

CARRS Cohort:
Proposed Measures
[Precision-CARRS]

MANUAL OF OPERATIONS:
ECHOCARDIOGRAPHY

INTRODUCTION

Echocardiography: HF prevalence is expected to increase due to population aging, higher burden of associated comorbidities, and increasing prevalence of HF with preserved Ejection Fraction (HFpEF).¹

Expected prevalence of HFpEF and HFrEF: HF can be **clinically staged** into categories:

A (asymptomatic with HF risk factors: hypertension, T2D, obesity, metabolic syndrome, atherosclerotic disease or ESRD, but no cardiac structural or functional abnormalities),

B (asymptomatic with structural abnormalities, defined as LV hypertrophy, dilation or dysfunction, or significant valvular disease),

C1/C2 (clinical HF without/with prior hospitalization),

D (progressive and/or persistent severe signs and symptoms of HF despite therapy).

The prevalence of stage B HF increases from 7.8/100 patient-years in individuals aged ≥ 45 years with no HF risk factors² to 24% prevalence in the Framingham Heart Study (mean age 51 years), increasing with age to 38% in subjects between aged 65-75 years.³ Incorporation of diastolic dysfunction into the Stage B definition reclassified 14% of the sample from Stage A to B (overall Stage B prevalence 38%) and provided incremental prognostic information.⁴ South Asians appear to develop HFpEF at younger age and leaner BMI than Whites,⁵ and have higher in-hospital mortality.^{6, 7} There are few reliable population-based HF estimates in India.⁸⁻¹⁰ Data from South Asian migrants to the UK showed HF at younger ages, worse diastolic function, a 3-fold higher LV hypertrophy (LVH) with a greater degree of concentric remodeling compared to Whites.^{11, 12}

Equipment: Philips Epiq 7 in Delhi and Philips Affiniti 50C in Chennai with cardiac probes.

Duration of testing: 30 minutes.

Technique: 2D echocardiograms will be performed according to American Society of Echocardiography guidelines¹³ in dedicated laboratories at AIIMS and Westminster (Chennai) by a team of trained experts. The echocardiograms will be sent to AIIMS and read in the core laboratory by Dr. Dr. Raghav Bansal. We will estimate: 1) **LV ejection fraction** (LVEF) using the modified Simpson's rule; 2) **LV dimensions** and wall thickness from the parasternal long-axis view; 3) **LV mass** by the linear method, indexed to body surface area as appropriate using Devereux's formula;¹⁴ 4) **LV diastolic function** using pulsed-wave doppler of mitral inflow (E and A velocities and E/A ratio) and peak septal and lateral mitral annular relaxation tissue Doppler velocities (e'); peak values of mitral E- and A-wave velocities and E/A ratios, A-wave duration (A_{dur}), and deceleration time of the E-wave (DT). In addition, tissue doppler imaging of the mitral annulus will be obtained in the apical four-chamber view and the early diastolic peak velocity (E') recorded; 5) **Left atrial volume** will be measured. **Staging: LV systolic dysfunction** will be defined as LVEF $< 50\%$, LV end-diastolic internal dimension index > 3.2 cm/m² or LV end-diastolic volume index > 102 mL/m².¹⁵ **Diastolic dysfunction** will be categorized as mild, defined as impaired relaxation without evidence of increased filling

pressures ($E/A \leq 0.75$, $\Delta E/A < 0.5$, $E/E' < 10$, $S > D$, $AR_{dur} < A_{dur}$); moderate, defined as impaired relaxation with moderate elevation of filling pressures or pseudo-normal filling ($E/A > 0.75$ to < 1.50 ; $DT > 140$ ms, $\Delta E/A \geq 0.5$, $E/E' \geq 10$, $S < D$ or $AR_{dur} > A_{dur} + 30$ ms); or severe, defined as advanced reduction in compliance or restrictive filling ($E/A > 1.5$, $DT < 140$ ms, $\Delta E/A \geq 0.5$ (reversible) or < 0.5 (fixed), $E/E' \geq 10$, $S < D$ or $AR_{dur} > A_{dur} + 30$ ms), as described previously.¹⁶

Reproducibility: We have already performed echocardiograms and CAC studies at both sites in 30 participants to establish a uniform protocol and have started analysis at the Core lab in AllMS. During the first 3 months of the grant period, we will finalize the protocols by re-establishing reproducibility and inter- and intra-observer variability between the two sites, as well as an over-read in 5% of scans at Emory University.

Manual of Operations: Detailed MOPs will be adapted from the enclosed ARIC protocol.

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Atherosclerosis Risk in the Communities Study

ARIC cohort – Visit 5

FINAL Echocardiography Reading Center Manual of Operations

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CONFIDENTIALITY STATEMENT:

The information contained in this document, especially any unpublished material, is the property of Brigham and Women's Hospital Echo Core Lab and is therefore provided to you in confidence as a member of the above-referenced study staff.

It is understood that this information will not be disclosed to others without written authorization from Scott D. Solomon, MD, Director of the Cardiac Imaging Core Lab.

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I. Introduction

The NHLBI Atherosclerosis Risk in the Communities (ARIC) study was initiated in 1985 and follows approximately 13,000 individuals in four U.S. communities for trends in incidence and mortality of coronary heart disease. Subjects are now in their seventh to ninth decade of life, a period of life during which the prevalence of heart failure and other cardiovascular morbid conditions increases dramatically. Over 9,000 participants expected in Visit 5 will undergo an echocardiographic examination. This represents a unique opportunity to investigate perturbations in cardiac structure and function across the spectrum of HF (stages A, B, and C) and their relationship to clinical outcomes.

The Brigham and Women's Hospital CICL will serve as the Echocardiography Reading Center for ARIC Visit 5. 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

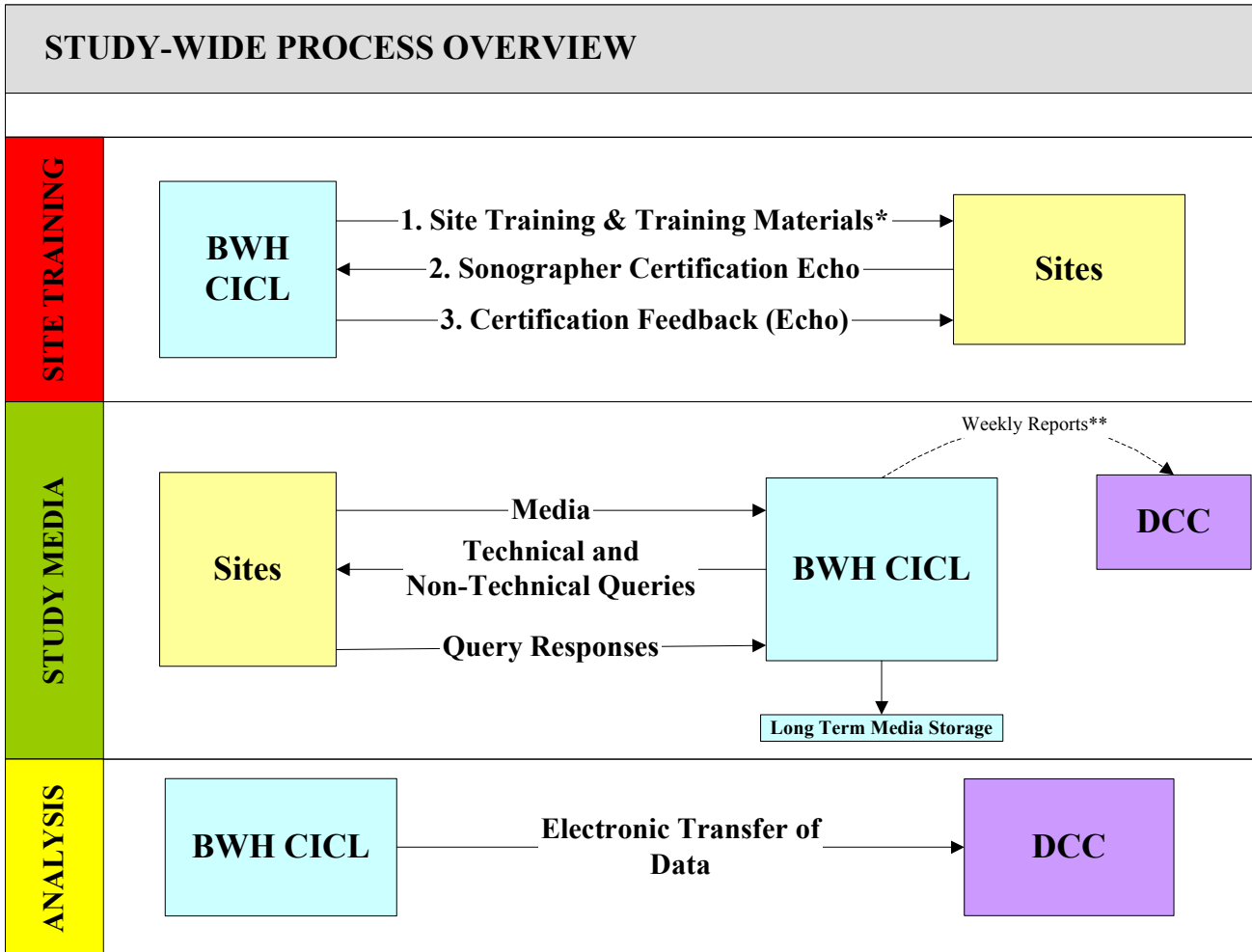
II. Overall Study Aims and Processes

OBJECTIVES	Echocardiography	<ul style="list-style-type: none"> The objective of the ARIC Visit 5 Echocardiography study is to describe and quantify perturbations in cardiac size and function across the spectrum of heart failure stages in the ARIC cohort. 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.
	Cardiac Imaging Core Lab	<ul style="list-style-type: none"> To provide high quality reproducible quantitative analysis of study echocardiograms
	Site Instruction Manual	<ul style="list-style-type: none"> To instruct field centers on how to perform and send study echos to the Cardiac Imaging Core Lab (CICL).

ROLES AND RESPONSIBILITIES	Field Centers	<ul style="list-style-type: none"> Perform high-quality study echocardiograms per the protocol contained in this document
	ARIC Coordinating Center	<ul style="list-style-type: none"> Ensure that the CICL stays informed of study-wide changes and updates as the study progresses. Serve as the primary liaison between the CICL 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	<ul style="list-style-type: none"> 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.

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

A. Brachial Blood pressure		◆ Ensure that BP obtained within 30 min of the echo examination
B. Parasternal Position		
<input checked="" type="checkbox"/> <i>Parasternal long axis</i>		<ul style="list-style-type: none"> ◆ 2D imaging (at deep depth) ◆ 2D imaging (at shallow depth) ◆ Color Doppler of the mitral and aortic valves
<input checked="" type="checkbox"/> <i>Parasternal short axis – Aortic valve level</i>		<ul style="list-style-type: none"> ◆ 2D imaging of AV ◆ Color Doppler of AV ◆ 2D imaging of right ventricular outflow tract ◆ Color Doppler of right ventricular outflow tract ◆ PW and CW Doppler of the RVOT
<input checked="" type="checkbox"/> <i>Parasternal short axis – Mitral valve level</i>		<ul style="list-style-type: none"> ◆ 2D imaging
<input checked="" type="checkbox"/> <i>Parasternal short axis – Papillary muscle level</i>		<ul style="list-style-type: none"> ◆ 2D imaging ◆ M-mode
<input checked="" type="checkbox"/> <i>Parasternal short axis – LV apex</i>		<ul style="list-style-type: none"> ◆ 2D imaging
C. Apical Position		
<input checked="" type="checkbox"/> <i>Apical 4 chamber view</i>		<ul style="list-style-type: none"> ◆ 2D imaging ◆ 2D imaging, focused/zoomed on LV ◆ 2D imaging, focused on LA ◆ Color Doppler of mitral valve/LA ◆ PW Doppler of mitral flow ◆ TDI of septal and lateral mitral annulus ◆ iRotate to 2-chamber view (2D imaging) ◆ iRotate to 3-chamber view (2d imaging) ◆ 3D full volume acquisition of LV ◆ 3D full volume acquisition of RV
<input checked="" type="checkbox"/> <i>Apical 4 chamber – focused on the RV</i>		<ul style="list-style-type: none"> ◆ 2D imaging ◆ Color Doppler of tricuspid valve/RA ◆ CW Doppler of tricuspid regurgitation ◆ TDI of lateral tricuspid annulus
<input checked="" type="checkbox"/> <i>Apical 5 chamber view</i>		<ul style="list-style-type: none"> ◆ 2D imaging ◆ Color Doppler of left ventricular outflow tract ◆ Pulse wave of LVOT flow ◆ CW of transaortic flow
<input checked="" type="checkbox"/> <i>Apical 2 chamber view</i>		<ul style="list-style-type: none"> ◆ 2D imaging focused/zoomed on LV ◆ 2D imaging focused on LA ◆ Color Doppler MV/LA
<input checked="" type="checkbox"/> <i>Apical 3 chamber view</i>		<ul style="list-style-type: none"> ◆ 2D imaging
D. Subcostal View		
<input checked="" type="checkbox"/> <i>Inferior vena cava</i>		<ul style="list-style-type: none"> ◆ 2D imaging (5 second acquisition)

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 5, a centralized training session will be held for all Field Center sonographers who will be performing echocardiograms for the ARIC 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 5 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.

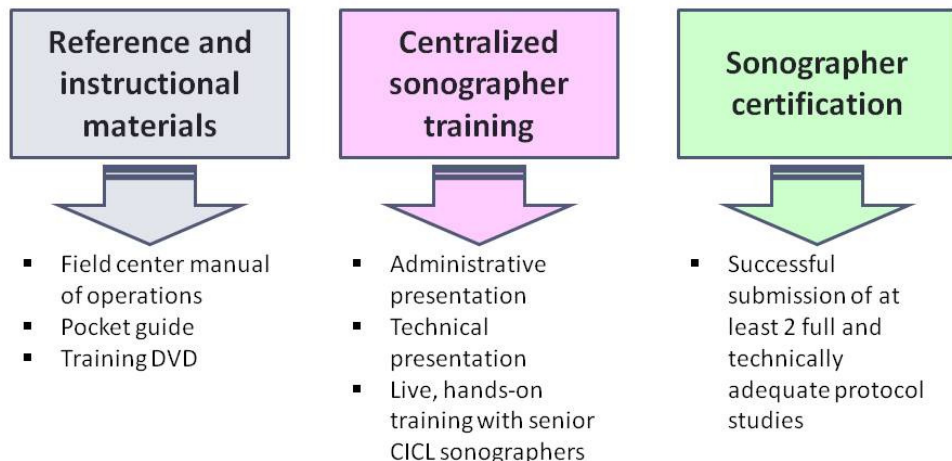
Reference materials at the Field Centers – Prior to and during the Visit 5 period, the Reading Center will provide the following reference materials for Field Center sonographers. These will also be available online via the CICL secure website.

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

Training DVD demonstrating a full ARIC 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 sending echocardiograms to the CICL.

Monitoring and feedback – During the Visit 5 period, CICL technical staff will continuously monitor the adequacy and quality of all studies received. Feedback regarding adequacy of each study received, including an itemized list of study deficits if deemed inadequate, are sent to the Field Center following analysis. If a study is deemed to be insufficiently performed, a request via the feedback form will be made to repeat the study if possible. A pattern of inadequate or poor quality studies will prompt directed discussion by CICL staff with the Field Center and/or sonographer and, possibly, retraining.



Sonographer Certification

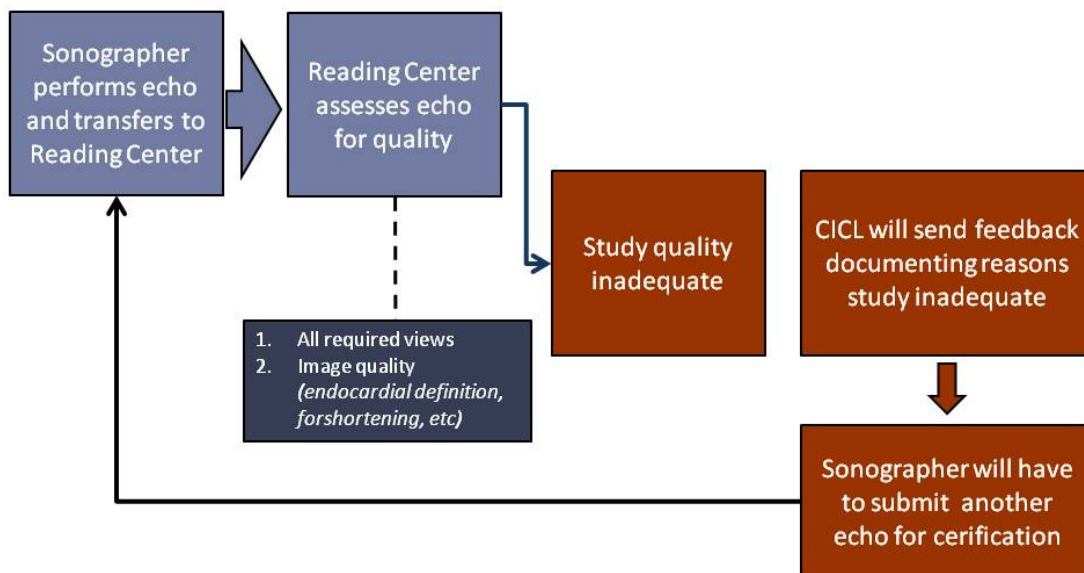
The purpose of certification is to ensure consistency in how echocardiograms are performed study-wide and to ensure performance of the highest quality echocardiograms. Any sonographer who will be performing study echocardiograms must first submit two certification studies performed in accordance with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



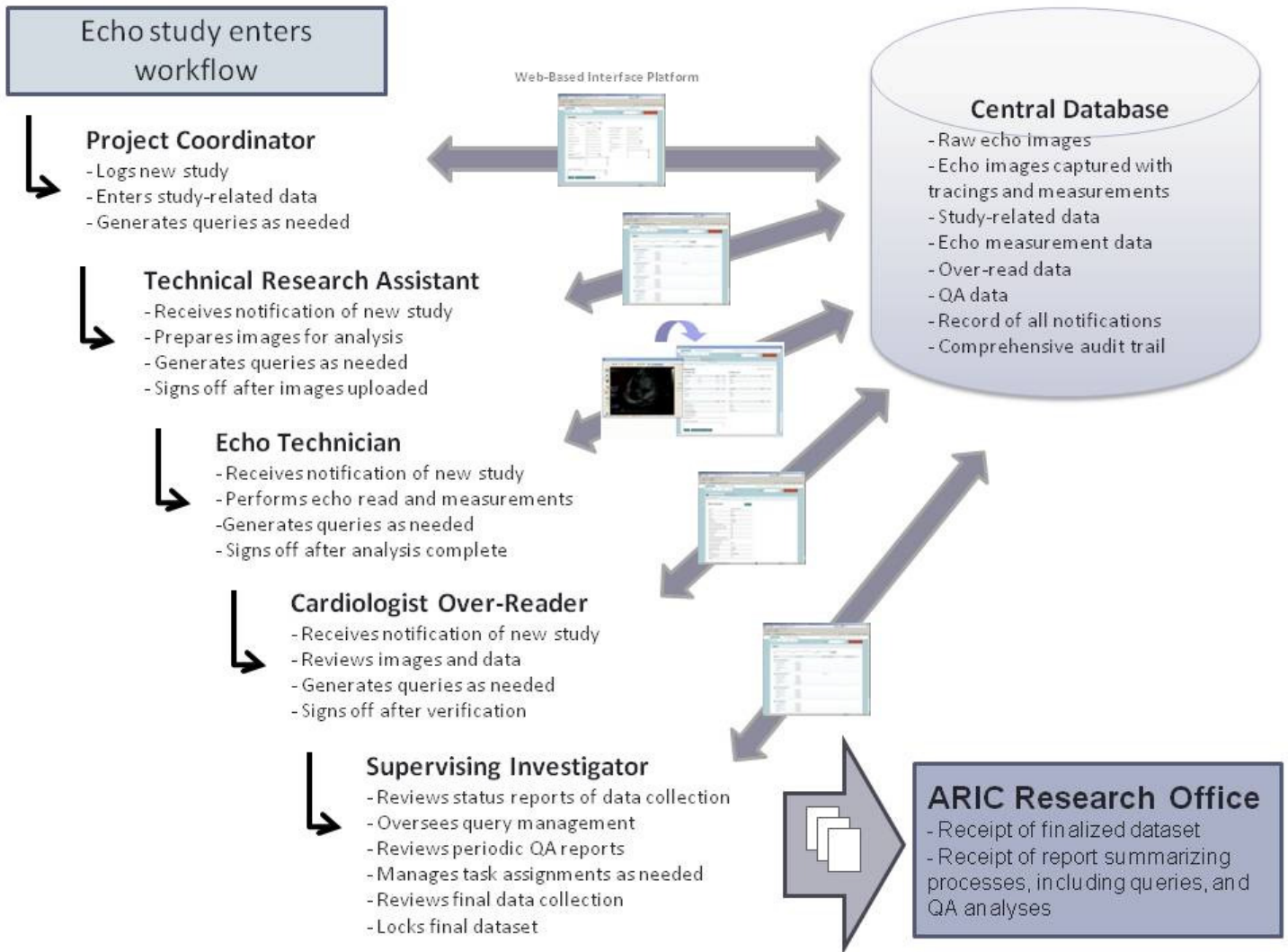
V. CICL Data Management Processes

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

The CICL 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 CICL 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 CICL 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 CICL. 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.



VI. Echo Reading Center Measurements

1. Assessment of Global Left Ventricular Size and Function

From the parasternal long or short axis view/M-Mode 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) [LVIDd]
- End-systolic left ventricular diameter (cm) [LVIDs]
- Interventricular septum thickness [ASWT]
- Posterior wall thickness [PWT]

Apical 4 Chamber View

- End diastolic volume (ml)
- End systolic volume (ml)

Apical 2 Chamber View

- End diastolic volume (ml)
- End systolic volume (ml)

Derived Measurements

- Ejection fraction (%) = $100 * (LVEDV - LVESV) / LVEDV$
- LV mass (g) = $0.8 * \{1.04 * [(LVIDd + IVSTd + PWTd)^3 - (LVIDd)^3]\} + 0.6$
- LV relative wall thickness = $(2 * PWT) / LVIDd$
- Mean LV wall thickness (cm) = $(PWT + ASWT) / 2$

2. Assessment of Left Ventricular Diastolic function:

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. In situations where the A wave merges with the E wave, deceleration time will be measured as the extrapolation of the E wave slope 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.

Peak tricuspid regurgitation velocity will be measured using continuous wave Doppler through the tricuspid valve.

Apical 4 Chamber View

Mitral Inflow Doppler at the tips of the mitral leaflets

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

Tissue Doppler Imaging

- Lateral early diastolic myocardial velocity ($E_{m \text{ lateral}}$)
- Lateral late diastolic myocardial velocity ($A_{m \text{ lateral}}$)
- Lateral systolic myocardial velocity ($S_{m \text{ lateral}}$)
- Septal early diastolic myocardial velocity ($E_{m \text{ septal}}$)
- Septal late diastolic myocardial velocity ($A_{m \text{ septal}}$)
- Septal systolic myocardial velocity ($S_{m \text{ septal}}$)

Tricuspid Regurgitation Doppler (Continuous Wave)

- Peak tricuspid regurgitation velocity (m/sec)

Derived Variables:

1. E/A ratio
2. $E/E_{m \text{ lateral}}$ ratio

3. Assessment of Left Atrial Size

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. LA volumes will be determined at mitral valve opening using the Simpson's method of discs.

Parasternal long axis view

- Maximal left atrial diameter (cm)

Apical 4 Chamber View

- 4-Chamber Left atrial volume at mitral valve opening (ml)

Apical 2 Chamber View

- 4-Chamber Left atrial volume at mitral valve opening (ml)

Derived Variable:

- LA volume index (ml/m^2) = LA volume/BSA

4. Assessment of Mitral Regurgitation

From the apical 4-chamber view, the borders of the mitral regurgitation color Doppler profile at its maximal extent during systole will be traced.

Apical 4 Chamber View

- Mitral regurgitation jet area (cm^2)

Derived Variable:

- MR jet area (cm^2)/ Left atrial area (cm^2)*100

5. Assessment of Aortic Stenosis

From the apical 5-chamber view, peak velocity and the velocity time integral will be measured from the pulsed wave Doppler of the left ventricular outflow tract and continuous wave Doppler through the aortic valve.

Apical 5 Chamber View

- LVOT peak velocity (m/sec)
- LVOT VTI (cm)
- AV peak velocity (m/sec)
- AV VTI (cm)

Machine Derived Variable:

- Peak and mean transaortic gradient (mmHg)

6. Assessment of Global Right Ventricular Function

From the apical 4-chamber view focused on the right ventricle, the endocardial borders will be traced in both end-diastole and end-systole to obtain right ventricular areas.

From the apical 4-chamber view TDI of the lateral tricuspid annulus, peak systolic velocity (S'_{TA}) will be measured.

Apical 4 Chamber View

- RV end diastolic area (cm²) [RVEDA]
- RV end systolic area (cm²) [RVESA]

Tissue Doppler Imaging

- Lateral systolic myocardial velocity (S'_{TA})

Derived Measurements

- RV fractional area change (unitless) = (RVEDA – RVESA)/RVEDA

7. Assessment of Pulmonary Vasculature

From the apical 4-chamber view, the peak tricuspid regurgitation velocity by continuous wave spectral Doppler will be measured.

From the parasternal short axis view at the level of the aortic valve, velocity time integral of the right ventricular outflow tract will be measured from pulsed wave Doppler of the RVOT.

Apical 4 Chamber View

Continuous wave Doppler

- Peak tricuspid regurgitation velocity

Derived Measurements

- RV fractional area change (unitless) = $(RVEDA - RVESA)/RVEDA$

Parasternal Short Axis View at the Level of the Aortic Valve

Pulsed wave Doppler

- RVOT VTI

Derived Measurements

- Peak RV-RA gradient (mmHg) = $4 * (\text{peak TR velocity})^2$
- Pulmonary Vascular Resistance (Wood Units) = $0.1618 + 10.006 * (\text{peak TR velocity}/\text{RVOT VTI})$

7. 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

Derived Measurements

- Arterial elastance (E_A) where $(E_A) = (SBP \times 0.9)/SV$
- LV end-systolic elastance (E_{ES}) where

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

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 $t_{Nd} = R \rightarrow \text{onset}/R \rightarrow \text{end}$

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

- EA/EES

8. Assessment of Left Ventricular Deformation

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 radial strain
- Standard deviation in time to peak radial strain (msec)
- 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)

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. 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 an ARIC 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 ARIC 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 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. 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 section X. (Study Results Reporting Schedule) of this document.

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]		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 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.

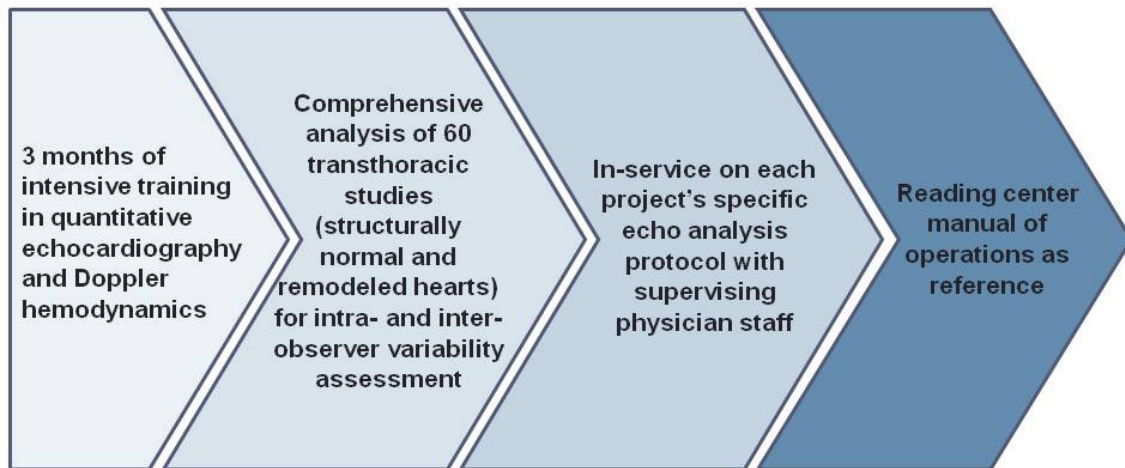
Example:

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.

IX. CICAL 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 CICAL 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 ARIC 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

Field Center sonographer intra- and interobserver reproducibility

Purpose: To establish the precision (repeatability) of 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.

Procedure: Volunteers at each Field Center will undergo repeat echocardiography, preferably by the same sonographer, using the same echocardiographic machine during the visit 5 period (as part of ARIC visit 5 study-wide reproducibility assessment). The same CICL technician will analyze the echo in a blinded fashion. Precision of the above key measures will be assessed for the overall study and by Field Center using the Bland-Altman method to compare repeated measures. The coefficient of variation will be reported and is calculated as the standard deviation in the difference between the 2 repeat measures divided by the mean measurement. A measure of bias defined as the mean difference between the two measures will also be reported as will the limits of agreement (defined as the standard deviation of the mean difference).

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 Visit 5 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 intraobserver 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.