**EchoGPS Pivotal Study**

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List of Abbreviations and Terminologies

**ACEP** American College of Emergency Physicians image quality scale

**AP2** Apical 2-Chamber View

**AP3** Apical 3-Chamber View

**AP4** Apical 4-Chamber View

**AP5** Apical 5-Chamber View

**AS** Aortic stenosis

**AVA** Aortic Valve Area

**BMI** Body Mass Index

**BPS** Biplane Simpson

**Control Exam** TTE examination using the Reference Device, Terason system, by a

trained sonographer without EchoGPS guidance

**EchoGPS** Image acquisition assistance software integrated in Terason uSmart 3200t, an FDA 510(k)-cleared ultrasound machine. This is investigational use-only software to be examined in this study, produced by Bay Labs, Inc.

**LV** Left ventricle

**MHI** Minneapolis Heart Institute

**NM** Northwestern Medicine

**PLAX** Parasternal Long-Axis View

**PSAX-AV** Parasternal Short-Axis at the Aortic Valve View

**PSAX-MV** Parasternal Short-Axis at the Mitral Valve View

**PSAX-PM** Parasternal Short-Axis at the Papillary Muscle View

**Study Device** Bay Labs EchoGPS software interfaced with the Terason uSmart 510(k)-cleared, commercially available ultrasound

**Reference Device** Terason uSmart 3200t, an FDA 510(k)-cleared ultrasound imaging device will be used as the Reference Device.

**Reference Scan** TTE examination by a registered sonographer using the reference device

**RN** Registered Nurse

**RV** Right ventricle

**Study Scan** TTE examination by a Registered Nurse (RN) using the

Study device

**SubC4** Subcostal 4-Chamber View

**SubC-IVC** Subcostal Inferior Vena Cava View

**TTE** Transthoracic echocardiogram

Study Summary

|  |  |
| --- | --- |
| **Title** | Study for Point-of-Care Echocardiography with Assistance Technology |
| **Methodology** | Establish TTE exams performed with Bay Labs EchoGPS assistance technology can be used by registered nurses (RNs) compared to findings from a commercially available, FDA 510(k)-cleared reference device (Terason uSmart 3200t, point-of-care ultrasound) without EchoGPS assistance technology by trained sonographers in patients referred for a clinical echocardiographic examination. |
| **Study Duration** | 2 months |
| **Study Center(s)** | Northwestern Medicine, Bluhm Cardiovascular Institute, 201 East Huron Street, Chicago, IL 60611  Minneapolis Heart Institite, 920 East 28th street, Minneapolis, MN 55407 |
| **Study Objectives** | To validate clinical use of EchoGPS software by registered nurses (RNs) with no prior scanning experience to acquired limited (10-view) two-dimensional point-of-care echocardiograms. |
| **Study Device** | Bay Labs EchoGPS software interfaced with the Terason uSmart 510(k)-cleared, commercially available ultrasound |
| **Study Subject Population** | Patients who are indicated for an echocardiographic examination. |
| **Study User Population** | Registered Nurses (RNs) with no prior ultrasound scanning experience |
| **Clinical Setting** | Echocardiography Lab |
| **Study Design** | This is an open study in patients with an indication for a standard echocardiographic examination. The patients will first be scanned by a RN, and 10 views will be obtained.  PLAX, PSAX-AV, PSAX-PM, PSAX MV, AP4, AP5, AP2, AP3, SubC4, SC-IVC  Following this examination, the patients will be scanned by a trained sonographer, and the same 10 views will be obtained (reference scan) using the same Terason ultrasound machine. The patient will then undergo their indicated echocardiographic examination. |
| **Number of Subjects** | 210 |
| **Number of Users** | 6 RN’s, 3 at each site |
| **Main Inclusion/ Exclusion Criteria** | Inclusion Criteria  All participants must meet the following inclusion criteria to participate in the study:   * Patients indicated for an echocardiographic examination * Patients ≥18 years old   Exclusion Criteria  Patients must NOT meet any of the following exclusion criteria to participate in the trial:   * Unable to lie flat for study * Patients experiencing a known or suspected acute cardiac event * Patients with severe chest wall abnormalities * Patients who have undergone pneumonectomy * Patients unwilling or unable to give written informed consent |
| **Primary Endpoints** | Primary Endpoints: Standalone Patient-Level Clinical Parameter Assessment   |  |  |  | | --- | --- | --- | | **Clinical Parameter** | **Performance Goal** | **Null Hypothesis** | | Qualitative Left Ventricular Size | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% | | Qualitative Left Ventricular Global Function | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% | | Qualitative Right Ventricular Size | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% | | Pericardial Effusion | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% | |
| **Descriptive Statistics** | Additional Patient-Level Clinical Parameters:   * Qualitative assessment of IVC size * Qualitative assessment of Right Ventricular function * Qualitative assessment of Left Atrial) size * Qualitative assessment of aortic valve, mitral valve, and tricuspid valve   View-level Results: % of patient studies with diagnostic (ACEP 3+) quality clip for each of the ten (10) Standard Views used in the study  Subgroup Analyses: Results per BMI group, sex, age, number of scans completed, etc.  Reference Scan: View-Level and Patient-Level results; paired comparison to non-specialist results |
| **Grading Methodology** | Overall: Five (5) expert cardiologist readers will independently provide assessments and they will be blinded to each other’s assessments. The median vote of the five (5) readers will be used to establish ground truth.  Patient-Level Primary Endpoints: For each clinical parameter, each reader will provide a Yes/No (i.e., binary assessment) for whether the patient study in its totality provides sufficient information to assess the clinical parameter.  Descriptive View-Level Results for diagnostic quality: Each reader will score each clip using the 1-5 ACEP scale. |
| **Statistical Analysis Plan** | The target probabilities of a Type I error and Type II error are 0.05 and 0.1 respectively. |

# Introduction

This document is a clinical research protocol describing a study to collect echocardiogram imagery using a device that has guidance assistance technology. The study will be conducted in accordance with the protocol, Good Clinical Practice Standards, and applicable regulatory requirements. The collected data may result in FDA clearance of EchoGPS guidance technology to guide a novice user to acquire echocardiograms.

## Background

The transthoracic echocardiogram (TTE) is a widely used diagnostic tool in the assessment of cardiovascular disease. TTE is a form of ultrasound imaging directed at the assessment of cardiac function and structure. Despite the prevalence of TTE, the technique is often cited as lacking reproducibility and quality (Johri *et al*., 2011; Pearlman & Gardin, 2011; Martin, 2011). This variability is partly due to the inherent operator dependence of ultrasound imaging. Lack of quality and reproducibility are attributes that hinder the beneficial adoption of point-of-care echocardiograms.

Seeking to address this problem, Bay Labs, Inc. has developed the EchoGPS software, which enables medical professionals across a broad range of medical training and experience to optimize acquisition of echocardiograms (cardiac ultrasound). EchoGPS software provides real-time user guidance during acquisition of echocardiography to assist the user in obtaining anatomically correct images that represent standard 2D (i.e., B-mode) echocardiographic diagnostic views (i.e. apical four chamber view) from corresponding windows (i.e., apical window).

The core technology behind the real-time user guidance in EchoGPS is a software algorithm developed using Deep Learning, which is a form of machine learning based on artificial neural networks (ANNs).

In this study an echocardiogram protocol using the EchoGPS interface with the Terason uSmart 3200t, an FDA 510(k)-cleared, commercially available ultrasound device will be performed.

The objective of the proposed clinical investigation is to establish the effectiveness of the Bay Labs, Inc. EchoGPS software in enabling non-specialists to acquire echocardiograms.

Participants will be scanned by a registered nurse (RN) using the Terason uSmart 3200t with EchoGPS (study exam). Participants will then be scanned by a registered sonographer using the Reference Device without EchoGPS guidance (reference exam), under the same protocol. These scans are expected to add relatively little burden to the subject (estimated to be less than 1 hour for both scans). For training purposes up to 24 volunteers will be scanned by the RN using the Terason uSmart 3200t with EchoGPS software.

## Study Software/Interface

The study software is called Bay Labs EchoGPS.

EchoGPS software provides real-time user guidance during acquisition of echocardiography to assist the user in obtaining anatomically correct images that represent standard 2D (i.e., B-mode) echocardiographic diagnostic views (i.e. apical four chamber view) from corresponding windows (i.e., apical window).

The core technology behind the real-time user guidance in EchoGPS is a software algorithm developed using Deep Learning, which is a form of machine learning based on artificial neural networks (ANNs).

**Guidance Meter:** The real-time feedback from the EchoGPS Guidance Meter emulates how an experienced sonographer evaluates in real-time the diagnostic quality of the image as they manipulate the transducer in position, orientation, and rotation.

The Guidance Meter provides dynamic feedback on the correctness and quality of the image for a particular view. The more the Guidance Meter is filled, the closer the ultrasound probe is to the ideal position to acquire a diagnostic quality image. Please see “Feature Learning and Supervised Training” section below for more information on the development of this algorithm.

The two triangular shaped notches towards the top of the meter represent a threshold for a diagnostic-quality image. If the meter reaches this level, the bar turns blue and EchoGPS will automatically record and save a clip.



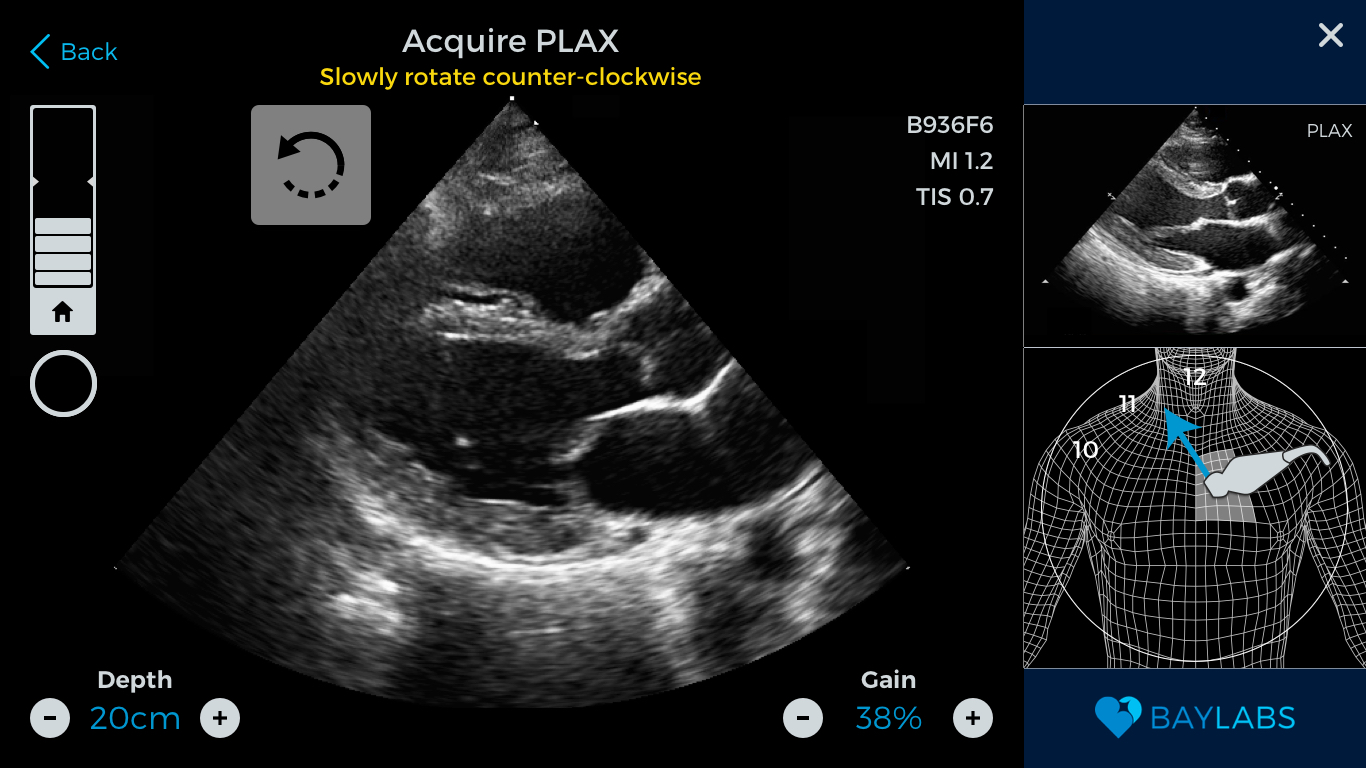
**Figure 1: Examples of Guidance Meter outputs (*left to right*: low, medium, and high diagnostic quality image)**

**Prescriptive Guidance:** The prescriptive guidance in EchoGPS emulates how a sonographer looks at an image and determines the necessary probe movement to obtain a more optimal image.

When acquiring an echocardiogram, the image that a user sees is a function of the position and orientation of the probe. Subtle movements of the probe in any geometric dimension can lead to a significantly different image. In many patient subjects, these subtle movements are necessary to acquire a diagnostic quality image. Sonographers build an intuition, through extensive training and experience, around seeing an image and recognizing what movements to make to optimize the image they are acquiring - they use their knowledge of the spatial relationships between structures to inform the movements they make. In contrast, given their lack of training and experience, new users find it difficult to know what movements to make to optimize an image.

We have trained prescriptive guidance algorithms to emulate the intuition of sonographers - similar to how a sonographer can look at an image and know what movement to make to optimize the image, the prescriptive guidance algorithm analyzes an image and based on structural spatial relationships recognizes what movement needs to be made to optimize the image so that the necessary structures are visible and clinically diagnostic. When a user is scanning with the EchoGPS software, the prescriptive guidance algorithms provide them with dynamic instructions on how to move the probe to improve the quality of the image and to acquire a diagnostic quality image. These real-time instructions update based on the current image generated by the user’s probe position and orientation. Examples of these instructions include “rotate the probe counter-clockwise” or “fan the probe’s beam up.”

Lastly, sequential instructions are provided as the operator progresses through a standard series of views. After acquisition of the first or ‘home’ views (e.g., apical four chamber view, AP4, from the apical window) instructions are provided in reference to the home view (AP4) and anatomy. For example, for AP2: “From ‘home base’ AP4, rotate ↺ ~60° slowly. Indicator toward patient's neck, keep probe tail down.”



**Figure 2: Example of Prescriptive Guidance**

**Auto-capture Feature:** The EchoGPS auto-capture feature emulates how a sonographer knows when an image is of sufficient quality to be diagnostic and records it.

During an exam, an automated image clip may be recorded when a particular view meets the desired quality level, i.e. “above threshold”. For non-specialist users, this feature reduces the cognitive burden of needing to know when an image is of diagnostic quality. For all users, including registered sonographers, this feature assists the user by enabling them to not have to take their hand off the ultrasound transducer or pressing any buttons to move on to the next view.



**Figure 3: Reaching a Diagnostic-Quality PLAX view**

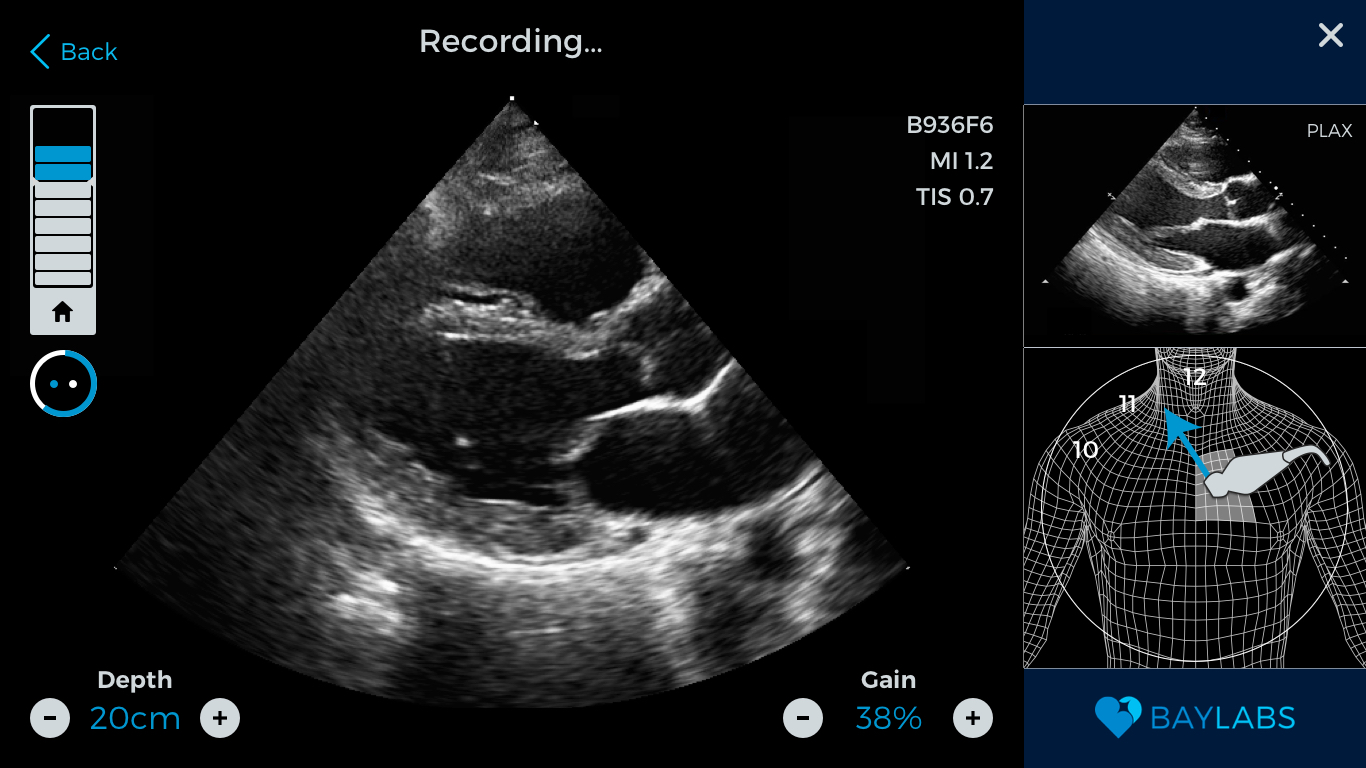
**Save Best Clip and Continue Feature:** This feature emulates a sonographer returning to the best image they can find in the event they are unable to acquire a better-quality image after further searching.

If the Guidance Meter is not reaching the threshold for automated capture, and a certain amount of time (i.e., 2 minutes) has elapsed, the user will be prompted by a message on the screen to “Save Best Clip and Continue.” When the user chooses to "Save the Best Clip and Continue," the system will save the 31 continuous frames (i.e., ~2 seconds) that provided the highest image quality. Then the system proceeds to the next view.

**Manual record:**

In addition to the Auto-capture and “Save Best Clip” features, the user also has the option to manually record a clip. This feature is available to meet the user needs of skilled users in certain situations where they have a particular clip they’d like to acquire.

When recording is activated, either manually or automatically, a loading indicator around the circular button signifies to the user that the image is being captured. See **Figure 4** to see the automatic image capture indicator around the circular button below the Guidance Meter.

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**Figure 4: EchoGPS Image Acquisition Screen - Recording**

The EchoGPS software communicates with the ultrasound image formation engine of the 510(k)-cleared Terason uSmart 3200t through an API provided by the manufacturer. The Bay Labs proprietary add-on software, EchoGPS, is being investigated for this study and is not FDA cleared by the Terason uSmart 3200t’s 510(k) clearance. EchoGPS user interface runs the guidance assistance (EchoGPS).

In this study Bay Labs EchoGPS software is integrated with the Terason uSmart system to create a unique user display to show real-time scanning images with dedicated protocol and view guidance for users. The architecture of this implementation also allows control of limited functions of the real-time scanning system, such as setting scanning depth and overall gain levels.

Bay Labs software runs on top of the Terason ultrasound device control software, without modifying safety parameters (e.g., acoustic output). The EchoGPS user interface does not entail modifications to the underlying Terason uSmart 3200t hardware in a manner that would affect the mechanical or electrical safety of the device. No hardware modifications have been made. Furthermore, EchoGPS software does not allow or produce changes to fundamental operational settings that might affect patient safety. The ultrasound engine of the underlying Terason uSmart 3200t, including transmit/receive parameters, image formation and image processing are not modified. Acoustic output levels of the system are controlled to meet FDA limits and these controls are not altered in this implementation. Verifying this, Noah Berger, Director, Software Engineering at Terason, states:

“Using automation calls to control Depth and Overall Gain will not create a situation such that the acoustic output and thermal characteristics of the transducer would exceed regulatory limits.  The automation functions for Depth and Gain work through the same mechanism as the corresponding controls on the main user interface.  User interface controls in general are maintained in modules separate from Acoustic and thermal limits.  Moreover, a hardware watchdog mechanism in the ultrasound engine disables transmit inside the engine in the event that the PC application software stops working.”

## Clinical Data

This proposed study is motivated by two internal studies done at Bay Labs, Inc.

**Study on automatic LVEF estimation technology (AutoEF)**: The first internal study was a retrospective analysis using Minneapolis Heart Institute’s extensive echocardiogram database to demonstrate the performance of Bay Labs’ automated ejection fraction software. This retrospective study indicated that Bay Labs’ automated LVEF software (AutoEF) is accurate in that its LVEF prediction is well within the variability of LVEF estimations of cardiologists. This result was presented to the FDA in a Pre-Submission Meeting.

**Study on acquisition guidance technology (EchoGPS) and automatic LVEF estimation technology (AutoEF) included in EchoGPS**: The second internal study tested the performance of EchoGPS, which combines EchoGPS and AutoEF. This study attempted to mimic the proposed study herein, and showed a number of relevant observations: The outcome of this internal study suggested that EchoGPS would be effective in assisting imagery acquisition and EF measurement. These initial results serve as a power analysis here (i.e., the maximum subjects to recruit, 100) to motivate the proposed study. Admittedly, however, this internal study did not have adequate patient disease diversity (a range of LVEF values), was not at a large enough sample size to allow sub-analysis, and was not in a clinical setting.

**MHI Study:** Bay Labs conducted a clinical study at the Minneapolis Heart Institute (MHI) in 2017. In this IRB-approved study, registered cardiac sonographers performed echo exams on 50 patients using EchoGPS and the “native” non-EchoGPS version of the cleared, base ultrasound system, the Terason uSmart 3200t. Ten (10) views (PLAX, PSAX-AV, PSAX-PM, PSAX-MV, AP4, AP5, AP2, AP3, SubC4, Sub-IVC) were included. Recorded images from the two systems were graded for diagnostic image quality using the ACEP scale by three blinded expert cardiologists. Patients were a convenience sample presenting to the Echo Lab for full echocardiograms which were conducted afterwards using the lab’s standard echo system.   The results showed that there was no statistically significant difference in diagnostic image quality between images acquired with and without use of the EchoGPS. These results show that EchoGPS does not introduce risks (e.g., reduced image quality) when used by a skilled sonographer who possesses a thorough understanding of sonography.

**BASE Study:** Bay Labs’ most recent internal testing for EchoGPS was held on August 6-15, 2018. The in-house study was called the Benchmark Algorithm and Secondary Evaluations (BASE) study. Five (5) registered nurses (RNs) who had never acquired echocardiogram images before participated in BASE as the users of EchoGPS. In fact, four (4) of the five (5) nurses had never used ultrasound at all (one RN had used an ultrasound for IV placement). Subjects (those being scanned as simulated patients) were selected to represent expected body-mass index (BMI) distribution (and resulting expected technical difficulty for acquiring ultrasound images) in a normal echocardiography laboratory. Novice users (RNs) were able to develop clinically valuable proficiency in acquiring six (6) standard views after a single day of didactic and hands-on training. Furthermore, the performance of novice users continued to improve with scanning experience, highlighting the potential for them to achieve a level of clinically meaningful proficiency in acquiring these six standard views that would be needed in their specific clinical setting.

In summary, we expect this proposed study at Northwestern Medicine and Minneapolis Heart Institute will measure the ability to use EchoGPS to acquire diagnostic quality clips by novice users. This will potentially benefit patients as they will have access to quality echocardiograms in settings where there is no trained user available to obtain echocardiograms.

## Clinical Data to Date

The echocardiogram is a pervasive measurement tool for the assessment of cardiovascular function. It has been validated in numerous clinical studies, and echocardiogram measurements are used as endpoints in clinical trials. The American Institute of Ultrasound in Medicine states (4/1/2012) on the Prudent Use and Clinical Safety:

“Diagnostic ultrasound has been in use since the late 1950s. Given its known benefits and recognized efficacy for medical diagnosis, including use during human pregnancy, the American Institute of Ultrasound in Medicine herein addresses the clinical safety of such use: No independently confirmed adverse effects caused by exposure from present diagnostic ultrasound instruments have been reported in human patients in the absence of contrast agents. Biological effects (such as localized pulmonary bleeding) have been reported in mammalian systems at diagnostically relevant exposures but the clinical significance of such effects is not yet known. Ultrasound should be used by qualified health professionals to provide medical benefit to the patient. Ultrasound exposures during examinations should be as low as reasonably achievable (ALARA).”

The use of ultrasound at the point-of-care has recently received attention. Several studies, including Decara *et al.* (2005), Razi *et al*. (2011), Platz & Solomon (2012), Hothi (2014), and Kimura *et al*. (2015) have investigated the use of point-of-care ultrasound. Abe *et al*. (2016) also demonstrated a novel method using point-of-care ultrasound to screen for aortic stenosis. These studies have demonstrated utility of point-of-care ultrasound. However, questions about quality and accuracy of such examinations, as compared to inpatient echocardiography exam by an echocardiography laboratory remain (Hothi, 2014; Kimura et al. 2015). Use of EchoGPS with Terason uSmart 3200t and measurement of its performance in this study protocol aim to address these questions of quality and accuracy.

# Study Objectives

The primary objective of this study is to validate clinical use of EchoGPS software by registered nurses (RNs) with no prior scanning experience to acquired limited (10-view) two-dimensional point-of-care echocardiograms.

# Study Design

## General Design

This is a non-randomized, two-center study in patients with an indication for an echocardiographic examination.

The patients who meeting the inclusion and exclusion criteria and consent to participate will undergo two scans during the course of the study. The first is an EchoGPS scan by a RN, and the second is a reference scan by a registered sonographer using the same device but without the guidance from EchoGPS. Ten echocardiographic views will be obtained.:

PLAX, PSAX-AV, PSAX-PM, PSAX-MV, AP4, AP5, AP2, AP3, SubC4, SC-IVC

Six RNs will be trained and evaluated the 10 view protocol. The RNs will not receive any guidance during the scanning. They will scan independently. There will be no time constraint for the RNs to obtain each view. The user interface will allow the RNs scanning to return to a view previously scanned and image and record again.

Following the scan by the RN, the patient will undergo a scan with the reference device by a registered sonographer on the same view protocol. The sonographer will not be present when the nurse obtains the 10 views, so they will not have seen the patient before doing their reference scans

Prior to initiating the study enrollment up to 24 volunteers will be asked to undergo the Study Exam for training purposes. Each RN will be trained on a minimum of 12 and maximum of 24 volunteers. Images generated during the training period will not be included in statistical analysis.

Following the examination, a panel of five (5) expert cardiologist readers will independently provide assessments of whether the patient study in its totality provides sufficient information to assess the clinical parameters and diagnostic image quality per clip. The readers will be blinded to each other’s assessments as well as whether the images were obtained from a RN or a sonographer. The results from the expert panel reads will be used for the statistical analysis.

To reduce sources of bias in the design, RNs, sonographers and cardiologists will be blinded to results determined by others.

## Primary/Secondary Endpoints

The primary endpoints for the study are patients level assessment of:

* + Qualitative assessment of LV size
  + Qualitative assessment of LV global function
  + Qualitative assessment of RV size
  + Quality assessment of pericardial perfusion

The secondary endpoints for the study are:

* + Patient-level assessment of:
    - Qualitative assessment of IVC size
    - Qualitative assessment of RV function
    - Qualitative assessment of LA size
    - Qualitative assessment of aortic valve, mitral valve, and tricuspid valve
  + View-level:
    - % of patient studies with diagnostic (ACEP 3+) quality clip for each of the ten (10) Standard Views used in the study
    - Acquisition time
  + Subgroup analyses: Results per BMI group, sex, age, etc.
  + Reference Scan comparison: View-level and patient-level results; paired comparison to non-specialist results

## Setting:

Study examinations will be performed in the echocardiographic laboratories.

## User training

## User Training and Qualification

Bay Labs will provide training the non-specialists (RNs) participating to demonstrate a basic level of competence using the device before their scans count towards the study endpoints. Users will receive a brief training (from Bay Labs personnel) on both basic echocardiography clinical information as well as product operation, until they are able to proficiently operate the device effectively and clinically. Furthermore, for the RNs a measure of the effectiveness of “steady-state” usage of the EchoGPS device after the short initial learning phase will be done.

Specialist users (sonographers) doing the reference scan will only receive product operation training on how to use the Terason uSmart system.

### Initial Training

RNs will be trained according to a training protocol with the following main components:

1. **Didactic Training and Hands-On Guided EchoGPS Training** **(2 days, 3 volunteer Scans per day)** - The Bay Labs training representative will provide brief classroom instruction. The RNs will be trained on use of the EchoGPS system via hands-on scanning of volunteer models. The Bay Labs training representative will provide verbal instruction during the course of each exam.
2. **Independent Hands-On Practice (2 days, 3 volunteer scans per day)** - The RNs will use of the EchoGPS system to scan models. The Bay Labs training representative will not provide any verbal instruction during the course of each exam. Between exams the training representative will provide feedback on areas of improvement.

### User Readiness Evaluation

At the end of Day 4 (the second day of the independent hands-on practice outlined in the previous section), the RNs will undergo a user readiness evaluation to determine whether they demonstrate the basic knowledge and skill necessary to use EchoGPS. Bay Labs is developing a set of evaluation criteria that will consist of three main components:

1. **Skills and Technique Evaluation** - The user will be evaluated whether they have gained the appropriate skills and ergonomic techniques for scanning using the EchoGPS system.
2. **Image Quality Evaluation** – The images acquired by the user during the Independent Hands-On Practice Scans will be evaluated.
3. **Self-Reported Confidence** - The user will be asked if they feel confident scanning independently on patients.

### User Qualification Process

As discussed above, instead of a set training program that all users must undergo before beginning to scan in the study, the RNs will be qualified to participate in the study after they demonstrate basic proficiency. This process aligns with the point-of-view of the European Association of Cardiovascular Imaging, which stated “knowing the… diversity of medical professionals who undergo training in FoCUS, it seems unlikely that strictly predefined minimal number of hours of hands-on image acquisition training or the number of personally performed...would ever fit for all.” (Neskovic et al., 2014)

**Figure 11** below provides an overview of the proposed training/qualification process for users in the Non-Specialist Study.

A close up of a map

Description automatically generated

**Figure 11: RN Study User Training and Qualification Process**

The first phase will cover the initial training program consisting of didactic training, hands-on guided practice, and independent practice. On Day 4, after the first nine (9) scans, the RN will scan 3 patients independently using the EchoGPS device. At the end of these scans, the training representative will complete the User Readiness Evaluation to decide whether the RN is qualified to participate in the study. If the RN passes, they move to the study phase, where their scans will be counted towards the study endpoints. If the RN fails, they will complete another set of three (3) independent practice scans and subsequently undergo the same readiness evaluation. This process will repeat until the RN passes the criteria. Bay Labs will report the number of scans each RN performs prior to qualification to participate in the study. The maximum number of training volunteers will be 24, in the event that an RN is unable to develop basic proficiency after five evaluation days. Based on internal testing, Bay Labs considers it very unlikely any user would reach this maximum.

# Subject Selection and Withdrawal

## Inclusion Criteria

All participants must meet the following inclusion criteria to participate in the study:

1. Patients indicated for a standard physical examination
2. Patients ≥65 years old

## Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to participate in the trial:

* Unable to lie flat for study
* Patients experiencing a known or suspected acute cardiac event
* Patients with severe chest wall abnormalities
* Patients who have undergone pneumonectomy
* Patients unwilling or unable to give written informed consent

## Subject Recruitment and Screening

Patients who have been identified as potential subjects will first be introduced to the general idea of the study by the study coordinator or other IRB-authorized study personnel by discuss participation and engage in the detailed informed consent process.

## Local Number of Participants:

210 patients will be enrolled in the study, 105 patients at each site. Each RN will scan 35 study patients after completing the training program.

In addition a minimum of 12 and a maximum of 24 models for training will be enrolled dependent on how many patients will be needed for the RNs to complete the training protocol .

## Early Withdrawal of Subjects

The subject may be withdrawn from the study if they are unable to lie still for the duration of the study, if, for example, they are physically uncomfortable in the left lateral decubitus position. In this case the study will halt, which does not pose any additional risk to the participant.

In addition, if a subject does not wish to participate in the scan, they may do so at any point before scan completion. In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time, for any reason. In the event a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

# Study Software

## Description

EchoGPS provides guidance and interpretation assistance for point-of-care echocardiogram examinations. Refer to Section ‎1.2 for further information about EchoGPS.

# Study Procedures

Patients who meet inclusion and exclusion criteria will be invited to participate in the study by the study coordinator of referring physician. Authorized research personnel will discuss their potential participation in the study.

Prior to any study activities subjects will be asked to agree to participation by signing the consent form. Participation in this study requires a single visit, which will typically last no more than 60 minutes in duration. This study will involve the following:

* Medical history will be obtained
* Limited TTE exam(s) will be performed
  + **Study Exam:** RN performs examination using the EchoGPS and 10 views will be obtained cohorts

PLAX, PSAX-AV, PSAX-PM, PSAX-MV AP4, AP5, AP3, AP2, SubC4, SC-IVC

* + **Reference Exam** Sonographer performs examination using the Terason system and obtains the same 10 views.

Either just before or just following the reference exam, the patients will undergo their clinically indicated echocardiographic examination.

# Risk/Benefits

Ultrasound and TTE pose no known risks to participants. Subjects may not receive direct benefit from the study. However, they may benefit from information generated from the TTE exams. In addition, others may benefit in the future if data collected in this study are shown to be useful for improving the quality of point-of-care echocardiogram examinations and in developing a point-of-care ultrasound device that improves the quality of these examinations. This gain in knowledge is reasonably expected, as there are no datasets demonstrating the study objectives and pilot studies completed by the study sponsor indicate, with reasonable likelihood, that the expected outcomes will be achieved.

# Sharing of Results with Participants

Individual echocardiographic finding will be shared with subjects’ primary care physicians. Informed consent document will be placed in Study Tracker per NMHC and MHI policy. Study results will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

# Statistical Procedures

## Parameters

## Patient-Level Diagnostic Quality in a Limited Echo Exam

EchoGPS is designed to provide a specific set of 2D (B-mode) images for ten (10) standard cardiac views. While this is not a full echo exam that might include other scanning modes such as Color Flow Mapping and spectral Doppler, it will provide the imaging needed for the most common study protocols that would be relevant in a point-of-care environment.

The primary endpoints in this study evaluate the effectiveness of the EchoGPS in enabling RNs to acquire images that answer a core set of clinical parameters in **Table 1**:

**Table 1: Patient-Level Success Criteria**

|  |  |
| --- | --- |
| **Parameter** | **Description** |
| **Qualitative Assessment of Left Ventricular Size** | Can perform qualitative assessment of left ventricular size and determine if normal or dilated. |
| **Qualitative Assessment of Global Left Ventricular Function** | Can perform qualitative assessment of global left ventricular function and determine if hyperdynamic, normal, reduced, or severely reduced. |
| **Qualitative Assessment of Right Ventricular Size** | Can perform qualitative assessment of right ventricular size and determine if normal or dilated. |
| **Qualitative Assessment of Pericardial Effusion** | Can qualitatively assess the presence or absence of pericardial effusion. |

These criteria allow for an assessment of whether the EchoGPS software produces images that are of sufficient quality to perform common clinical assessments of cardiac function. These provide a representative sampling of the types of assessments that are expected to be useful in the clinical settings in which EchoGPS would be used (e.g., cardiology office, primary care, emergency department, etc.)

In addition, as secondary endpoints we will evaluate:

* Qualitative assessment of IVC size
* Qualitative assessment of RV function
* Qualitative assessment of LA size
* Qualitative assessment of aortic valve, mitral valve, and tricuspid valve

**Table 2** below shows which standard views are useful for assessing each of the core items discussed above.

**Table 2: Features/Functionality Visible in Standard Views**

|  |  |  |
| --- | --- | --- |
| **Patient Study Success Criteria** | **Standard Views** | **# of Views** |
| Qualitative Left Ventricular Size | PLAX, PSAX-PM, AP4, AP5, AP2, AP3, SubC4 | 7 |
| Qualitative Left Ventricular Global Function | PLAX, PSAX-PM, AP4, AP5, AP2, AP3, SubC4 | 7 |
| Qualitative Right Ventricular Size | PSAX-PM, AP4, AP5, SubC4 | 4 |
| Pericardial Effusion | PLAX, PSAX-PM, A4, AP5, AP2, AP3, SubC4, SubC-IVC | 7 |

As shown in **Table 2** above, there is often redundancy in the standard views to assess particular features or functionality of the heart. This explains why although even highly skilled sonographers do not obtain diagnostic-quality clips for every standard view in an echo exam, clinicians are very often able to obtain diagnostic information from the patient study in its totality.

The independent readers will be asked if they can assess the clinical parameters outlined above (yes or no) for each clinical parameter.

**ACEP scale**

The following scale has been developed by the American College of Emergency Physicians (ACEP) and it assesses the diagnostic quality of images using a categorical scale from 1 to 5. The independent cardiology readers will assess all the clips from all the views acquired by both the RNs and the sonographers using this scale.

. **Table 3: ACEP Scoring System**

|  |  |
| --- | --- |
| **ACEP Score** | **Description** |
| 1 | No recognizable structures, no objective data can be gathered |
| 2 | Minimally recognizable structures but insufficient for diagnosis |
| 3 | Minimal criteria met for diagnosis, recognizable structures but with some technical or other flaws |
| 4 | Minimal criteria met for diagnosis, all structures imaged well and diagnosis easily supported |
| 5 | Minimal criteria met for diagnosis, all structures imaged with excellent image quality and diagnosis completely supported |

### Primary Endpoints

There will be separate performance goals for each of the four (4) patient-level clinical parameters discussed in **Table 3** above, to reflect the differences in difficulty for satisfying each of the parameters.

Using a median-vote paradigm the following performance goals for patient-level clinical parameters will be tested:

**Table 4: Primary Endpoint #1 - Patient-Level Clinical Parameter Assessments**

|  |  |  |
| --- | --- | --- |
| **Patient-Level Clinical Parameter** | **Description** | **Performance Goal (% of studies with a majority-vote ‘Yes’ for the parameter)** |
| **Qualitative Assessment of Left Ventricular Size** | Can perform qualitative assessment of left ventricular size and determine if normal or dilated. | 80% |
| **Qualitative Assessment of Global Left Ventricular Function** | Can perform qualitative assessment of global left ventricular function and determine if hyperdynamic, normal, reduced, or severely reduced. | 80% |
| **Qualitative Assessment of Right Ventricular Size** | Can perform qualitative assessment of right ventricular size and determine if normal or dilated. | 80% |
| **Qualitative Assessment of Pericardial Effusion** | Can qualitatively assess the presence or absence of pericardial effusion. | 80% |

The performance goals for the 4 primary patient level clinical parameters lead to the following study hypothesis:

**Table 5: Study Hypotheses**

|  |  |  |
| --- | --- | --- |
| **Clinical Parameter** | **Performance Goal** | **Null Hypothesis** |
| **Qualitative Assessment of Left Ventricular Size** | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% |
| **Qualitative Assessment of Global Left Ventricular Function** | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% |
| **Qualitative Assessment of Right Ventricular Size** | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% |
| **Qualitative Assessment of Pericardial Effusion** | 80% | H0: % of patient studies where parameter can be assessed ≤ 80% |

**Descriptive Statistics:**

The following descriptive statistics be evaluated for the secondary endpoints:

**Study exam:**

* **Additional Patient-Level Clinical Parameters for study exam:** 
  + Qualitative assessment of IVC size
  + Qualitative assessment of RV function
  + Qualitative assessment of LA size
  + Qualitative assessment of aortic valve, mitral valve, and tricuspid valve
* **View-level Results:** % of patient studies with diagnostic (ACEP 3+) quality clip for each Standard View
* Subgroup Analyses: Results per BMI group, sex, age, etc.

**Reference exam**

* Patient level clinical parameters for reference exam
  + Qualitative assessment of LV size
  + Qualitative assessment of LV function
  + Qualitative assessment of right ventricular size
  + Qualitative assessment of pericardial perfusion
  + Qualitative assessment of IVC size
  + Qualitative assessment of RV function
  + Qualitative assessment of LA size
  + Qualitative assessment of aortic valve, mitral valve, and tricuspid valve
* View-Level results on % patients with diagnostic (ACEP 3+) quality clip for each standard view

**Comparison of study exam and reference exam**

* View and Patient-Level results; paired comparison of study and reference exam

## Sample Size Determination

Performance of the EchoGPS will be regarded as successful if the proportion of scans acquired by RNs that are rated as exceeding the acceptance criterion for each of the following anatomic parameters (See **Table 4** above for details):

1. LV Size
2. LV Function
3. RV Size
4. Pericardial Effusion

**Table 6** below displays the acceptance criterion and anticipated diagnostic performance for each of the four patient-level anatomic parameters.

**Table 6:** **Anticipated Performance and Acceptance Criteria for Multiple Diagnostic Endpoints**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **(1)** | **(2)** | **(3)** | **(4)** | **(5)** |
| **Sequence of Hypothesis Testing** | **Clinical Parameter** | **Anticipated Performance**  **(% of studies for which clinical parameter can be assessed)** | **Acceptance Criterion** | **Sample Size required at 90% power** |
| 1 | LV Size | 88.0% | 80.0% | 203 |
| 2 | LV Function | 88.0% | 80.0% | 203 |
| 3 | RV Size | 88.0% | 80.0% | 203 |
| 4 | Pericardial Effusion | 88.0% | 80.0% | 203 |

Using an alpha of 0.05 with a desired power of 0.90, the sample size necessary to reject the null hypothesis for each parameter is given in column (5) (PASS 16 Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). The applicable statistical test is a one-sample, one-sided, exact binomial test using normal approximation. Since the highest individual sample size required is 203, assuming that all four anatomic parameters are tested (see below), the minimum total number of scans that need to be acquired and evaluated is 203. To ensure that the 6 RNs scan the same number of patients, the total number of patients is set to 210.

To control Family Wise Error Rate, a Fixed Testing Sequence will be used with the pre-specified sequence indicated in column 1. The observed success rate on LV Size will be compared to the acceptance criterion of 80% using a one-tailed exact Binomial test. If the significance level of that comparison is less or equal to 0.05, hypothesis testing will proceed with LV Function. If, however, the significance level for LV Function is greater than 0.05, hypothesis testing will end and no further statistical test will be reported (“Multiple Endpoints in Clinical Trials Guidance for Industry: Draft Guidance,” 2017). Similarly, if hypothesis testing proceeds to LV Function, the observed rate of success will be compared to the acceptance criterion of 80%. If the significance level of that comparison is less or equal to 0.05, hypothesis testing will continue with RV Size, but end at LV Function otherwise. If hypothesis testing proceeds to RV Size, the observed rate of success will be compared to the acceptance criterion of 80%. If the significance level of that comparison is less or equal to 0.05, hypothesis testing will continue with Pericardial Effusion, but end at RV Size otherwise.

## Subject Population(s) for Analysis

All eligible subjects will be used for the statistical analysis. The data from the training patients will not be included in the statistical analysis.

# Safety and Adverse Events

## Definitions

The study is considered low risk. However, adverse events may include allergic reaction to ultrasound gel and discomfort during the procedure. Unanticipated Problems would include events that interrupt the study. We do not anticipate any Serious Adverse Events.

## Recording and Reporting of Adverse Events

Site will report adverse events in writing to the sponsor within 5 business days for each event. These events will be logged by the sponsor and reviewed routinely to determine if adverse events could be avoided and if these events should affect the study.

## Randomization Codes and Unblinding Procedures

N/A

## Stopping Rules

If a subject expresses discomfort during an exam participation in the study will end. If more than 15% of studies are terminated before completion, we will pause study enrollment and identify potential solutions for resolving before continuing.

## Medical Monitoring

N/A

# Data Handling and Record Keeping

## Confidentiality

To protect disclosure of subject identities, only authorized research personnel and Bay Lab representatives will have access to information that identifies a participating subject. All subjects will be identified by a unique subject number and initials; the subject’s name or any other subject-identifiers (such as date of birth or medical record number) will not appear on any data collection forms or documentation sent to Bay Labs. Representatives of Bay Labs and regulatory authorities may review records for validation purposes or to ensure compliance with protocol.

In addition to ultrasound imaging, procedure dates, age, gender, height/weight and the physical examination report will be collected for this study. Authorized research personnel will remove subject identifiers from the hard copy reports and replace with the applicable subject ID prior to release to the sponsor. An enrollment log identifying each subject with his/her assigned unique study ID, subject initials and date of exams will be maintained at the study sites. As an additional assurance on confidentiality, Bay Labs is a HIPAA compliant organization and information provided to Bay Labs will be kept in a HIPAA compliant network.

## Image Transfer and Storage

Images acquired for the Study Exam and Control Exams will be identified by participants unique study ID, subject initials and date of exam - participant names and other identifying information will not be on the images. NM Information Services (IS) will establish a direct image transfer from participating sites by pairing the Terason machine IP address to a separate, password protected folder in the clinical Syngo workstations, only authorized study personnel will have access to this folder. Images will be batched and transferred to NM at the end of the day for analysis by a registered echocardiologist. De-identified images will also be uploaded to a secure FTP network for assessment by Bay Labs.

## Source Documents

Source data shall be retained at the study centers and shall be made available for inspection by the study sponsor and authorized regulatory bodies upon request. Source data shall be de-identified to protect the privacy of the study subject and comply with HIPAA regulations.

The signed consent documents, data collection forms and physical examination reports will be stored at the Bluhm Cardiovascular Institute Clinical Trials Unit (Arkes Pavilion, Suite 1700).

## Records Retention

Echocardiograms will be retained indefinitely by Bay Labs, Northwestern and MHI for their own patient data respectively. No identifying information will be on the echocardiograms. Site will maintain all additional study records (e.g., consent forms, data collection forms) for minimum of 3 years following completion of the study.

## Data Management

Electronic data capture (EDC) system (RedCap) will be used for data collection in this study. Bay Labs will provide training in the use of EDC to all necessary site personnel. Each investigator and study personnel will be assigned a unique password and only that individual should access subject records under that password.

Panel read evaluation.

Bay Labs will collect all the echocardiograohic clips obtained from both the RNs and sonographer. These clips will be randomized and then presented to 5 cardiology experts. The experts will be blinded to whether the clip was obtained from a RN or a sonographer.

# Study Monitoring, Auditing, and Inspecting

The study will be monitored by periodically to ensure compliance with the protocol and to review any recorded adverse events. The data from each TTE acquisition will be monitored for completeness on a regular basis.

# Ethical Considerations

As this study is low risk, the ethical considerations are largely mitigated. Adverse events may result from subject discomfort or allergic reaction. Subjects will be informed that they may opt-out of the study at any time.

Clinical findings may occur during the echocardiogram examination. In accordance with the hospitals’ standard process, any clinical or incidental findings will be shared with the attending physician for follow-up according to the hospital’s standard protocol.

## Provisions to Protect the Privacy Interests of Participants

Information will be shared only with necessary research personnel. Specifically, unless required by law, only the study investigator, members of the investigator's staff, sponsor and representatives of the sponsor, the study site, representatives of the FDA, and other international regulatory agencies will have the authority to review study records (including the results of the tests conducted during this study). All paper records are kept in a locked cabinet in a locked office that is not open to the public. Electronic research data will be password protected; only authorized personnel can access the data. Subjects will receive unique study code numbers; any information that is collected for a subject on a CRF will have the subject's unique study code number and initials.

Data used by the sponsor for reports or publications will never include identifiable information such as name, DOB, address, or medical record number and in most cases, will not include any identifiers other than sex, age, race, and diagnosis, since most reports are concerned only with descriptive summaries and statistical analyses of “grouped” data.

## Human Subjects Protection

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). The study will not start before the IRB gives written approval in accordance with ICH E6‑GCP and all applicable regulatory bodies/local health authorities give approval. Any amendments to the protocol or changes to the consent form must also be approved by the IRB.

## Informed Consent Process

The informed consent process will be conducted in clinic or by phone. Informed consent must be obtained from each patient prior to conducting any study activities beyond standard of care, by using the informed consent form (ICF) approved by the IRB.

The valid, signed and dated consent form, along with any supporting documentation (e.g., a consent process checklist) will be filed in the participant’s research record.

# Research-Related Injury

No more than minimal risk anticipated for this project. No compensation will be provided.

# Economic Burden to Participants:

No economic burden to participants. The study will cover cost of research echocardiograms.