Screening for Peripartum Cardiomyopathies using Artificial Intelligence (SPEC-AI)-Nigeria

NCT05438576

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Screening for Peripartum Cardiomyopathies using Artificial Intelligence (SPEC-AI) – Nigeria

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Protocol Revision Log:

Protocol Date (Version)	**Key Changes Made**
March 1, 2022, Version (1.0)	Initial version
April 14, 2022, Version (1.1)	Protocol restructured and expanded to be consistent with ICH guidelines
July 25, 2022, Version (1.2)	Minor updates to add current NCT clinical trial number; clarifications to protocol methods; reframing sampling size justification to increase clarity
April 21, 2023, Version (1.3)	Protocol updated to modify overall target enrollment to 1,400 study participants, in order to achieve an accrual target of 1,200, with each site accruing 200 participants (6 sites).

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Study Summary

Title	Screening for Peripartum Cardiomyopathies using Artificial Intelligence (SPEC-AI) – Nigeria
Running Title	Screening for cardiac dysfunction in pregnancy
Protocol Number	22-000539
Phase	Other
Methodology	Prospective randomized controlled trial
Overall Study Duration	12 months
Subject Participation Duration	Participation will range from a single encounter/visit to a maximum of 12 months
Single or Multi-Site	Multi-Site
Objectives	To determine the effectiveness of an AI-enabled ECG to detect cardiomyopathy and its impact on clinical outcomes in a predominantly Black obstetric population in Nigeria
Number of Subjects	1,400 enrolled / 1,200 accrued
Diagnosis and Main Inclusion Criteria	The condition being studied is pregnancy related cardiomyopathy Inclusion Criteria: • Adult female age of 18 – 49 years • Currently pregnant or within 12 months postpartum • Able to provide consent
Study Product, Dose, Route, Regimen	Intervention: AI algorithm to evaluate electrocardiogram data and generate prediction probabilities for a diagnosis of cardiomyopathy. To be performed intermittently at pre-specified time points during the study Drug, Dose, Route: Not applicable
Statistical Methodology	The analysis plan will focus on comparing AI-ECG algorithm predictions of low ventricular ejection fraction (<50%) with baseline echocardiograms as the reference criterion (clinical standard) and evaluating the impact of AI-ECG screening on maternal outcomes.

1. Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations, Mayo Clinic research policies and procedures and local regulations in Nigeria as applicable including data privacy rules and ethics board requirements

1.1. Background

An artificial intelligence (AI) model was developed by members of our Mayo Clinic team to identify cardiac dysfunction (defined as left ventricular ejection fraction (LVEF) ≤35%) using an electrocardiogram (ECG) alone with high discrimination - area under the curve (AUC) of 0.93. (Z. I. Attia et al., 2019) We validated this AI-ECG model in the emergency room setting among patients with undifferentiated dyspnea (D. Adedinsewo et al., 2020) and in a clinical trial among patients seen in the primary care setting and it remained robust. (Yao et al., 2021)

Given that cardiovascular disease (CVD) is the leading cause of pregnancy-related mortality, we retrospectively evaluated the AI-ECG among pregnant and postpartum women seen across the Mayo Clinic enterprise and found it to be effective with an AUC of 0.92 (D. A. Adedinsewo et al., 2021). These prior studies provide preliminary data and support the feasibility of using the AI-ECG in a clinical setting. It also establishes the premise for its application to routine obstetric and postpartum care. Black women are disproportionately affected by pregnancy-related cardiac dysfunction (cardiomyopathy) and underrepresented in clinical research studies. To reduce health disparities and promote health equity, a prospective evaluation of the AI-ECG in a Black obstetric population is essential.

Although maternal mortality has been on the decline worldwide, maternal mortality rates in the U.S. have increased over the last 20 years with rates 3 times higher now than in the 1980s. (CDC:Division of Reproductive Health; G.B.D. Maternal Mortality Collaborators, 2016) . Cardiomyopathy (a disease of the heart muscle that makes it difficult to pump blood to the rest of the body) is responsible for the majority of deaths among pregnant and postpartum women, with Black women bearing a disproportionate burden of disease. (Melinda B Davis et al., 2021; Mehta et al., 2020) Failure to identify CVD symptoms is believed to be contributing to this critical health inequity. (ACOG, 2019) In low-income countries, particularly sub-Saharan Africa, maternal mortality rates are up to 40 times higher (1074/100,000 live births) than in the U.S. (G.B.D. Maternal Mortality Collaborators, 2016). This issue is of global concern which made it a key priority item on the United Nations Millennium development goals. (Hogan et al., 2010) *What remains unknown are effective methods to screen for cardiomyopathy during pregnancy and the postpartum period*. Symptoms of normal pregnancy and cardiomyopathy frequently overlap (Hameed et al., 2015) making it difficult for clinicians to identify high-risk women in routine obstetric practice. Thus, there is a *critical need* to identify simple and effective screening tools to detect cardiomyopathy in pregnant and postpartum women. In the absence of this knowledge, the development of effective intervention strategies to decrease cardiomyopathy-related maternal mortality among Black women will remain challenging.

Our *long-term goal* is to identify effective strategies for cardiomyopathy detection among pregnant and postpartum women so that appropriate interventions can be developed to decrease cardiomyopathy-related maternal mortality. The *overall objective of this proposal* is to determine if an AI-ECG is an effective tool to screen for cardiomyopathy among pregnant and postpartum women. Our *central hypothesis* is that an AI-ECG improves the diagnosis of cardiomyopathy among pregnant and postpartum women. We have based our central hypothesis upon data from a retrospective analysis we conducted among pregnant and postpartum women seen across the Mayo Clinic enterprise which showed the AI-ECG was effective for cardiomyopathy detection. (D. A. Adedinsewo et al., 2021) Our *rationale* for this project is that its successful completion would provide a cost-effective and scalable option for cardiomyopathy screening in the obstetric population and enable the development of appropriate interventions targeted at reducing cardiomyopathy-related mortality. We are *well-positioned to lead this project* based on our team's expertise and experience with developing and validating AI-ECG models for CVD detection. Members of our team were the first to develop and publish results supporting the AI-ECG as an effective method to screen for cardiomyopathy. (Z. I. Attia et al., 2019)

Following the successful completion of this project, we expect to have established the effectiveness of a novel AI-ECG to detect cardiomyopathy in Black pregnant and postpartum women that will ultimately improve diagnosis and decrease maternal mortality. This achievement would not only cause a positive paradigm shift in the field of obstetric care, but it would also help (1) promote health equity, (2) increase the inclusion of women in cardiovascular clinical research, and (3) support the use of AI tools to improve cardiovascular care.

1.2. Investigational Agents

This protocol intends to evaluate a standard clinical 12-lead ECG recordings (Fig 1) and portable ECG device recordings (Fig 2 and 3) analyzed with AI-ECG algorithms for cardiomyopathy detection. These algorithms are investigational at this time and not yet approved for medical use by the US Food and Drug Agency.

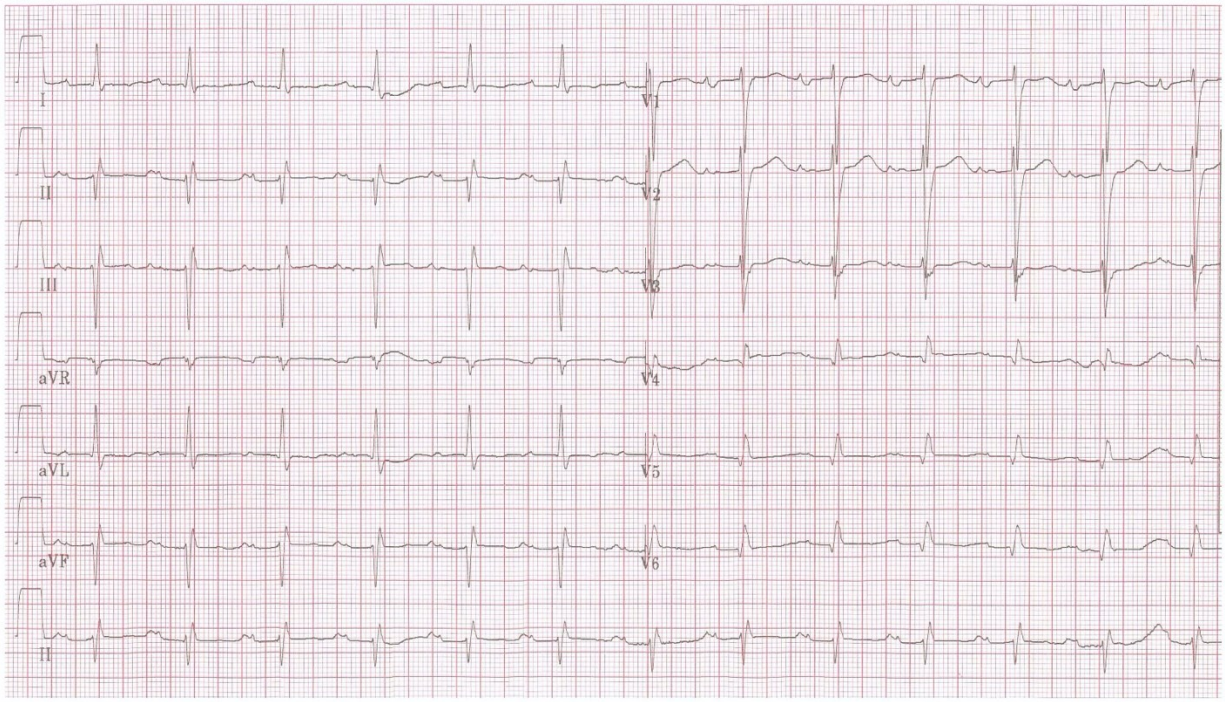

Figure 1. Standard 12-lead ECG

Figure 2. AliveCor 6L wireless ECG device with portable 6-lead ECG displayed

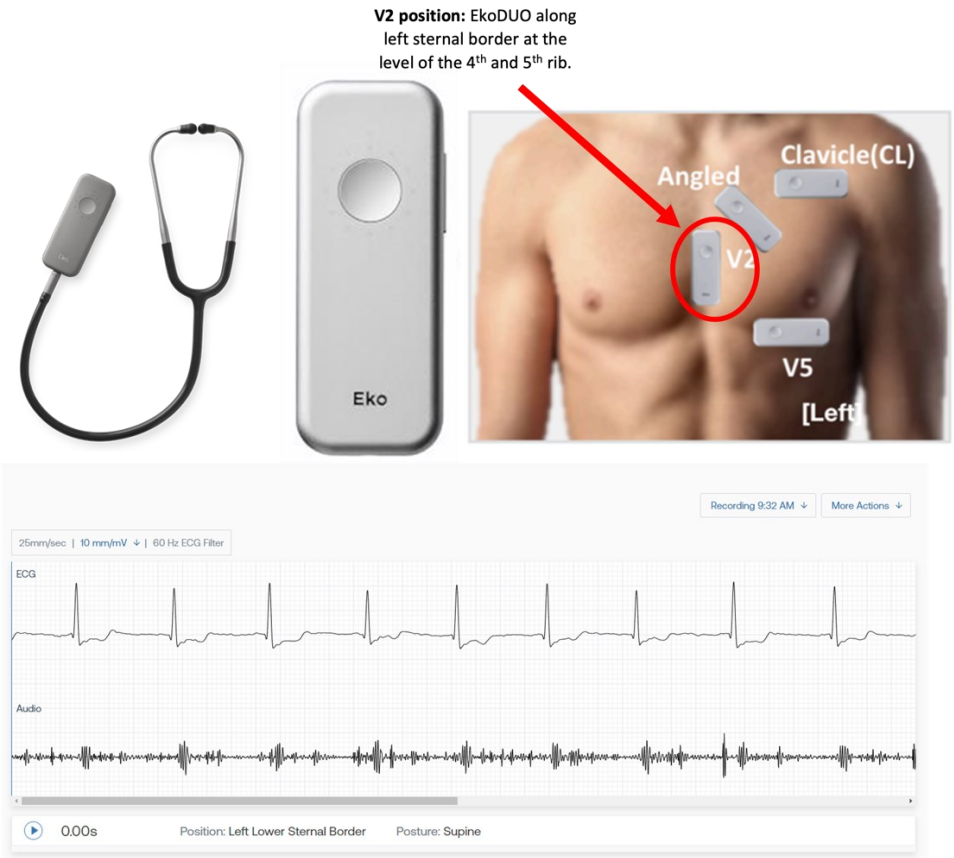

Figure 3. Eko DUO Digital Stethoscope with portable single-lead ECG displayed

1.3. Preliminary Data

An artificial intelligence (AI) model has been developed by members of our Mayo Clinic team to identify cardiac dysfunction (originally defined as left ventricular ejection fraction (LVEF) ≤35%; although alternative LVEF thresholds are under investigation including <=40% in the current registration trial for the LVEF algorithm) using an electrocardiogram (ECG) alone with high discrimination - area under the curve (AUC) of 0.93. (Z. I. Attia et al., 2019). The initial model was developed using a dataset of 97,829 patients (with paired ECG and echocardiograms).

The ROC curve from the published manuscript is shown below.

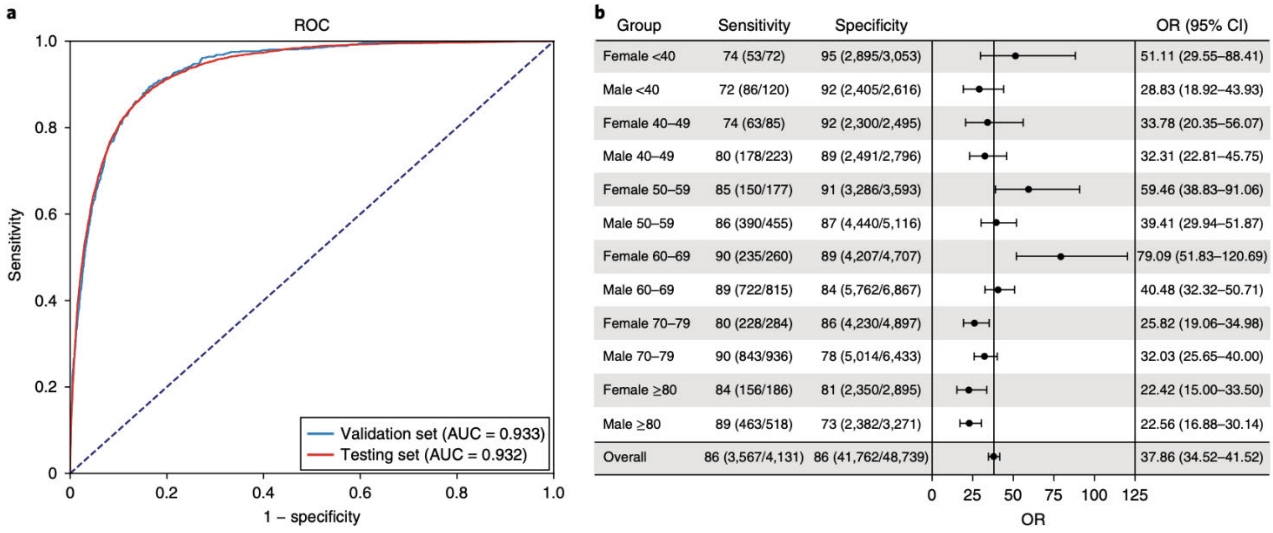

Figure 4. Network ROC and sensitivity and specificity across age and gender subsets.

An ongoing pilot study has collected prospective ECG and echocardiogram data under Mayo Clinic IRB 21-003427 and we have enrolled 66 out of a target 100 study participants including standard 12-lead and portable ECG device recordings obtained at pre-specified intervals during the study.

1.4. Risks and Benefits

The risks of this research study are expected to be minimal and represent the general risks associated with prenatal wellness screening and routine medical care. However, there are some risks that are associated with study procedures. Anticipated study related risk includes the potential skin irritation from placement of ECG lead electrode stickers directly on the skin for 12-lead ECG recordings. To minimize risk for skin irritation, the ECG lead electrode stickers will only be placed on the skin for the duration that the ECG is recorded as with standard clinical practice with an estimated duration of contact less than 5 mins.

Another risk in this study is the communication of results for the attention control arm. Two experimental algorithms will be used that predict biological sex and age. There is a potential for discordance in sex to be reported along with large variances in estimated age. The implications of such predictions is not yet known. Study staff will be trained on the algorithms and a study information sheet will be used to describe the study procedures and test results.

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

- All enrolling sites in Nigeria will maintain their own confidential screening logs following local institutional procedures, local regulations and ethics boards requirements.

- Confidentiality of patient information will be maintained by assigning study identifiers to the medical data.

- Digital ECG data will be sent using a secure, encrypted online-based file share service with detailed instructions provided to study sites and as detailed in the study's Manual of Operations. No identifiable data received will be shared external to Mayo Clinic. Only study staff will have access to the data collected.

- Additional Considerations: The following is a list of study participant confidentiality safeguards:
    - ***Data flow procedures*** – Data identifying participants should not be transmitted from study sites to the Coordinating Center.
    - ***Electronic files*** – Data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file with device password protection.
    - ***Forms*** – Forms or pages containing personal identifying information should be separated from other pages of the data forms and retained in a secure location.
    - ***Data listings*** – Participant name, name code, hospital chart, record number, Social Security Number, or other unique identifiers should not be included in any published data listing.
    - ***Data distribution*** – Data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
    - ***Data disposal*** – Computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
    - ***Access*** – Participant records should not be accessible to persons outside the study without the express written consent of the participant.
    - ***Storage*** – Study forms and related documents retained both during and after study completion should be stored in a secure location.
    - ***Passwords*** – Passwords provide limitations on general access to computer systems and to the functions that individuals can use. Passwords should be changed on a regular basis.
    - ***User Training*** – Study staff with access to clinical computer systems should be trained in their use and in related security measures. Training should include explanations of how to access the system and a discussion of the need for, and importance of, system security.

There may be direct benefit to study subjects participating in this research study as early heart failure or other heart condition may be detected sooner than it may have been otherwise. Other than that, study participants may not receive any other direct benefit from participating in this study. The results of this study could potentially lead to a positive paradigm shift in the field of obstetric care, and help (1) promote health equity, (2) increase the inclusion of women in cardiovascular clinical research, and (3) support the use of AI tools to improve cardiovascular care.

2. Study Objectives

2.1. Primary Objective

The overall objective of this study is to determine if an artificial intelligence enhanced electrocardiogram (AI-ECG) is an effective tool to screen for cardiomyopathy (LVEF < 50%) in a predominantly Black population of pregnant and postpartum women.

2.2. Secondary Objectives

a) Determine if an AI-ECG improves the detection of cardiomyopathy among Black pregnant and postpartum women.

b) Determine the effectiveness pf an AI-ECG for cardiomyopathy detection at different LVEF cut offs (<45%, <40%, ≤ 35%)

2.3. Exploratory Objectives

(a) Determine the diagnostic yield of an AI-ECG on cardiovascular outcomes among pregnant and postpartum women.
(b) Determine the impact of an AI-ECG on echocardiography utilization
(c) Develop and evaluate the diagnostic performance of an AI-enhanced point of care screening tool using portable, smartphone-compatible ECG devices (AIPOC-ECG) for the detection of cardiomyopathies in pregnant and postpartum women.

3. Study Design

3.1. General Description

Nigeria is estimated to have the highest incidence of peripartum cardiomyopathy in the world, as high as 1 in 100 deliveries (M. B. Davis, Arany, McNamara, Goland, & Elkayam, 2020). As such, a prospective randomized-controlled study will be conducted at multiple sites in Northern and Southern Nigeria with study participants randomly assigned in a 1:1 fashion to the intervention vs. the control arm over a 12 to 18-month period.

Following informed consent, all participants will have ECGs acquired at baseline and at selected intervals during pregnancy and postpartum (Fig 5 and 6). Half of the participants will be randomized to either undergo:

- AI-ECG screening for cardiomyopathy + baseline echocardiography + AI-ECG age and sex estimation (intervention arm) or
- Standard of care + AI-ECG age and sex estimation only (Zachi I Attia, Paul A Friedman, et al., 2019) (attention control arm).

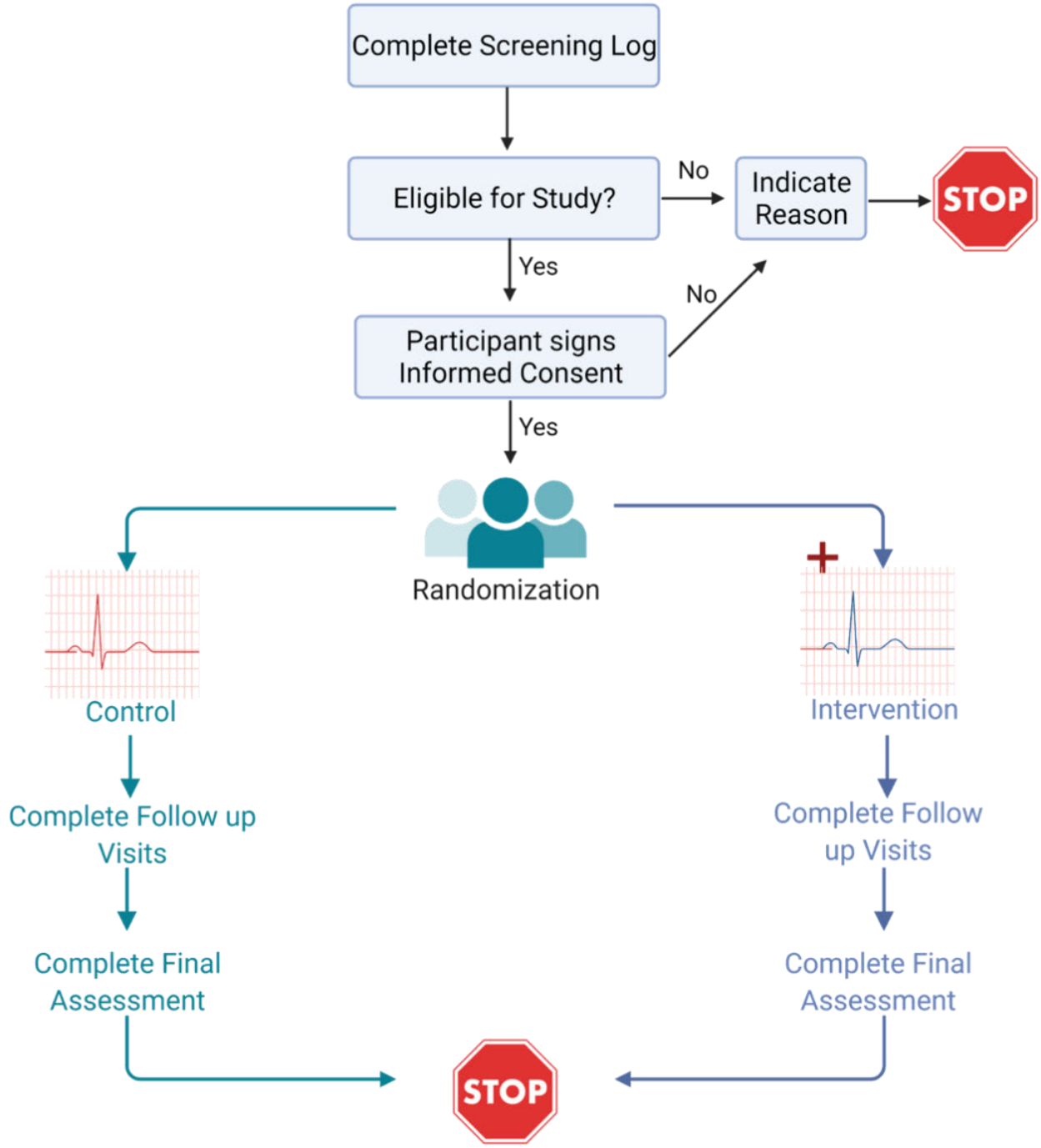

Figure 5. Patient enrollment flow diagram

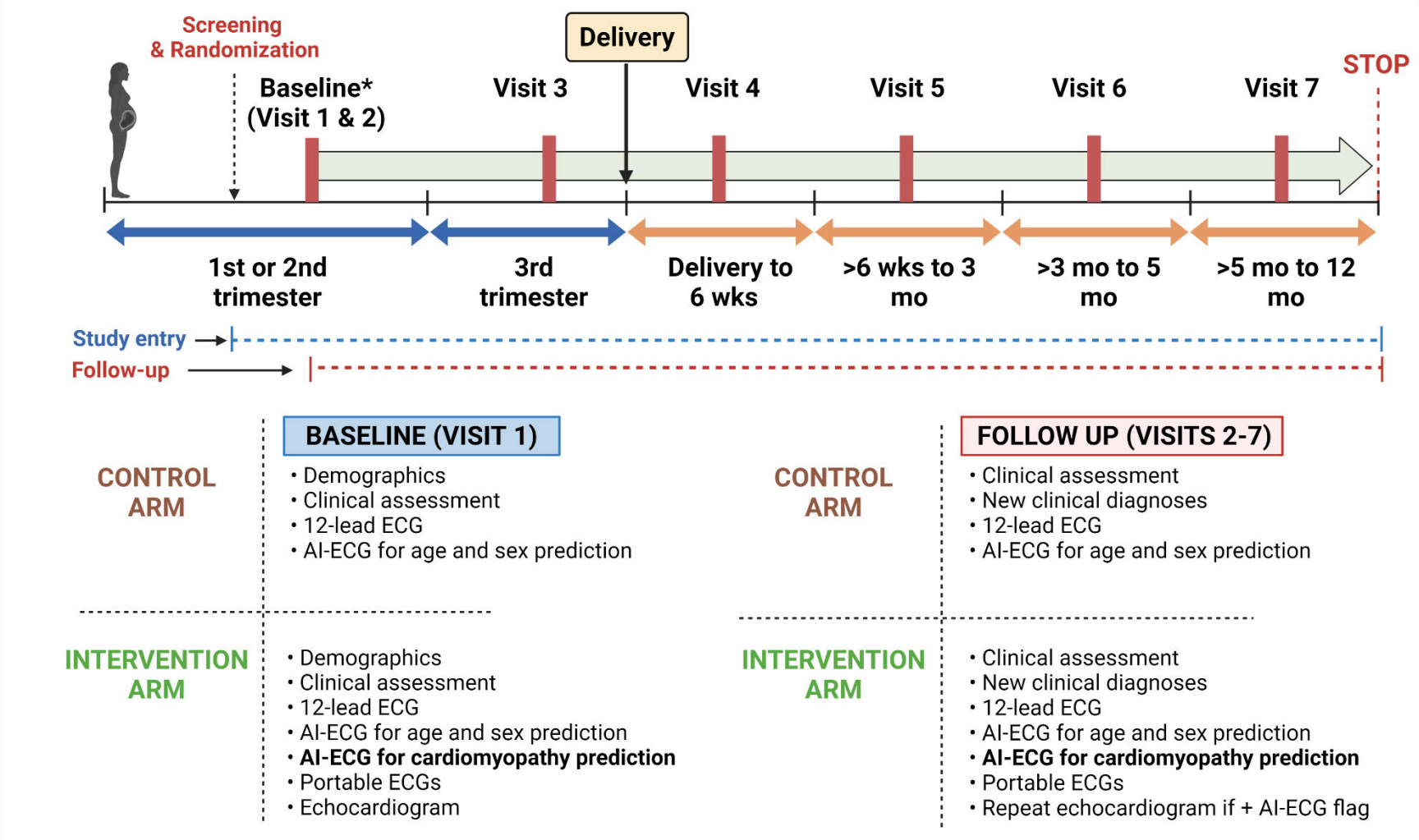

Figure 6. Study procedures

All patients will have follow-up and medical record review to ascertain the development of study clinical outcomes. Patients can enter the study at any time point (Fig 6) during pregnancy or the postpartum period (up to 12 months after delivery). All women will have a standard 12-lead ECG performed at the time of enrollment and at pre-specified intervals through 12 months postpartum or study end (whichever is earlier). ECGs will be performed up to 7 times during the study period including during each trimester of pregnancy (up to 3 ECGs), post-delivery ECGs may be taken between delivery and 6 weeks (1 ECG), between 6 weeks and 3 months (1 ECG), between 3 and 5 months (1 ECG), and between 5 and 12 months postpartum (1 ECG). Only participants in the intervention arm will have a baseline echocardiogram as well as simultaneous portable ECGs recorded with near real-time provision of AI-ECG cardiomyopathy prediction. Additionally, a newly positive AI-ECG screen for cardiomyopathy during any of the 6 visits will trigger an echocardiogram for participants in the intervention arm. This strategy for performing echocardiograms was selected as it is not practical to obtain an echocardiogram during each prenatal care visit due to time, skilled expertise required, and cost. In addition, the negative predictive value of the AI-enabled ECG is known to be very high (consistently exceeding 95%) in multiple internal and external patient populations (D. Adedinsewo et al., 2020; Attia et al., 2021; Z. I. Attia et al., 2019). Patients in the intervention group with cardiomyopathy detected on an echocardiogram will have a repeat echocardiogram performed at the end of the study period (or at 12 months postpartum depending on which is earlier) as part of the study protocol to assess for left ventricular recovery (Fig 6).

All echocardiograms will be reviewed by the local cardiologists and performed in accordance with American Society of Echocardiography guidelines for ejection fraction assessment as part of the study. LVEF measurements will be recorded for study participants using REDCap.

3.2. Number of Subjects

A total of 1,400 study participants will be enrolled, in order to achieve an overall accrual target of 1,200 participants across sites

3.3. Duration of Participation

An individual participant will be seen ranging from a single visit to a maximum of 7 visits (at pre-specified time points) depending on the time they enter the study (Fig 6). The maximum duration of participation for any one participant is 18 months if they enter the study in the first trimester (after the first 8 weeks to allow room for pregnancy confirmation). In addition, the maximum study duration is estimated to be 18 months due to funding/budgetary restrictions. The minimum duration of participation is one visit (1 day) if they enroll after 9 months postpartum and baseline visit is performed on the same day.

3.4. Identification of Source Data

Study-specific case report forms (CRFs) will be used to document demographic and clinical data obtained as part of the study.

All recorded or clinical and demographic data will be stored and shared with the Mayo study team as a limited data set using a secure online REDCap database with password protection. The Coordinating Center will provide individual (staff-specific) usernames and passwords to the electronic REDCap database for the study investigators and research staff at each site in Nigeria. This will help ensure attribution of data and changes to existing data to the individual study staff member. Mayo Clinic servers will be utilized to store the data and will be maintained by study staff. Any data recorded on paper documents will kept in locked cabinets at participating sites (See Guidance Document on Study Operations and Procedures for details).

The following source data will not be directly collected in the CRFs, but will be collected through the secure file share transfer portal as previously described and integrated into the master database:

- Digital ECG data
- AI-ECG predictions

4. Subject Selection Enrollment and Withdrawal

4.1. Inclusion Criteria

- Adult female age 18 – 49 years
- Currently pregnant or within 12 months postpartum
- Willing and able to provide informed consent

4.2. Exclusion Criteria

- Under 18 years of age
- Complex congenital heart disease (single ventricle physiology or significant shunts with cardiac structural changes)
- Significant conduction abnormalities (ventricular pacing on recorded ECG, pacemaker dependence, or severely abnormal/bizarre QRS morphology on ECG tracings)
- Unable or unwilling to provide consent

4.3. Subject Screening, Recruitment, and Enrollment

Study participants will be enrolled from multiple healthcare institutions in Nigeria, estimated to have the highest incidence of peripartum cardiomyopathy in the world (incidence of 1 in 100 deliveries) (M. B. Davis et al., 2020). No subjects will be enrolled at Mayo Clinic.

All enrolling sites in Nigeria will conduct enrollment at identified clinics or hospitals. All enrolling sites will develop a site-specific recruitment and enrollment plan following local institutional procedures, local regulations and ethics boards requirements.

4.3.1 Screening, Recruitment, and Enrollment Plan

The local site investigator and/or study coordinator will pre-screen potential participants by reviewing medical records of patients already seen or newly identified patients. A study staff member will present the study information to the potential participants during a clinic or hospital encounter. If the participant is interested and willing to consent immediately, then an approved study staff will review the informed consent process with the participant. If the participant needs additional time to think about the study and participation, they will be given a copy of the informed consent form (ICF), and any other related IRB study approved document(s). Study staff will follow up with the potential participant at 1-2 weeks to learn if he/she is still interested and would like to participate. If a potential participant is still interested, a screening visit will be scheduled to review the ICF to obtain signatures required to enroll in the study.

The site Study Coordinator/staff will utilize the steps that follow to screen participants for the study. A detailed operational plan along with templates (i.e., screening logs) is contained in the Study Protocol Manual of Operations.

I. Pre-Screening Phase
    a. Potential participant will be identified during clinic or hospital encounters

II. Screening Phase
    a. Study staff will meet with potential participant to explain the study
    b. Study staff will confirm that participant meets eligibility criteria
    c. Study staff will have the participant sign an Informed Consent Form and provide copies to participant while placing originals in participant file.
    d. Study staff will collect contact information for participant

The study coordinators will be hired and trained locally to present the trial information without bias or pressure and in a culturally appropriate manner. Translators will be used at the local site as needed. Screening and enrollment failures and related reasons for same will be discussed at the monthly review meetings and potential actions will be taken as need. Attention will be paid to adhering to regulatory issues.

4.4. Early Withdrawal of Subjects

4.4.1. When and How to Withdraw Subjects

Participation is strictly voluntary. Participants may withdraw at any point in the study which will not negatively impact future care. Investigators may withdraw participants at any point if they feel it is in the best interest of the participant to do so. Reasons for withdrawal will be documented locally.

4.4.2. Data Collection and Follow-up for Withdrawn Subjects

In the event a participant discontinues study interventions before study completion, every effort will be made by the study team to have the participant continue to complete all other study

procedures. However, if the participant is not willing to continue study participation, the study team will attempt to collect the final visit data.

5. ECG Testing and Echocardiogram Details

5.1. Description

Standard ECGs: The study will provide each participating site with a standard 12-lead ECG machine for use for the study as well as standard operating procedures (SOPs) on how to complete and transmit de-identified electronic ECGs to Mayo Clinic with a study identifier attached to each ECG file. Each site will perform a 12-lead ECG during each participant visit using standard clinical protocols. The ECGs recorded will be stripped of personally identifying and study identifier will be attached to the digital 12-lead ECG file. The ECG file will be exported and transmitted to Mayo Clinic study staff in XML format using the secure Mayo Clinic On-Demand File transfer portal. If the stripping of identifiable information should be missed by the site, Mayo Clinic staff will remove the identifying information, and or treat the data as confidential and will keep the file secure in the Mayo Clinic Research Server where only study staff will have access to it.

Echocardiogram: The coordinating center will cover the costs associated with performing echocardiograms per study protocol among study participants randomized to the intervention arm at each site. Results of the echocardiogram will be documented in REDCap. A repeat echocardiogram will be performed if a subsequent AI-ECG result flags positive cardiomyopathy in the intervention arm (if the baseline echocardiogram was normal). The results from the repeat echocardiograms will also be reported in REDCap. All echocardiograms will be reviewed by the local cardiologist at each site and performed in accordance with the American Society of Echocardiography guidelines for ejection fraction assessment.

Portable point-of-care (POC) ECGs (Eko DUO Stethoscope and AliveCor Kardia Mobile devices): will be recorded simultaneously in the intervention arm based on device manufacturer protocols following training at each site. AliveCor and Eko health will provide the portable ECG recordings taken at the participating sites to Mayo Clinic for analysis by our data engineering/science team. The de-identified data collected under this IRB may be used for future research. Participants in the intervention arm will have a seated wireless AliveCor Kardia Mobile 6-lead ECG (Figure 1) and a supine/seated Eko DUO Digital Stethoscope ECG recorded before or after a standard 12-lead ECG. The duration of patient involvement in the study will include consent review and signature, completion of a standard 12-lead ECG for all participants as well as the portable ECG recordings as described above. All ECG data will be recorded by study coordinators at each site following appropriate training on how to obtain the ECGs. The portable electrocardiographic tracings recorded by both devices are strictly for research purposes as it relates to this study and is not intended for use in guiding the patient's clinical care.

AliveCor Kardia 6L device: This is an FDA approved handheld smart device. This device will be observed for handheld recording as approved by FDA. The ECG signal is communicated wirelessly via Bluetooth to a mobile computing platform (MCP, which is a smartphone or tablet)

running the Kardia application (App). The Kardia App processes the signal into a real-time ECG. The data from Leads I and II are used to calculate, on a mobile or web-based app and in real time, Leads III, aVR, aVL, aVF. The results of the electrocardiographic tracings recorded by the AliveCor devices will not be entered into the electronic medical record or used to guide the patient's clinical care. De-identified data from the recordings will be uploaded to the AliveCor cloud, which is only accessible to the study team by username and password. For individuals unable to record from all three electrodes, data can be acquired from two electrodes only, as shown in Figure 1. The AliveCor recordings will be identifiable by an assigned study ID and date of transmission. Data from the AliveCor device will be transmitted via the research study's smartphone/tablet app to the cloud, where it will be password protected via account log-in, and only accessible to the research team for download to the Mayo research server. The AliveCor cloud server will only be utilized during the duration of the research study and is not accessible to external parties.

Eko DUO Digital Stethoscope: This is an FDA-cleared and CE-marked electronic stethoscope that allows audio recording of heart sound to produce a phonocardiogram (PCG) as well as a single-lead ECG recording. Based on the AI-ECG model for cardiomyopathy detection developed by Attia et. al. (Z. I. Attia et al., 2019), Eko health has developed a single-lead version of the same model to be used with the Eko DUO digital stethoscope which can provide near real-time AI-ECG predictions for cardiomyopathy at the point of care (Zachi I Attia, Jennifer Dugan, et al., 2019). The results of the electrocardiographic tracings recorded by the Eko DUO stethoscope will not be entered into the electronic medical record or used to guide the patient's clinical care. The Eko DUO recordings will be identifiable by an assigned study ID and date of transmission. Raw data from the Eko DUO Stethoscope device will be transmitted via the research study's smartphone/tablet app to the cloud, where it will be password protected via account log-in, and only accessible to the research team for download to the Mayo research server. The Eko DUO cloud server will only be utilized during the duration of the research study and is not accessible to external parties.

Using the AliveCor or Eko DUO device to record electrocardiographic tracings should not cause discomfort or inconvenience other than a minimal delay to acquire the readings. The AliveCor Kardia 6L and Eko Duo are 510(k) cleared devices. Between uses the electrodes and all surfaces will be cleaned using antiseptic (75% alcohol) wipes. Sequential numbers will be used for enrollment de-identification for the portable ECG recordings. Acquired data from each device will be stored on HIPAA-compliant, encrypted servers.

6. Study Procedures

6.1. Schedule of Events

6.1.1 - Control Arm

Assessment	Screening	Baseline, Randomization Visit 1	Visits 2 -7

Inclusion/Exclusion Criteria	**X**	**X**	
Informed Consent[a]		**X**	
Demographics		**X**	
Clinical Assessments[b]		**X**	**X**
Medical History		**X**	
New Clinical Diagnosis			**X**
Current Medications		**X**	
Blood Chemistries[c]		**X**	
Hematology[d]		**X**	
Urine Analysis[e]		**X**	**X**
Inclusion/Exclusion Criteria	**X**	**X**	
Enrollment/Randomization		**X**	
12 lead ECG		**X**	**X**
AI-ECG – Sex and Age Determination		**X**	**X**

[a]Consent may be obtained prior to baseline/randomization visit
[b]Height, weight, blood pressure and heart rate
[c]To be abstracted from medical records – Serum Cr, eGFR
[d]To be abstracted from medical records – Hemoglobin (g/dl) or Hematocrit (%) or Packed Cell Volume; Hemoglobin Genotype (Hb AA, AS, SS, Sc); Rhesus factor (negative or positive), infectious screen.
[e]To be abstracted from medical records – Positive for proteins (Yes or No)

6.1.2 - Intervention Arm

Assessment	Screening	Baseline, Randomization Visit 1	Visits 2-7
Inclusion/Exclusion Criteria	**X**	**X**	
Informed Consent[a]		**X**	
Demographics		**X**	
Clinical Assessments[b]		**X**	**X**
Medical History		**X**	
New Clinical Diagnosis			**X**
Current Medications		**X**	
Blood Chemistries[c]		**X**	
Hematology[d]		**X**	
Urine Analysis[e]		**X**	**X**
Enrollment/Randomization		**X**	
12 lead ECG		**X**	**X**
AI-ECG - Sex, Age, and Cardiomyopathy Determination		**X**	**X**
Portable ECG[f]		**X**	**X**
Echocardiogram[g*]		**X**	

[a]Consent may be obtained prior to baseline/randomization visit
[b]Height, weight, blood pressure and heart rate
[c]To be abstracted from medical records – Serum Cr, eGFR
[d]To be abstracted from medical records – Hemoglobin (g/dl) or Hematocrit (%) or Packed Cell Volume; Hemoglobin Genotype (Hb AA, AS, SS, Sc); Rhesus factor (negative or positive), infectious screen.
[e]To be abstracted from medical records – Positive for proteins (Yes or No)
[f]Portable ECGs will be performed only among those in the intervention arm

[g]Echocardiograms will be performed on all participants in the intervention arm at baseline and *if any new subsequent ECGs flag positive based on the AI-ECG predictions for cardiomyopathy (low ejection fraction) provided the baseline echocardiogram was normal. Participants with cardiomyopathy detected at any time point during the study will have a repeat echocardiogram at the end of study participation or 12 months postpartum (whichever is earlier) to assess for left ventricular recovery.

6.2. Visits

All patients will have follow-up and medical record review to ascertain the development of study clinical outcomes. Patients can enter the study at any time point during pregnancy or the postpartum period (up to 12 months after delivery). All women will have a standard 12-lead ECG performed at the time of enrollment and at pre-specified intervals through 12 months postpartum or study end (whichever is earlier). ECGs will be performed up to 7 times during the study period including during each trimester of pregnancy (up to 3 ECGs), between delivery and 6 weeks (1 ECG), between 6 weeks and 3 months (1 ECG), between 3 and 5 months (1 ECG), and between 5 and 12 months postpartum (1 ECG). Only participants in the intervention arm will have a baseline echocardiogram as well as simultaneous portable ECGs recorded with near real-time provision of AI-ECG cardiomyopathy prediction. Additionally, a newly positive AI-ECG screen for cardiomyopathy during any of the 6 visits will trigger an echocardiogram for participants in the intervention arm. This strategy for performing echocardiograms was selected as it is not practical to obtain an echocardiogram during each prenatal care visit due to time, skilled expertise required, and cost. In addition, the negative predictive value of the AI-enabled ECG is known to be very high (consistently exceeding 95%) in multiple internal and external patient populations (D. Adedinsewo et al., 2020; Attia et al., 2021; Z. I. Attia et al., 2019). Patients in the intervention group with cardiomyopathy detected on an echocardiogram will have a repeat echocardiogram performed at the end of the study period (or at 12 months postpartum depending on which is earlier) as part of the study protocol to assess for left ventricular recovery.

All echocardiograms will be reviewed for adherence to the American Society of Echocardiography guidelines for ejection fraction assessment as part of the study. LVEF measurements will be recorded for study participants using REDCap.

6.2.1. Screening

To be conducted as described in section 4 of this protocol

6.2.2. Randomization/Baseline visit

After informed consent has been obtained, the following procedures will be completed per the schedule of events table:

Control Arm

- Enrollment Randomization
- Demographic information
- Clinical Assessments
- Medical history
- Current Medications
- Blood Chemistries
- Hematology
- Urine Analysis
- 12-lead ECG
- AI-ECG Sex & Age Determination

Intervention Arm

- Enrollment Randomization
- Demographic information
- Clinical Assessments
- Medical history
- Current Medications
- Blood Chemistries
- Hematology
- Urine Analysis
- 12-lead ECG
- AI-ECG Sex, Age, & Cardiomyopathy Determination
- Portable ECGs
- Echocardiogram(s)

Visits 2-7

Control Arm

- New Clinical Diagnosis
- Clinical Assessments
- Current Medications
- Urine Analysis
- 12-lead ECG
- AI-ECG Sex & Age Determination

Intervention Arm

- New Clinical Diagnosis
- Clinical Assessments
- Urine Analysis
- 12-lead ECG
- AI-ECG Sex, Age, & Cardiomyopathy Determination
- Portable ECGs

- Repeat echocardiogram for Positive AI-ECG screen/new cardiomyopathy diagnosis (if baseline echocardiogram was normal)

6.3. Positive AI-ECG Screen/New Cardiomyopathy Diagnosis (Intervention arm only)

In the event that the AI-ECG detects cardiomyopathy (and baseline echocardiogram showed normal ejection fraction), this would trigger an echocardiogram as part of the research study protocol and the results would be reviewed by a local cardiologist and provided to the managing obstetrician which have already been identified at each site. For participants with newly diagnosed cardiomyopathy (confirmed by echocardiography), the decision to initiate guideline directed medical therapy or other treatment will be based on a clinical evaluation by a local cardiologist at each site, local clinical practice standards, treatment options available and patient preferences.

6.4. Age and Sex ECG Estimation

The application of the AI-ECG algorithms to estimate age and sex will occur at the coordinating center. As such, the estimation will be asynchronous with the clinical visits at each sites. The Coordinating Center will process ECGs as they arrive (~ monthly for each site) and return a report back to study investigators with the model results. These results may be communicated to the participant at a subsequent study visit (at the provider's discretion).

7. Statistical Plan

7.1. Sample Size Determination

LVEF<50% is not expected to be diagnosed in the control arm due to the lack of routine echocardiograms, but for sample size calculations, we have assumed that 1% will be diagnosed based on literature derived incidence rate of 1 in 100 deliveries (M. B. Davis et al., 2020). With the AI-ECG screening, we hypothesize that an increase in the number of cases will be detected. For sample size estimation consideration, an unpublished, ongoing pilot study conducted in the US estimates the prevalence as 5.3% (3/57) for <=35% and 7% (4/57) for <50%. Sample size estimation is based on a conservative estimate of 4% in the AI-ECG arm. At the alpha=0.05 and 80% power, the sample size is estimated to be 424/group. For the secondary composite endpoint, approximately 5% of the sample is expected to experience hypertensive disorders (Ying, Catov, & Ouyang, 2018). We hypothesize that the addition of AI-ECG will increase the detection of cardiomyopathies and other structural defects of the heart. Accordingly, we assume composite event rates of 5% vs. 10% for the control vs. AI-ECG arm. At 80% power and alpha=0.05, a sample size of 434/group is required. For the final sample size, these estimates are rounded up to 500/group (1000 total) to account for the uncertainties in the calculations. Due to the variability in the occurrence of cardiomyopathy across sites, need to account for study participant withdrawal from the study, no-shows to study visits, and loss to follow up, we plan to enroll 1,400 patients to achieve an accrual target of 1,200 participants while ensuring balanced accrual across all 6 sites.

7.2. Study Endpoints

7.2.1. Primary Study Endpoints

The primary study endpoint will be left ventricular ejection fraction (LVEF) <50% diagnosed by echocardiography during pregnancy or within 12 months postpartum

7.2.2. Secondary Study Endpoints

Our secondary endpoints will include:

- A composite outcome of all-cause mortality and adverse cardiovascular events (including cardiomyopathy or systolic heart failure, diastolic heart failure, hypertensive disorders of pregnancy, preeclampsia/eclampsia, valvular heart disease, heart failure-related hospitalization, sustained ventricular arrhythmias, resuscitated cardiac arrest, and other pregnancy-related complications)
- Identification of LVEF ≤35%, < 40% and <45% at any time among study participants during the study period
- Impact of AI-enabled ECG screening on echocardiography utilization

7.3. Statistical Hypotheses and planned analyses

7.3.1. Descriptive Statistics

Descriptive statistics including measures of central tendency for numeric variables and frequency distributions for categorical variables will be calculated, as appropriate for all variables. Demographic, clinical, and outcome variables (primary and secondary) will be tabulated for all enrolled study participants. These data will be summarized for the entire cohort and stratified by randomized group and region. We will summarize the measures of diagnostic performance (i.e., AUC, sensitivity, specificity) stratified by study entry to account for the differential follow-up testing that may have occurred as a result of the AI-ECG screening

7.3.2. **Primary Hypothesis:**

AI-ECG is an effective tool to screen for cardiomyopathy, defined as LVEF < 50%, in pregnant women.

Statistical Hypothesis:

- H_0: P_ai-ecg = P_control
- H_A: P_ai-ecg ≠ P_control
  Where P defines the proportion of participants that have documented LVEF <50% by the conclusion of the study.

Primary analysis: A chi-square test without continuity correction will be applied to the resulting two by two table (rows: random treatment assignment, columns LVEF < 50% reported by conclusion of the study). The primary analysis will be conducted at the alpha=0.05 level of significance (two-sided).

7.3.3. **Second**ary Hypotheses:

AI-ECG will provide consistent performance across race, ethnicity, and postpartum enrollment status.

Secondary analysis: The introduction of stratification factors of race, ethnicity and postpartum status (all unique tables) will be used to produce a stratified contingency table. The Breslow-Day test of homogeneity of the odds ratio will be used to test for effect modification (differential treatment effects by strata). There is the potential for sparse strata with this analysis. If the odds ratio is not estimatable due to zero cells, the empirical logit estimator as well as pooled strata (to increase sample size for each strata) will be utilized.

An AI-ECG is an effective tool to screen for cardiomyopathy at different LVEF cut-off values (<45%, <40%, ≤ 35%).

Secondary analysis: Within the intervention arm that obtains Echos as a part of the study protocol, the AI-ECG model performance will be evaluated. First, the existing algorithm, without retraining, will be used to evaluate discrimination (area under the receiver operating characteristics curve) at various thresholds for LVEF (i.e., 50% as planned for the primary along with 45%, 40% and 35% as noted here). Performance of the model by the patient stratification factors of Age, Race, Ethnicity, and postpartum status will be considered. For these, the reporting standards outlined in the STARD criteria will be adhered too, e.g., inclusion of measures of precision (confidence intervals) and fractional values associated with measures of performance.

7.3.4. **Exploratory Hypothese**s:

AI-ECG will improve the diagnosis of cardiovascular disease and associated clinical outcomes among pregnant and postpartum women.

Statistical plan: The analysis of this endpoint will use the same techniques as the primary and secondary analyses. Here, a composite score of any cardiovascular disease diagnoses during the course of the study will be utilized as the outcome measure.

An AI-enhanced point of care screening tool using portable, smartphone-compatible ECG devices (AIPOC-ECG) will be effective for the detection of cardiomyopathies among Black pregnant and postpartum women.

Statistical plan: The primary analysis will utilize the predictions based on the clinical 12 lead ECG machine. This exploratory analysis will compare the model performance on the point of care devices with the clinical standard ECG machine.

7.4. Additional Statistical Considerations

7.4.1. Handling of Missing Data

Missing data may occur throughout the study. The primary analysis, which is based on the AI-ECG prediction for cardiomyopathy is expected to be calculated once digital is received. In the event that the digital ECG file is missing or corrupted, attempts will be made to re-record the ECG. In order to ensure that these repeated ECGs are obtained in a timely fashion, ECGs will be reviewed at the local sites daily and will be transmitted to the coordinating center at Mayo Clinic at the end of every week for additional review. For demographic and medical history data, any missing data will be reported as such in the final analysis.

7.4.2. Multiplicity

There will be no adjustment to the level of significance for multiple testing. All results will be reported unadjusted at the alpha=0.05 level of significance using estimates and 95% confidence intervals.

7.4.3. Interim Analysis

There is no planned interim analysis.

7.4.4. Analysis Sets

The analysis set for this study will follow the modified intention to treat principle. To be included in the analysis, the participant needs to be randomized and complete at least the baseline assessments and testing.

7.4.5. Pre-specified analysis

A detailed study protocol and statistical analysis plan (SAP) will be written to support both the clinicaltrials.gov registration and publication in top medical journals. Safety and Adverse Events

7.5. Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the

subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e., unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e., drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- substantial disruption of the ability to conduct normal life functions
- birth defect/congenital anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

7.6. Recording/Reporting of Adverse Events

Anticipated study related risk is limited to potential skin irritation from placement of ECG lead electrode stickers directly on the skin for ECG measurements. No other adverse event is expected in relation to this study.

Reports of skin irritation in relation to ECG electrode stickers will be captured in REDCap.

Adverse events/experiences will only be collected within 3 hours following study interventions or within the duration of the specific clinical encounter where study interventions were

performed (depending on which is longer). An expected hospitalization for childbirth or other pregnancy related complication will be excluded.

7.7. Stopping Rules

No study stopping rules are proposed based on the risk profile for the study. In the event the feasibility of the study is not tenable due to challenges in recruitment or other study operational considerations, the study may be terminated at the request of the study PI in conjunction with the institutional review board of record.

7.8. Medical Monitoring

It is the responsibility of the Principal Investigator and site PIs to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

8. Data Handling and Record Keeping

8.1. Confidentiality

Confidentiality of patient information is maintained by assigning study identifiers to the medical data before data is transmitted to Mayo Clinic. [redacted] No data received will be shared external to Mayo Clinic. Only study staff will have access to the data collected. The CRF exported from REDCap is attached in the appendix section.

In the event that a subject revokes authorization to collect or use PHI, the investigator retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts would be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Source documents will be stored at each local site according to local data privacy rules and regulations.

All essential study documents will be retained by the local PI in a Participant Binder and generally include the following:

- Source documents
- Signed consent forms

8.3. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF is expected to be recorded. All missing data must be explained. All entries will be documented electronically using REDCap.

Data Management

This study will use REDCap to capture all clinical and study related data entries with the exception of ECGs. REDCap will utilize a user-friendly interface for data collection which will allow data entry by study coordinator/staff at each study site.

Data Tracking, editing, updating and reporting will be tracked in REDCap. For statistical analysis, data can be exported as CSV, SAS or R files for analysis.

ECG Data

The standard 12-lead ECG:

- will be collected and stored using a GE MAC 2000 device. ECGs will be exported from this machine and securely transferred to Mayo Clinic for analysis.

Portable ECGs:

- Data from the AliveCor device will be transmitted via the research study's smartphone/tablet app to the cloud, where it will be password protected via account log-in, and only accessible to the research team for download to the Mayo research server. The AliveCor cloud server will only be utilized during the duration of the research study and is not accessible to external parties. The AliveCor cloud server will only be utilized during the duration of the research study and is not accessible to external parties.
- Raw data from the Eko DUO Stethoscope device will be transmitted via the research study's smartphone/tablet app to the cloud, where it will be password protected via account log-in, and only accessible to the research team for download to the Mayo research server. The Eko DUO cloud server will only be utilized during the duration of the research study and is not accessible to external parties.

Echocardiographic data

Echocardiographic data will be stored in accordance with local standard data protection and privacy rules and established clinical process at each participating site. Specific echo measurements will be abstracted from the echocardiogram report and entered into REDCap following review by an echo-cardiologist (in accordance with the American Society of Echocardiography guidelines) at each participating site.

Quality Control Procedures
Instructions for use for the ECG devices, data entry forms on REDCap and additional reporting forms are attached in the appendix section.

Study-Specific ECG Device Use Guidelines
The following Instructions for Use (IFU) are attached in the appendix:
- KardiaMobile 6L IFU
- EkoDuo IFU
- GE ECG machine IFU

Data and Form Checks
Data quality control checks will be performed in REDCap to identify potential data anomalies, such as: missing data, outliers, illogical dates, erroneous entries and other data inconsistencies. Data quality checks have also been built into REDCap to prevent entry of erroneous data such as preventing "text" entries in a numeric field and use of pre-specified checkboxes to limit data entry errors.

8.4. Records Retention

The study investigators will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

After the study ends, study staff shall maintain participant forms in a secure location for 3 years, as indicated by the protocol, federal regulations, and IRB guidance.

9. Study Monitoring, Auditing, and Inspecting

9.1. Study Site Monitoring Plan

Site monitoring conducted by the coordinating center (Mayo Clinic) will take place every quarter via virtual video conferencing in addition to one more in-person site visit during the study period.

During the scheduled monitoring visits, the coordinating site will:
- Ensure the rights and safety of participants
- Confirm that the study is conducted in accordance with guidelines
- Ensure maintenance of required documents
- Verify adherence to the protocol
- Monitor the quality of data collected
- Ensure accurate reporting and documentation of unanticipated problems

During monitoring visits, the data recorded on CRFs will be reviewed to ensure:
- Informed consent has been obtained and documented in accordance with IRB regulations
- There are no omissions in the reports of specific data elements

- Missing examinations are indicated
- Participant disposition when exiting the study is accurately recorded

Site investigators must ensure that the study coordinator or identified study staff has access to all study documents, including informed consent forms, intervention accountability records, and source documents.

Once the site visit is complete, a site monitoring report will be drafted to provide feedback regarding any problems or issues that may have been uncovered during the visit. The report will state the problems uncovered during the visit and describe recommendations to correct them. A timeline will be included in the report to ensure that the follow-up of the issues is completed and implemented into the study's procedures.

10.Ethical Considerations

This study is to be conducted according to United States government regulations and Regulatory standards, Mayo Clinic Institutional research policies and procedures, ethical principles of the International Conference on Harmonization (ICH) as well as local (Nigeria) federal, institutional procedures, regulations and ethics boards requirements.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB) for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All study participants will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by each local IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

10.1. Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

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