AMERICAN SOCIETY OF ECHOCARDIOGRAPHY – VALVULAR ASSESSMENT LEADING TO UNEXPLORED ECHOCARDIOGRAPHIC STRATAGEMS (ASEF-VALUES)

PROTOCOL VERSION 3.0

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PROJECT SUMMARY & SPECIFIC OBJECTIVES

Mobile health –mHealth - the use of mobile computing and communication technologies in healthcare is a rapidly expanding area within global health. The healthcare sector in resource limited areas faces several challenges including the inadequacy of human resources, a lack of modern medical diagnostics, and an increasing burden of chronic diseases are well identified barriers towards achieving improved access to healthcare. Mobile health interventions with cellular phones have been used in these regions to overcome these challenges through three main delivery methods: automated text messaging and telehealth applications for remote consultation. Newer, point-of-care diagnostics with smartphone-connected medical devices including wearable and wireless devices, nanosensors, portable imaging technologies and telemedicine 'apps', and have promising applications to improve healthcare delivery and patient outcomes in such regions. New methods are required to translate these advances that require community engagement, integration with established healthcare information technology infrastructures of regional healthcare systems, and an implementation system for rural healthcare. This project seeks to demonstrate the impact of mHealth through evaluative mechanisms and randomized trial design to assess the outcomes of mHealth as compared to standard-care among patients with rheumatic and structural heart disease in an endemic area of a resource limited community. The specific objectives of the program and clinical trial are listed below;

Specific Objective #1: To assess the impact of mHealth device assessments used as point-of-care clinical decision support tools on treatment and long-term outcomes among patients with rheumatic and structural heart disease through randomized clinical trial design.

Specific Objective #2: To develop information technology systems of integration for input of mHealth device assessment to the institutions electronic medical record and for paperless data capture.

Specific Objective #3: To develop a community-based participatory model to determine the implementation methods for mHealth towards device-enabled healthcare and to advance echocardiographic education in rheumatic and structural heart disease with new imaging technologies.

RESEARCH STRATEGY

Title: ASE-Foundation Valvular Assessment Leading to Unexplored Echocardiographic Stratagems (ASEF VALUES) Program. A Randomized Trial of Pocket-Echocardiography Integrated Mobile Health Device Assessments in Modern Structural Heart Disease Clinics

Overview and Innovation

The present study is the first investigation evaluating the long-term outcomes of smartphone-enabled care and mobile health device assessments as clinical decision support tools among patients with rheumatic and structural heart disease in an endemic area of resource limited area. The current investigation will harness a collaboration of domestic and international healthcare workers and will utilize a randomized controlled trial and a community-based participatory research model to determine the effectiveness of mobile health devices. The findings of the current investigation will represent knowledge translation for pocket-echocardiography and the pragmatic use of mHealth towards empowering healthcare practitioners and patients in resource limited communities.

BACKGROUND

A. Significance

Mobile health (mHealth) - the use of mobile computing and communication technologies in healthcare is a rapidly expanding area within global health and particularly within developing countries [1]. mHealth interventions have been designed to provide support and services to healthcare workers, including new methods for medical education and to enhance the communication between providers and patients. Technological advancements and the miniaturization of diagnostic instruments to modern smartphone-connected devices such as pocket-sized ultrasound, cardiac rhythm monitoring and lab-on-a-chip technologies, represents significant progress for providing diagnostic support at the point-of-care and for improving the efficiency of healthcare delivery across low and middle-income countries [2].

The healthcare sector in resource-limited areas face several challenges including the inadequacy of human resources, a lack of modern medical diagnostics, and an increasing burden of chronic diseases, common barriers towards achieving improved and universal access to healthcare [3]. Mobile health interventions with cellular phones are being used in these regions to overcome these challenges through three main delivery methods: automated text messaging, telehealth applications for remote consultations, and point-of-care diagnoses with new smartphone-connected medical devices. Text messaging represents a simple, cost-effective, and sustainable intervention for medication adherence monitoring [4], encouraging behavioral change [5], and enhancing practitioner and patient communication. Leveraging the advances in global connectivity and utilizing mobile phones as vectors for health care delivery studies are emerging that provide evidence for the feasibility of Internet-based telehealth for rural healthcare. These studies include the diagnoses of complex structural heart disease with handheld ultrasound and image review by expert physicians in distant locations [6], the use of robotic guided imaging to perform examinations remotely and in the absence of dedicated healthcare personnel [7], and the diagnoses of microbiological specimens with genomic and advanced point-of-care techniques among patients with communicable diseases [8]. Numerous smartphone-connected mHealth devices have become available and newer devices are under development. These range from disease-specific diagnostic devices such as the iECG for cardiac rhythm analysis, optical imaging for retinal screening, pulmonary function testing with exhaled breath analysis, and lab-on-a-chip micro-fluidic technologies for point-of-care laboratory results [9]. Despite the availability of these devices, nearly all

mHealth devices have been designed for use in industrialized nations. For these advances to be translated to resource-limited areas a thorough understanding of the regional healthcare infrastructure and future sustainability models for mHealth integration are required [10].

Recent shifts in the global burden of CV diseases have been observed with decreasing prevalence in high-income countries and increasing prevalence in low-income countries, with future projections of over 25-million deaths by 2030. The Prospective Urban Rural Epidemiologic Study [13] of over of 150,000 individuals from 600 communities across 14 low and middle-income countries has recently demonstrated a greater than 70-percent cumulative risk factor burden of hypertension, diabetes, and hyperlipidemia. This burden of chronic disease has resulted in a greater than 2-fold increased rate of major cardiovascular events and mortality in these countries as compared to high income countries. Coupled with an estimated 15-million cases of rheumatic and structural heart disease has created a major global health concern that requires new efforts to diagnose, treat, and manage large populations at risk. This global burden of disease presents both opportunities and challenges for the application of mHealth to improve patient outcomes and healthcare delivery. Such opportunities include the use of point-of-care diagnostic devices including handheld mobile echocardiography to quantify the severity of valvular heart disease, the estimation of functional limitation with wearable activity monitors, and to determine the severity of breathing impairment and pulmonary system abnormalities. Plausible utilization patterns for mHealth in structural heart disease may involve the assessment of symptoms, functional and structural abnormalities at the point-of-care that may facilitate clinical decisions, treatment, and follow-up among the highest risk patients. The challenges are several and include the integration of mHealth devices within the regional healthcare infrastructure, healthcare practitioner education towards technology-enabled care and use of mHealth in a cost efficient fashion.

B. Technology-Enabled Care

To address the integration challenges for mHealth in these areas, our group has recently demonstrated the utilization patterns for modern mHealth devices in a resource constrained area in Africa. In 2014, we assessed the mobile phone ownership rates and measured the sophistication of cellular phone utilization in a cross-sectional community sample in rural Uganda. We determined a high cellphone ownership rate of 85% among a random sample of 600 individuals and a high 'digital literacy' rate defined as usage of text messaging, Internet and 'apps' and mobile-banking. These findings led a proof-of-concept study investigating the use of modern mHealth devices including the iECG, smartphone-connected blood pressure and glucose monitors, as well as miniaturized pocket-ultrasound devices among 350 patients referred for the evaluation of acute or

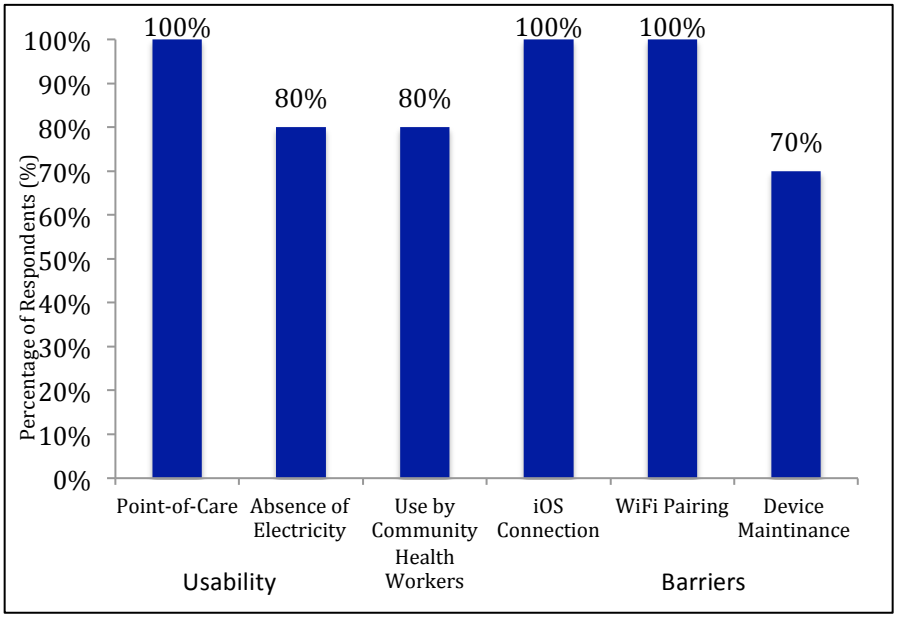


Figure 1: Healthcare personnel and device usability factors and barriers

chronic diseases [11]. In accordance with the WHO-HTA (World Health Organization Health Technology Assessment) and ASSURED criteria [12] for technology-implementation, we demonstrated the specific device- and personnel-related factors that lead to high utilization, including the presence of automated diagnostic algorithms, as well as important barriers to use, including devices that require a broadband connection and devices operating on the iOS platform (figure 1). In this study was the creation of an mHealth clinic to provide services to rural populations with hypertension, diabetes, and cardiovascular disease through a community engagement model with healthcare providers, patients and local organizations.

Community-based mHealth screening represents a novel strategy towards improving CV-related morbidity and mortality. Recently, the SEARCH-AF investigators [14] reported on the feasibility and diagnostic yield of community-based screening for atrial arrhythmias with a smartphone iECG among a general population in rural Australia. The automated diagnosis of device-captured atrial fibrillation was performed by 5 pharmacists in over 1,000 screened participants and demonstrated a greater than 7-percent prevalence of atrial fibrillation and a 1.5-percent incidence of newly diagnosed atrial fibrillation. The early diagnosis resulted in an incremental cost effectiveness of extending iECG to the community in excess of US$30,000 for the prevention of one non-fatal stroke. Similarly, the ASE-REWARD study investigators demonstrated a 20-percent incidence of major cardiac abnormalities including rheumatic, congenital and structural heart disease in over 1,100 individuals with handheld and portable echocardiography within a screening program in an underserved population in rural India [6]. In the aggregate, mHealth may demonstrate potential as point-of-care tool for screening of common conditions at the community and population-based levels.

In industrialized nations there is an expanding use of mHealth technologies as patient-centric tools for remote and self-monitoring towards cost containment. In contrast, in developing nations mHealth is focused on improving healthcare access as a practitioner-based tool particularly where conventional diagnostic devices are not available. Empowering healthcare practitioners with mHealth in such regions, where on average 20 health workers and 1 doctor provide services to over 10,000 people, can increase the scale of diagnostics from one device used per patient to one device used for several [13]. The modern advances in mHealth, sensors, and remote communication tools are approaches that may increase the diagnostic yield at the point-of-care and reduce costs as an alternative to conventional diagnostic and laboratory devices. In parallel, efforts to develop community based mHealth adoption must be strengthened with partnerships that focus on the education and dissemination of these advances by tailoring mHealth solutions to specific community and healthcare system needs. The overall goals of this project are to determine the impact of smartphone-based mHealth device assessments on clinical decisions among patients with rheumatic and structural heart disease through randomized trial design, community engagement and pragmatic technology utilization. We hypothesize that mHealth for the identification of structural heart diseases facilitates earlier treatment decisions through point-of-care assessments of symptom, structural and functional abnormalities, and in turn leads to improved long term outcomes. This hypothesis will be addressed with the following 3 specific objectives:

Specific Objective #1: To assess the impact of mHealth device assessments used as point-of-care clinical decision support tools on treatment and long-term outcomes among patients with structural heart disease through randomized clinical trial design.

The primary objective of the current investigation is to evaluate the comparative efficacy of mHealth device assessments as a clinical decision support tool and to determine the outcomes of treatment with

valvuloplasty or valve replacement and long-term morbidity among patients with structural heart disease compared to standard-care.

The study will be performed under the American Society of Echocardiography Foundation- Valvular Assessment Leading to Unexplored Echocardiographic Stratagems (ASEF-VALUES) program - a philanthropic and educational collaboration to explore healthcare solutions for patients with SHD using new technologies. Within the program will be a nested, single-site, randomized trial at conducted at the Sri Satya Sai Institute of Higher Medical Sciences (SSSIHMS) a charitable, tertiary-care, and teaching institution in Bangalore, India. Collaboration between local and international healthcare professionals (either onsite or in remote tele-echocardiography) will promote educational activities towards high quality echocardiographic assessments and personnel training.

Time Frame: Organization for the program began in 2013. Execution of the trial is planned for 08/2014 with patient follow-up to be completed in 10/2015

Clinical Trial Design: Prospective, single center, randomized study

Study Participants: Inclusion of consecutive patients referred for the evaluation of rheumatic and structural heart disease. The study participants are symptomatic outpatients with a new or an established diagnosis of SHD. The definition of SHD included valvular disease, left/right ventricular failure, congenital heart defects and included adult, pediatric, and pregnant patients. We decided a priori to also include SHD patients with a prior valvuloplasty or valve replacement. Exclusions included neonatal patients and those with an unstable hemodynamic status.

Participating Physicians: Cardiologists from across India are invite to participate in the program and clinical trial. All participating physicians will perform the initial mHealth and standard of care assessments. We anticipate inclusion of 40 participating physicians from India, 5 from the United States, and 15 ASE sonographers across the United States.

Randomization: Consecutive subjects will be randomly assigned to an initial evaluation with mHealth or to standard-care at the time of randomization. Study subjects were evaluated in either one of 5-mHealth or 5-standard-care clinical sites. All study participants will undergo a comprehensive transthoracic echocardiogram for anatomical assessments of the severity of SHD and consultation by expert cardiologists prior to a percutaneous or surgical procedure (mHealth workflow outline below and consort trial flow).

Blinding and Masking: Randomization will be concealed until the primary and secondary endpoints were analyzed. The performance of the initial diagnostic assessment, mHealth or standard-care, will not permit patients to be masked to the assigned randomization. The operating cardiologists and cardiac surgeons performing percutaneous valvuloplasty or valve replacement will be blinded to a study subject's group allocation.

Sample Size Estimation: The philanthropic nature of the current program precludes an accurate sample size calculation. Therefore, randomization will be achieved with a simple randomization schedule for 400 individuals. Consecutive study participants will be allocated to each study arm by study staff not involved in patient care or outcome adjudication to maintain concealment of allocation.

Initial mHealth Assessments: Each mHealth clinic will be equipped with wireless mHealth devices and were selected to assess SHD including: (1) structural abnormalities with pocket-echocardiography (Vscan®, General Electric Healthcare, Whitefield Bangalore); (2) vital signs with smartphone-connected oxymetry and blood pressure monitors (iHealthLabs®, San Francisco); (3) functional assessments on a 6-minute walk test with a trial-axial activity monitor (Ozeri®, San Diego); (4) cardiac rhythm abnormalities with smartphone-connected-iECG (AliveCor®, San Francisco) and; (5) point-of-care testing with fingerstick B-type natriuretic peptide (Alere Triage®, Waltham, MA and Gurgoan, India). Device description and data capture below.

After enrollment, all subjects will undergo a comprehensive transthoracic echocardiographic examination (General Electric Vivid E9, Philips Healthcare ie33) using standard adult probes performed by onsite ASE-sonographers according to ASE guidelines [14]. Local and ASE cardiologists interpreted all echocardiographic studies by using a paperless and cloud-based system as previously reported [15]. mHealth devices with the exception of pocket-echocardiography and point-of-care BNP will be connected via Bluetooth to a tablet computer (Samsung Galaxy Tab™, Samsung Electronics, Seoul, South Korea). The mHealth clinics are designed to operate without WiFi and used only local power supply. The institutional electronic medical record will be modified to input all mHealth and standard-care findings to facilitate paperless data collection at the time of the initial encounter and during trial follow-up.

Initial Standard-Care Assessments

The standard-care clinics utilized available resources including a 12-lead ECG, radiographic, and laboratory testing as clinically required. Participating cardiologists who have experience treating patients with SHD will conduct the initial assessments, interpret all point-of-care mHealth or standard-care assessments, will make preliminary treatment decisions, and will determine the frequency of follow-up visitations.

Outcomes

The primary outcome will be the time to treatment with valvuloplasty or valve replacement over 12-months after the initial mHealth or standard-care assessment. Secondary outcomes include the occurrence of a cardiovascular hospitalization and/or death on follow-up. The primary investigators at SSSIHMS will adjudicate all clinical endpoints and will determine the necessity for percutaneous or surgical treatment. Outcomes will be obtained at the time of a procedure and will be determined by telephone, text message, or by community health worker visitation to the home.

Specific Objective #2: To develop information technology systems of integration for input of mHealth device assessment to the institutions electronic medical record and for paperless data capture. We aim to determine the utilization of smartphone-connected mHealth devices through two main patterns; 1) at the point-of-care for comprehensive assessments of functional and structural abnormalities, and 2) to capture device assessments electronically with direct input of findings to electronic medical records for clinical decisions. Transthoracic echocardiographic interpretation will be achieved by a paperless and cloud-based reporting platform (StudyCast) [15].

Specific Objective #3: To develop a community-based participatory model to determine the implementation methods for mHealth towards device-enabled healthcare and to advance echocardiographic education in rheumatic and structural heart disease with new imaging technologies. We aim to utilize a community-based participatory research model to determine the implementation barriers of mHealth and to determine the specific devices needed. Towards this objective we will design mHealth educational modules and to conduct serial tele-conferences with local healthcare practitioners in a collaborative environment prior to initiation of device use. The purpose of this upfront collaboration is to achieve device familiarity, to gauge workflow metrics that are most applicable to the regional healthcare system, and to create novel Internet based educational modules and presentations for continued use. Community-based participation will be achieved with collaboration between local and regional healthcare workers including physicians, nurses, community health workers and administrators, information technology, engineers, local industry support including device manufacturers (General Electric Healthcare, Alere Inc.).

mHealth Workflow Outline

75 – 100 patients per day over 3 days

Randomization - Central waiting area

Blinding and Concealment of Allocation
Patients proceed either to the mHealth clinic or the standard of care clinic
All patients identified by a hospital wrist-band and medical record number



Standard of Care Clinic
1-2 healthcare workers
1 computer/laptop with EMR Access

1. History and Physical Examination
   Patient care time 30-45 minutes per encounter

mHealth Clinic
1-2 physicians, 1 IT volunteer
1 computer/laptop with EMR Access

In the following order

1. Activity Monitoring – 6 minute walk test (outside clinic) Estimated time 15 minutes per test. Performed by 1-2 healthcare workers with results recorded on paper. Patients then proceed to the mHealth clinic site

2. History

3. iECG and analysis –2 minutes

4. iBlood Pressure – 1 minute

5. iBNP for selected cases

6. Pocket-Echocardiography

6 minute walk test measures and mHealth device measures to be recorded in the modified EMR drop downs

All patients proceed to TTE for comprehensive assessment of structural heart disease

Cloud-based and paperless reporting with StudyCast

12-month outcome adjudication for treatment decisions for valvuloplasty or valve replacement and cardiovascular hospitalization and/or death

mHealth and standard of care clinics

- IT Requirements
    - 1 computer with EMR in each mHealth (5) and standard of care clinic (5)
    - Modifications to the EMR for mHealth data entry
- Power outlet if devices need to be charged
- Extra batteries for iECG and activity monitoring
- 5 power converters
- 1 Android based smartphone per mHealth clinical station – 5 smartphones – devices to be decided for mHealth compatibility
- Participating cardiologists who have experience treating patients with SHD conducted the initial assessments, interpreted all standard-care assessments, made preliminary treatment decisions, and determined the frequency of follow-up visitations

ACTIVITY MONITORING – 6 MINUTE WALK TEST

- 5 outdoor activity monitoring sites (20 meters with 1 meter marks)
- 2 healthcare workers both individuals will be familiar with device use – 1 individual monitors and the other records
- Recording of baseline vital signs
- Recording of 6 minute vital signs, activity results and symptoms
- Paper based recording then entered in the EMR dropdowns once at the mHealth clinic

    - Patient identification number
    - Baseline Vital signs
        - Resting Heart Rate: blank for data entry
        - Resting Oxygen Saturation: blank

    - 6 Minute vital signs and activity results
        - Symptoms: None, chest pain, shortness of breath, palpitations, lightheadedness, fatigue
        - Other Symptoms:
        - Duration of Activity: Time in minutes and seconds
        - Heart Rate:
        - Oxygen saturation:
        - Number of steps:
        - Distance:
        - Walking Speed:

Pocket Echocardiography

- Performed by one local physician and one visiting sonographer
- Qualitative assessments (mild, moderate or severe) of chamber size, volumetric estimations and severity of valvular stenosis, regurgitation, and left and right ventricular dysfunction will be interpreted at the time of randomization and the initial assessment.
- Left ventricular ejection fraction was stratified into normal ≥ 55% or low if it was <55% by visual estimation and the presence of valvular abnormalities (regurgitant or stenotic)
- The severity of regurgitant lesions was based on two-dimensional findings (atrial or ventricular enlargement, hyperdynamic left ventricle) and qualitative color Doppler findings (width of vena contracta and jet area), whereas the severity of stenotic lesions was based on two-dimensional findings of valve opening and leaflet mobility, thickness, and calcification. (mild, moderate, or severe), or mitral stenosis (progressive, severe, very severe) were recorded according to The American Society of Echocardiography recommended definitions.
  Results inputted directly into the electronic medical record.

iECG – SMARTPHONE BASED ECG

- Performed by the healthcare worker – 2 minutes to perform the test and to interpret
- This can be performed with either the patient holding the ECG case or with the case applied to the chest (if the patient can not comply, tremor etc.)
- If WiFi hotspot is available the PDF of the rhythm strip can be emailed to a generic email account but will need to be amended with the patient MRN or participant number
- Drop downs- two dropdowns each with the following as more than one finding may be present
    - Interpretable – Yes/No
    - Sinus Rhythm
    - Sinus bradycardia
    - Supraventricular tachycardia
    - Atrial fibrillation or Atrial flutter
    - First degree AV Block
    - Second degree AV Block
    - Complete heart block
    - Frequent PAC, PVC

iBlood Pressure

- Performed by healthcare worker – 1 minute to perform the test
- Blood pressure result will be transmitted to the Android based phone
- Results entered in the EMR
- Dropdown:
    - Blood Pressure: blank for results entry
    - Heart Rate: blank for results entry

iBNP – details to follow (2 minutes to perform – 15 minutes for results)

- Will be used in a separate station after completion at the mHealth clinic and among a select group of patients (euvolemic and symptomatic, moderate-severe MS etc.)
- Performed by 2 healthcare workers – one physician and one assistant
- Requires a fingerstick (assistant to be familiar with safety measures)
- Paper record with patient MRN for results to be inserted in the EMR

Standard-Care Clinics

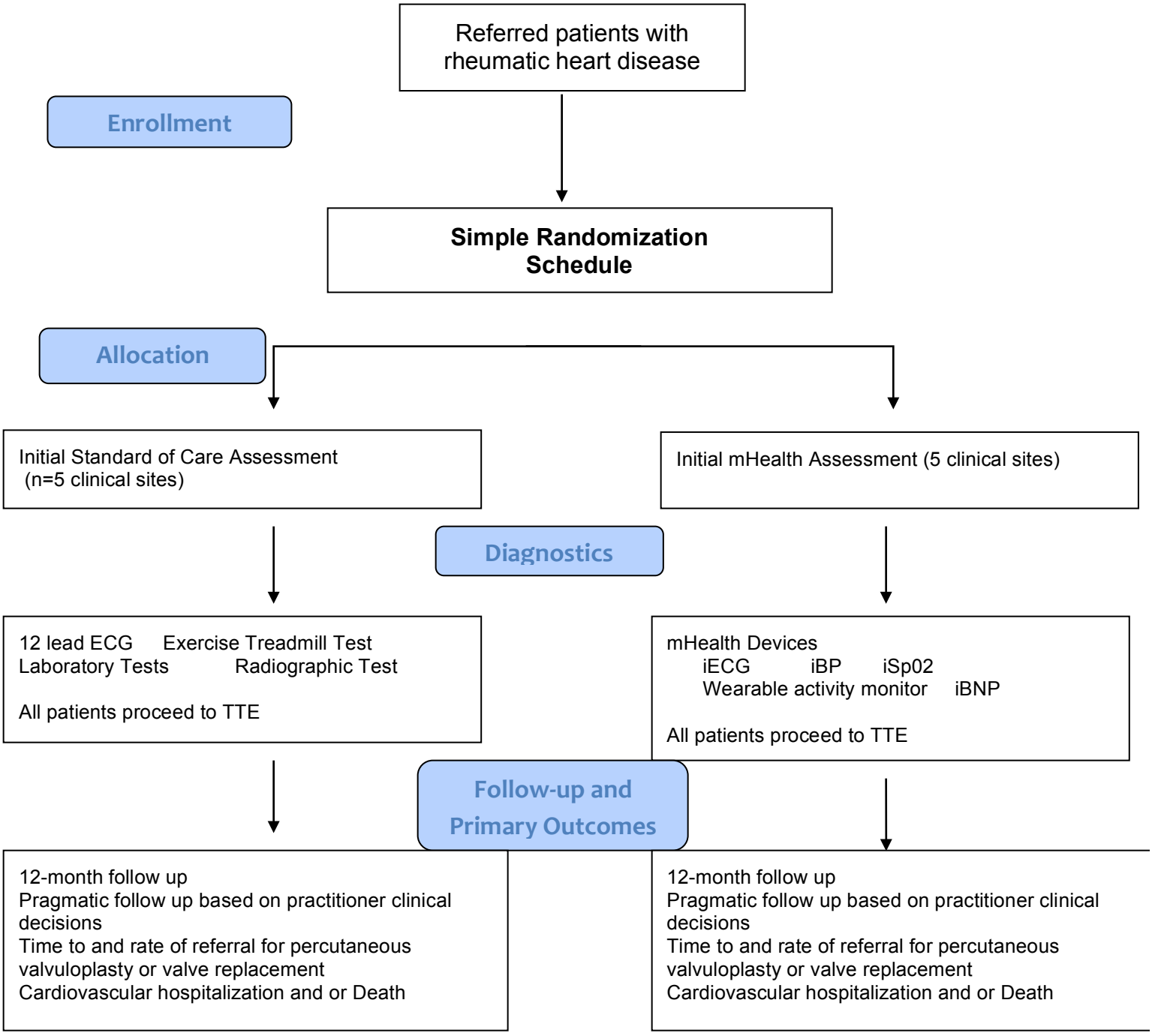
- The standard-care clinics utilized available resources as clinically required including:
  - 12-lead ECG
  - Radiographic testing
  - Laboratory testing
  - Participating cardiologists who have experience treating patients with SHD conducted the initial assessments, interpreted all standard-care assessments, made preliminary treatment decisions, and determined the frequency of follow-up visitations

Transthoracic Echocardiography and Cloud-based Reporting

- After enrollment, all subjects will undergo a comprehensive transthoracic echocardiographic examination (General Electric Vivid E9, Philips Healthcare ie33) using standard adult probes performed by onsite ASE-sonographers according to ASE guidelines.
- Each echocardiography study interpretation will be performed using a standardized template that included information about chamber dimensions, valve morphology, color flow, global and regional left ventricular (LV) systolic function, and any apparent congenital cardiac malformations. Any other abnormality, if found, will also be recorded. The reports were finalized on a Web-based system with the goal of accomplishing this on the day of initial scanning. The reports were subsequently downloaded and printed by the local coordinators who distributed these reports to the patients.
- A paperless echocardiographic image transfer and reporting system will be utilized to provide immediate access of all studies for analysis and interpretation with the following details: upon completion of each transthoracic study a provisional echocardiographic report will be generated by the scanning sonographer. Studies will be uploaded to a cloud-based Web server (Studycast; Core Sound Imaging, Inc., Raleigh, NC) for access on any Web-enabled computer device.

Company	mHealth Device		Medical Use
iHealth Labs	Wireless Blood Pressure Monitor		Blood Pressure and Heart Rate
	Wireless oxygen monitor		Oxygen Saturation and Heart Rate
General Electric	Pocket Handheld Ultrasonography		Portable ultrasonography
AliveCor	Handheld Cardiac Rhythm Monitor		Continuous heart rate and rhythm monitor
Ozeri	Activity Monitoring		Tri-Axial activity monitor
Alere Diagnostics	Point-of-care BNP testing		Microfluidic BNP/NT-pro-BNP assay

CONSORT TRIAL FLOW



Secondary Analysis/Objectives

- Diagnostic accuracy of pocket-echocardiography to transthoracic echocardiography for the severity of structural heart disease
- Functional class assessment between activity monitoring and patient reported
- Creation of mHealth educational modules