – Prior to the start of Visit 2, a centralized training session will be held for all Field Center sonographers who will be performing echocardiograms for the HCHS/SOL study. A CICL project investigator, a senior CICL sonographer, and the CICL project coordinator will be present. Training will consist of a didactic session, reviewing the exam protocol, machine presets, required views, image acquisition/optimization tips, and mechanisms for the Field Center staff to contact CICL staff regarding technical questions or issues. A hands-on session will then be led by the CICL sonographer, initially demonstrating a full study exam on a model patient using the echo machine model identical to that used for Visit 2 echos, then allowing each sonographer to perform the full exam under direct supervision. A presentation and demonstration of the process for transmitting studies to the CICL will be made.

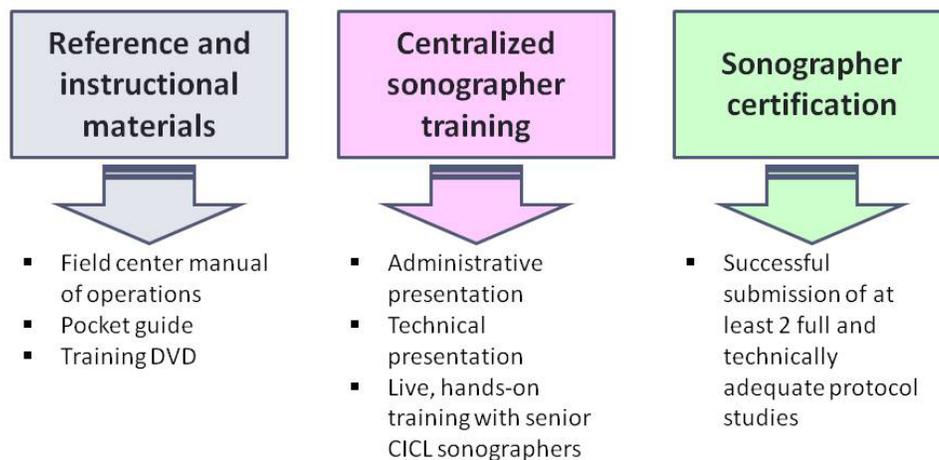
**Reference materials at the Field Centers** – Prior to and during the Visit 2 period, the Reading Center will provide to following reference materials for Field Center sonographers. These will also be available online via the CICL secure web portal.

**Field Center Manual of Operations** containing the protocol required views and instructions for optimizing image quality.

**Training DVD** demonstrating a full HCHS/SOL echo study performed per the study protocol with narrative and moving echo clips.

**Pocket Guide** which is a 1 page guide (laminated and put on a key ring) listing key study data including required views to obtain and instructions for transmitting echocardiograms to the CICL.

**Monitoring and feedback**– During the Visit 2 period, CICL technical staff will continuously monitor the adequacy and quality of all studies received according to the criteria outlined in the table below:



## Criteria for Evaluating Quality of Echocardiographic Images Received from Sites

Criteria for Evaluating Image Quality	
View	Scoring
Parasternal long axis view	<ul style="list-style-type: none"> <li>• <b>2 points:</b> 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)</li> <li>• <b>1 point:</b> Image is not completely on axis, or the 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)</li> <li>• <b>0 points:</b> Image is completely off axis, or endocardial border not well visualized &gt;15% of anatomic segments of the main structures imaged</li> </ul>
Apical 4 chamber view	<ul style="list-style-type: none"> <li>• <b>2 points:</b> 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)</li> <li>• <b>1 point:</b> 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)</li> <li>• <b>0 points:</b> Image is completely off axis, or endocardial border not well visualized &gt;15% of anatomic segments of the main structures imaged (e.g. there is dropout of <math>\geq 2</math> (of 6) anatomic segments of the LV)</li> </ul>
Short axis at the mid-ventricular level	<ul style="list-style-type: none"> <li>• <b>2 points:</b> 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)</li> <li>• <b>1 point:</b> 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)</li> <li>• <b>0 points:</b> Image is completely off axis or endocardial border not well visualized &gt;15% of anatomic segments of the main structures imaged (e.g. there is dropout of <math>\geq 2</math> (of 6) anatomic segments of the LV)</li> </ul>
Apical 2 chamber view	<ul style="list-style-type: none"> <li>• <b>2 points:</b> 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)</li> <li>• <b>1 point:</b> 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)</li> <li>• <b>0 points:</b> Image is completely off axis or endocardial border not well visualized &gt;15% of anatomic segments of the main structures imaged (e.g. there is dropout of <math>\geq 2</math> (of 6) anatomic segments of the LV)</li> </ul>
Doppler views	<ul style="list-style-type: none"> <li>• <b>2 points:</b> Clear signals captured over at least 3 cardiac cycles for all Doppler measures</li> <li>• <b>1 point:</b> Clear signals captured over at least 2 cardiac cycles for most Doppler measures</li> <li>• <b>0 points:</b> Absent or unclear signals captured for most Doppler measures</li> </ul>
Criteria for Scoring	
Grading	Total Points
Good quality	9-10 points
Acceptable quality	6-8 points
Fair quality	4-5 points
Poor quality	$\leq 3$ points

Feedback regarding adequacy of each study received, including an itemized list of study deficits if deemed inadequate, are sent to the performing sonographer and Field Center coordinator. The CICL will continuously monitor for study-wide, site-specific, and sonographer-specific trends in quality. Study-wide and site-specific trends in quality will be discussed on regular HCHS/SOL Echo Center teleconferences attended by sonographers and site investigators (to be held weekly during the initial phase of the study, and

monthly thereafter). In instances where suboptimal trends in quality are identified (e.g. frequency of poor or fair quality images observed in excess to that from other sites and/or sonographers), CICL staff will discuss and review directly with the site and/or sonographer the possible contributing factors (including participant variables, machine variables, and other variables). In these instances, the CICL will provide detailed feedback, additional training, and/or on-site support, as appropriate.

**Sonographer Certification**

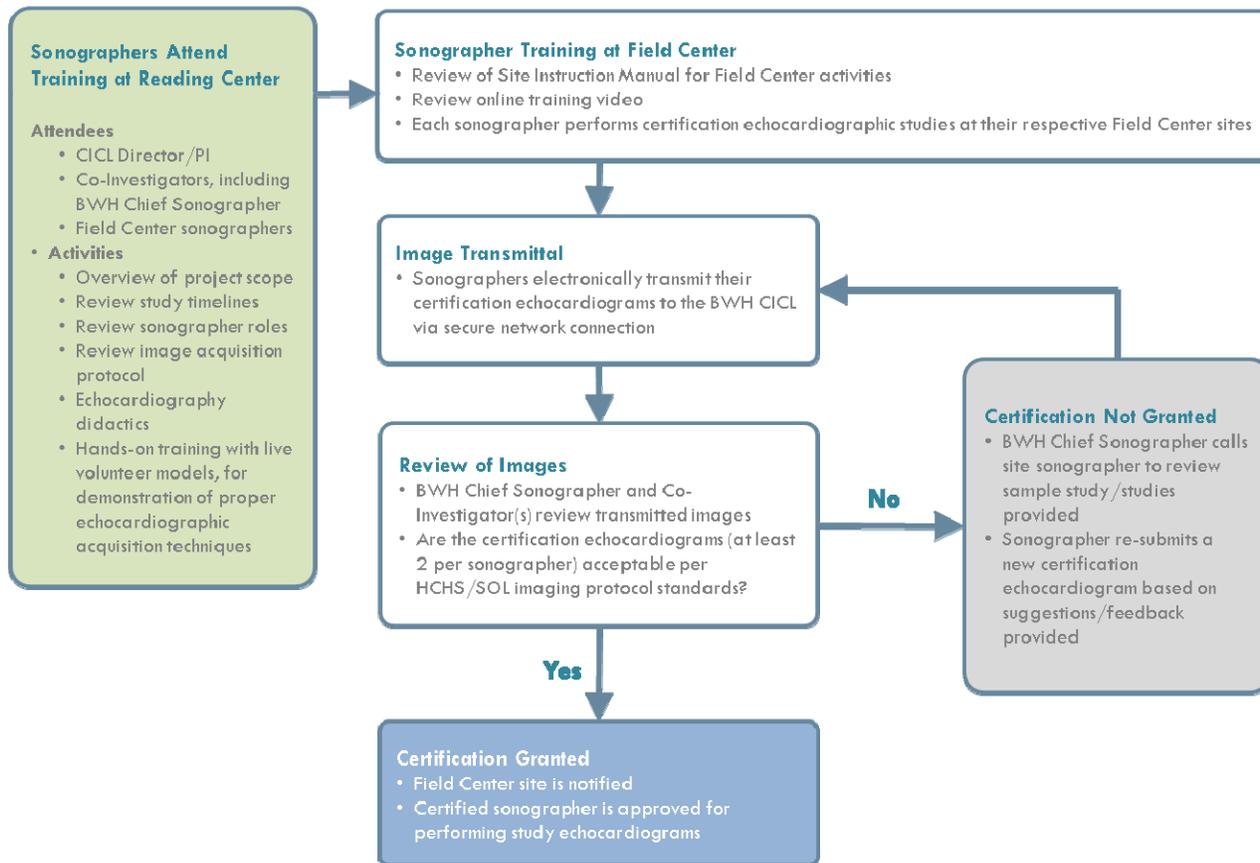
The purpose of certification is to ensure consistency in how echocardiograms are performed study-wide and to ensure performance of the highest quality echocardiograms. Any sonographer who will be performing study echocardiograms must first submit two certification studies performed in accordance with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

A general outline of the process is outlined below.

**Sonographer Certification Process Overview**



## V. CICAL Data Management Processes

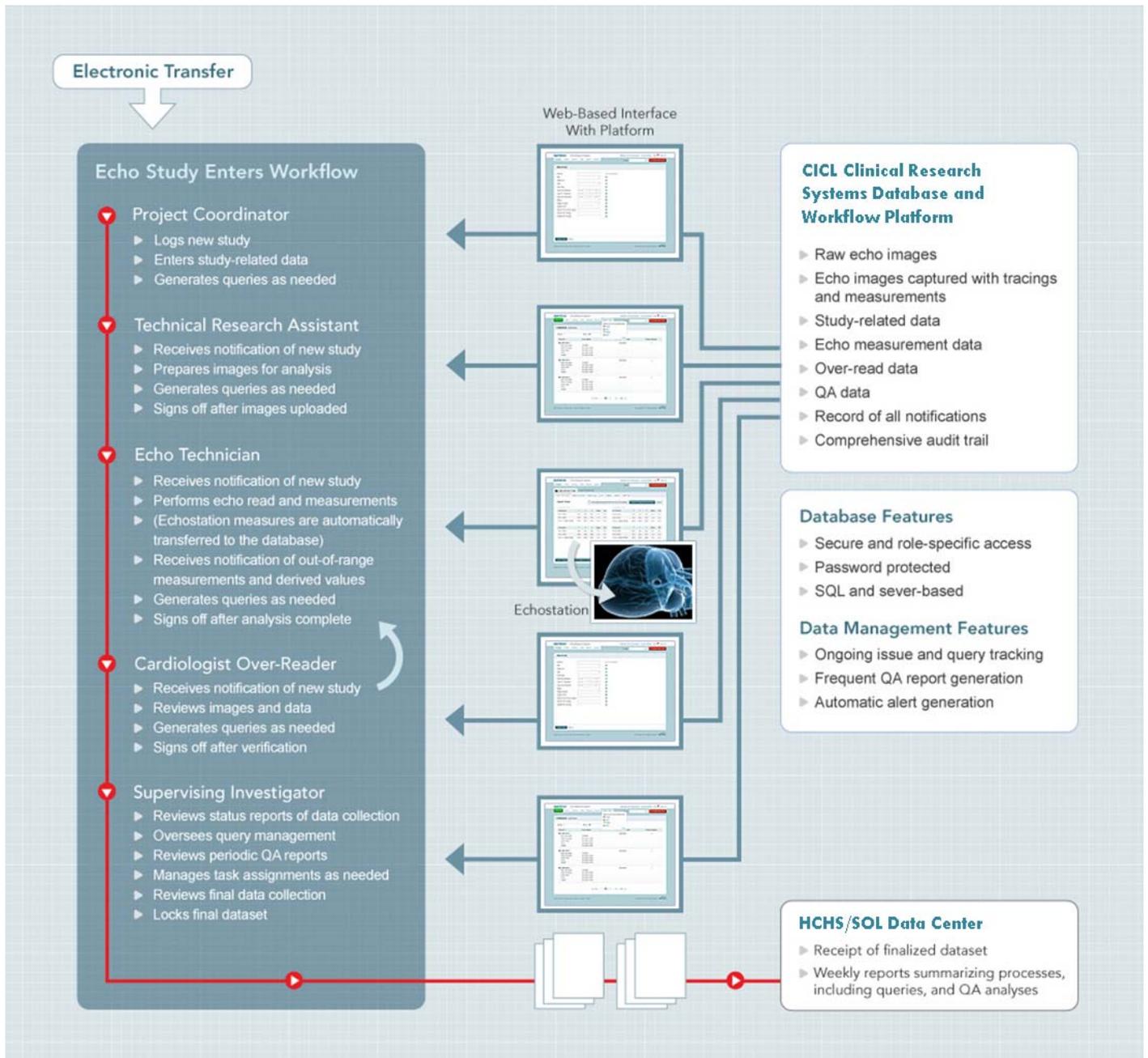
All echocardiographic studies will be transferred from Field Centers to the Reading Center electronically using secure VPN-based image transfer technology. A dedicated workstation at each Field Center with high-speed internet capability will be set up for study transfers. Field Centers will retain a hard copy of each echocardiogram, stored in a secure location at the Field Center. Field Centers will be automatically notified upon successful receipt of the submitted studies.

The CICAL 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, Site Representative, 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 CICAL 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 CICAL since 1998. All 2D speckle-tracking measurements will be performed using the Tomtec® software. TomTec 2D 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 Brigham and Women's Hospital CICAL. 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.

# CICL Echocardiography Image Analysis Workflow



## VI. Echo Reading Center Measurements

### 1. Conventional Parameters to be Measured

All standard echocardiographic measures conform to recommendations and standards set out in the American Society of Echocardiography (ASE) Chamber Quantification guidelines.<sup>198</sup>

Conventional Measure	Details
<b>LV structure</b>	
LV wall thickness	LV anteroseptal and inferolateral wall thickness will be measured from the parasternal long axis view at the LV minor axis (level of the mitral valve tips in diastole).
LV chamber dimensions	LV internal end-systolic and end-diastolic measurements will also be made in the parasternal long axis view.
LV mass, LV mass index, relative wall thickness	LV mass will be calculated by the ASE recommended formula for estimation of LV mass from LV linear dimensions and indexed to BSA, and height <sup>2,7</sup> : <b>LV mass(g) = 0.8*(1.04*[(LVIDd+IVSTd+PWTd)<sup>3</sup> - (LVIDd)<sup>3</sup>]+0.6</b>
LV end-systolic and end-diastolic volume	Relative wall thickness will be calculated as: <b>(2 x PWT)/LVIDd</b> LV volumes will be calculated using the biplane method of disks (modified Simpson's method), by endocardial border tracing at end-diastole and end-systole in the apical 4- and 2-chamber views.
<b>LV systolic function</b>	
LV ejection fraction	EF will be calculated using the modified Simpson's method as: <b>[(LV end-diastolic volume – end-systolic volume)/end-diastolic volume] x 100.</b>
<b>LV diastolic function</b>	
Tissue Doppler mitral annular peak early diastolic velocity (E')	Peak tissue Doppler early diastolic velocity will be measured from both the lateral and medial aspect of the mitral annulus.
Pulse wave Doppler mitral inflow early (E wave) and late (A wave) velocities	Mitral flow velocity will be assessed by pulsed wave Doppler from the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflets.
E wave deceleration time (DT)	The deceleration time of the E wave will be measured as the interval from the peak E wave to its extrapolation to the baseline.
Isovolumetric relaxation time (IVRT)	The IVRT will be measured as the time interval between the cessation of the mitral inflow A wave and the onset of systolic LVOT flow.
<b>Aortic Structure</b>	
Aortic root dimension	Aortic root will be measured from the parasternal long axis view at the sinuses of Valsalva. Presence of absence of plaque in the ascending aorta (plaque severity if present: mild <2 mm; moderate 2-4 mm; severe ≥4 mm)
<b>LA structure</b>	
LA volume index	LA volume will be measured using the uniplane modified Simpson's rule and indexed to body surface area.
<b>Pulmonary vasculature</b>	
Peak right ventricular-atrial systolic gradient	The peak RV-RA systolic gradient will be determined from the peak tricuspid regurgitation velocity by continuous wave spectral Doppler. Peak systolic gradient will be calculated using the modified Bernoulli equation as: <b>Peak RV-RA gradient = 4 x (peak TR velocity)<sup>2</sup>.</b>
Pulmonary vascular resistance (PVR)	PVR will be calculated using the peak TR jet velocity and the right ventricular outflow tract velocity-time integral as validated by Abbas et al. <sup>158</sup> <b>PVR (in Wood Units) = 0.1618 + 10.006 x (peak TR velocity/RVOT VTI)</b>
Maximal Inferior Vena Cava (IVC) Diameter	Maximal IVC diameter will be measured from the subcostal position.
<b>RV function</b>	
RV fractional area change (RVFAC)	RV fractional area change (RVFAC) will be assessed quantitatively as the percent change in cavity area from end-diastole to end-systole by tracing the endocardial borders from the apical 4 chamber view.
Tissue Doppler tricuspid annular peak systolic velocity	Peak tissue Doppler systolic velocity will be measured from the lateral aspect of the tricuspid annulus.
<b>Valvular function</b>	
Aortic stenosis (AS)	The presence of AS will be assessed by measurement of the transaortic peak velocity and velocity-time integral and severity categorized based on ACC/AHA guidelines using peak

	transvalvular velocity and mean gradient criteria. If classification by the two criteria do not agree, the more severe will be reported.
<b>Vascular function and left ventricular-arterial interaction</b>	
LV end-systolic elastance (E <sub>ES</sub> )	Using Time from R to onset of aortic ejection (R→onset), Time from R to end of aortic ejection (R→end), SBP, DBP: <sup>199</sup> $E_{ES} = [DBP - (E_{Nd(est)} \times SBP \times 0.9)] / [SV \times E_{Nd(est)}]$ <p>Where:  <math display="block">E_{Nd(est)} = 0.0275 - 0.165 \times EF + 0.3656 \times (DBP/SBP) + 0.515 \times E_{Nd(avg)}</math> <math display="block">E_{Nd(avg)} = \sum a_i \times t_{Nd}^i</math>           where <math>t_{Nd} = R \rightarrow onset / R \rightarrow end</math>            and <math>a_i</math> are (0.35695, -7.2266, 74.249, -307.39, 684.54, -856.92, 571.95, -159.1)            for <math>i = 0</math> to <math>7</math></p>
Arterial elastance (E <sub>A</sub> )	(E <sub>A</sub> ) = (SBP x 0.9)/SV
Systemic vascular resistance index (SVRI)	<b>SVR = (Mean arterial pressure/cardiac index) x 80</b> Where cardiac index = $[\Pi \times (LVOT \text{ diameter}) / 2 \times LVOT \text{ VTI}] / BSA$

## 2. Deformational measures using 2D speckle tracking

Deformational Measure	Details
<b>Primary strain and strain rate measures</b>	
<b>Longitudinal*</b>	Average strain and strain rate values are measured from 12 myocardial segments in the apical 4 chamber and 2 chamber views <i>Measures: Average peak strain</i> <i>Average peak systolic strain rate</i>
<b>Circumferential*</b>	Average strain and strain rate values are measured from 6 myocardial segments in the parasternal short axis view at the mid-papillary LV level <i>Measures: Average peak strain</i> <i>Average peak systolic strain rate</i>
<b>Dyssynchrony</b>	
<b>Longitudinal</b>	Calculated as the standard deviation in time to peak (S or SR) using segmental data from 12 segments in the apical 4 and 2 chamber views <i>Measures: Standard deviation in time to peak strain</i> <i>Standard deviation in time to peak systolic strain rate</i>
<b>Circumferential</b>	Calculated as the standard deviation in time to peak (S or SR) using segmental data from 6 segments in parasternal short axis view at the LV base <i>Measures: Standard deviation in time to peak strain</i> <i>Standard deviation in time to peak systolic strain rate</i>

\*Segmental data will also be collected for all measures (strain, systolic strain rate)

## **VII. 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.

## **VIII. Identification and Reporting of Echocardiographic 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 an HCHS/SOL 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 HCHS/SOL Echocardiography Reading Center. All quantitative measures of cardiac structure and function will be performed off-site at the Echocardiography Reading Center, typically within 3-6 weeks of study performance. Reporting of findings to participants or site investigators may occur at multiple points:

### **A. Findings that Require Expedited Evaluation and Notification**

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 a) tamponade, b) aortic dissection, c) thrombosed or frankly dysfunctional prosthetic valve, d) pseudoaneurysm, e) intracardiac abscess or obvious vegetation, f) intracardiac thrombus. Site investigators are responsible for reviewing and acting on all 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. According to study protocol, each field center has a plan for handling these types of alerts. The Echocardiography Reading Center will also be informed to facilitate an expedited analysis of the study.
2. Over-reading 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 centers 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. As mentioned above, each field center has a plan for handling these types of alerts per study protocol, including relaying findings to study participant and, where consent has been provided, to the participant's treating provider.

### **B. Identification and Reporting of Non-Critical Abnormalities**

Over-reading 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.

### **C. Routine Reporting of Study Results to the HCHS-SOL Participants**

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). Routine reports are assembled at the Coordinating Center to incorporate all study results for a study participant. Such reports make reference to any "alert" values previously reported to a study participant (inclusive of the ones mentioned above).

Example of a Routine Reporting:

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	Sex	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		6.0-6.3	6.4-6.8	≥6.9
		Women		5.4-5.7	5.8-6.1	≥6.2
LV wall thickness (cm)	[VALUE]	Men		1.1-1.3	1.4-1.6	≥1.7
		Women		1.0-1.2	1.3-1.5	≥1.6

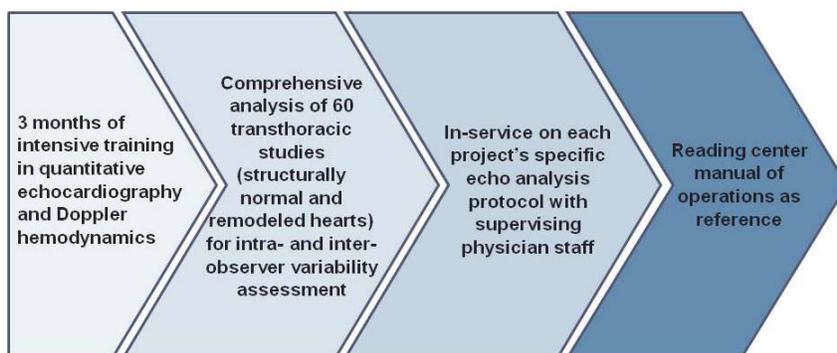
If specific triggered abnormalities were detected by the over-reading cardiologist (see above), additional text will be added as follows:  
**Template:** “Your echocardiogram displayed evidence of [moderate/severe] [xxx]. These findings should be discussed with your physician and follow-up studies may 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.”

**IX. CICL 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 CICL 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 HCHS/SOL 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.

**Echo Technician Training and Certification**



## X. Quality Assurance Plan

Variability in echocardiographic measurements arises from variability in image acquisition and, in large part, from variability in image analysis. Sonographer and technician training and certification as described above are key to minimize this variability but additional quantitative procedures are also necessary. The following quality control procedures are designed to establish the precision of key measures and to quantify and minimize variability in quantitative measures for the HCHS/SOL study. **Essential features include:**

Measure/Task*	Pilot Phase	During Visit 2	Reporting to Coordinating Center
Physician Over-reading	100% of pilot studies will be over-read by CICL staff cardiologists/ echocardiographers	100% of studies will be over-read by CICL staff cardiologists/ echocardiographers	Monthly
CICL technician intra-observer reproducibility	Duplicate blinded reads of 15 studies previously read by same technician	Repeat blinded reads of total of 240 studies per technician, at 20 studies per 3 month interval	Every 3 months
CICL technician inter-observer reproducibility	Duplicate blinded reads of 15 studies previously read by a different technician	Repeat blinded reads of total of 240 studies per technician, at 20 studies per 3 month interval	Every 3 months
CICL technician temporal drift		Duplicate blinded reads of the same 20 studies every 3 months	Every 3 months

\*Key measures will be assessed using the Bland-Altman method to compare repeated measures, reporting the coefficient of variation, bias, and limits of agreement.

### Field Center Sonographer Intra- and Inter-Observer Reproducibility

Echocardiograms at the 4 Field Centers will be performed by certified cardiac sonographers. Field Center sonographers will not be making any measurements. Variability related to image acquisition will primarily be related to image foreshortening, image quality, and Doppler sweep speed. These will be addressed during sonographer training/certification and through continuous CICL monitoring of all studies received according to the criteria outlined in the table in Section IV above entitled "Criteria for Evaluating Quality of Echocardiographic Images Received from Sites".

The Field Center will receive emailed quality feedback for echos submitted to the CICL. In situations where concerns arise regarding the quality of a study submitted by the Field Center, the sonographer and coordinator at the specific field center will receive additional quality feedback and recommendations from the CICL. This feedback will include technical instructions for quality improvement. The CICL may send email queries to the Field Center in cases where additional information or clarification is needed. Field Centers should respond to queries within 3 business days; the query will contain easy to follow instructions for the Field Centers on how to resolve the query. Field Centers should contact the Reading Center with questions related to queries received.

Depending on the results of ongoing quality review of sonographer images, the need for assessment of Field Center specific repeatability (i.e. intra- and inter-sonographer reproducibility) will be evaluated in collaboration with the HCHS/SOL Quality Committee. Potential need for Field Center reproducibility assessment would be focused on the following key measures: LV mass index, LV end-systolic and end-diastolic volume, LV EF, tissue Doppler peak early diastolic mitral annular velocity, left atrial volume index, and average longitudinal strain. More details regarding procedures for Field Center reproducibility assessment are available on request.

As seen in other large cohort studies, and in accordance with the CICL experience conducting echocardiographic studies in clinical trials and epidemiologic studies, the most important potential source of variability lies at the level of measurements performed at the Reading Center. Therefore, the CICL will prioritize maintaining standardized performance and minimizing reproducibility of measurements at the Reading Center, as further detailed below.

### Echocardiography Reading Center Staff Physician Over-Reading of Echocardiograms

All study echocardiograms will be over-read by board-certified cardiologists with advanced training in echocardiography. The purpose of physician over-reading is both to verify the appropriateness of key quantitative measures (LVEDV, LVESV, LVEF, LA volume, LVEDD, LV wall thickness, mitral regurgitation jet area, peak aortic transvalvular velocity, peak tricuspid regurgitation velocity) and to review studies for potentially clinically relevant abnormalities which may need to be communicated to participants and/or their physicians (as detailed in Section VIII above entitled "Identification and Reporting of Echocardiographic Findings to Field Center").

Over-reading of echocardiograms will be performed by board-certified cardiologists and echocardiographers who are Reading Center Co-Investigators (Drs Cheng, Mangion, Shah, Skali, and Wu). Over-reading will be performed for 100% of study echocardiograms and will be required prior to transfer of study data to Coordinating Center. Sign-off by the Echo Technicians performing quantitative measurements automatically moves studies to the worklist for the Cardiologist Over-Reader. Over-readers review all study images and must complete a pre-defined Over-Reading Form integrated into the CICL database, consisting of verification of the appropriateness of

key quantitative measures, qualitative grading of severity of select valvular lesions not quantitatively evaluated, and verification of the absence or specification of the presence of a critical abnormality as detailed in the Section VIII above entitled "Identification and Reporting of Echocardiographic Findings to Field Center". Once marked as verified by the Over-Reader, the study analysis is marked as complete and the analysis data are then available for transfer to the Coordinating Center.

### Echocardiography Reading Center Technician Intra- and Inter-Observer Reproducibility

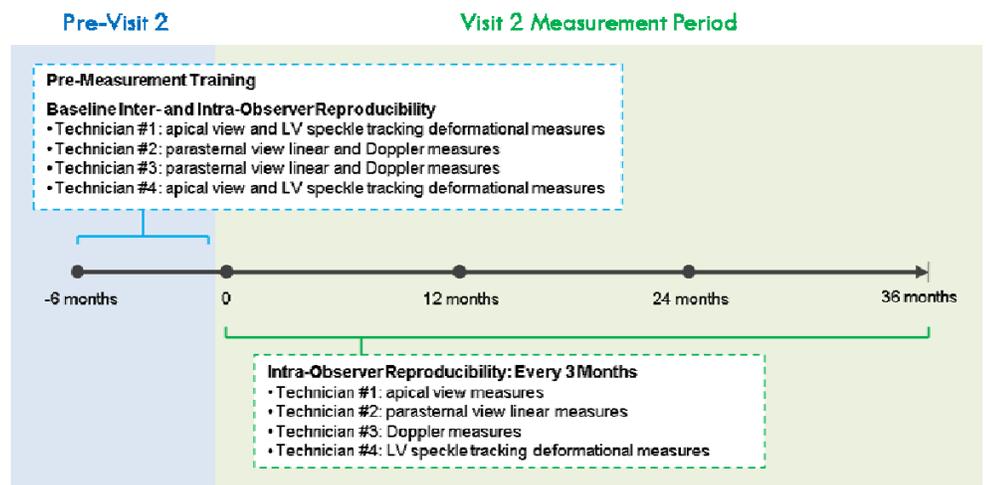
The Reading Center will employ a modular analysis model, whereby each Reading Center technician will be responsible for specific quantitative measures for each echocardiogram. As a result, each quantitative measure will be performed by a single technician for all Visit 2 echocardiograms, minimizing inter-observer variability. Thus, the focus of the Reading Center quality assurance procedures will be to quantify and minimize intra-observer variability and temporal drift. The purpose of the Reading Center quality assurance procedures is 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.

For the assessment of intra-observer variability, the primary study technician repeats study analysis in a blinded fashion. Each technician performs duplicate blind re-reads of approximately 40 studies every 3 months. For the assessment of inter-observer 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 are randomly selected from each 3 month period for re-analysis.

Technicians are blinded to original study ID. Inter-observer variability will be documented prior to any transitions in technicians performing measurements.

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 3month 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.

Based on the CICL experience from the ARIC visit 5 echocardiographic reproducibility data, we have established that the above described approach is feasible and reliable. We have performed repeat measurement analyses for each of the 4 CICL technicians to assess inter-reader reproducibility at baseline and to regularly monitor intra-reader reproducibility per technician (each assigned to a single set of echo measures) over the course of the measurement period. Our results to date, including reproducibility results from recently completed large cohort studies, have not identified any clinically significant systematic bias.



Reproducibility of Echocardiographic Measurements in ARIC				
	Inter-Reader Variability		Intra-Reader Variability	
	r	CV, %	r	CV, %
<b>Conventional Measures</b>				
End-diastolic volume, ml	0.95	11.3	0.98	8.1
End-systolic volume, ml	0.98	13.7	0.99	12.5
Ejection fraction, %	0.95	7.2	0.93	8.7
End-diastolic diameter, cm	0.97	3.9	0.97	4.3
End-systolic diameter, cm	0.96	8.8	0.97	8.2
Posterior wall thickness, cm	0.88	9.8	0.95	6.7
<b>Tissue Doppler Measures</b>				
E wave, cm/s	0.98	3.1	0.98	3.3
Tissue Doppler E', cm/s	0.98	5.5	0.98	5.8
E/E' ratio	0.98	8.7	0.99	4.2
<b>Deformational Measures</b>				
Longitudinal strain, %	0.91	10	0.87	8
Circumferential strain, %	0.90	11	0.93	6

r, correlation coefficient; CV, coefficient of variation

### **Documentation and Reporting of QA Assessments**

In collaboration with the HCS/SOL Quality Committee and Coordinating Center, the CICL will aim to provide data regarding quality of image acquisition from each Field Center by month 6 of the Visit 2 period. Data on *intra-observer variability* for key echocardiographic measures will be reported to the Coordinating Center every 3-4 months or as agreed with HCHS/SOL steering committee and Coordinating Center. Data regarding *temporal drift* will be reported to the Coordinating Center every 3-4 months or as agreed with HCHS/SOL steering committee and Coordinating Center. Reproducibility results will be reported primarily as the coefficient of variation, bias, and limits of agreement.

**Pilot Test Results** – The CICL will provide a written evaluation of the pilot testing performed prior to Visit 2. Results will include feedback regarding: (1) timeliness of study transfer to CICL from Field Centers; (2) source of and potential solutions to any technical difficulties encountered in transmitting studies to the CICL; (3) completeness and accuracy of information provided to the CICL by Field Centers on the Echocardiogram Tracking Form; (4) overall protocol study quality determined by image quality, presence/no. of missing views, and no. of quantitative measures limited by image quality.