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Smartphone Monitoring for Atrial fibrillation in Real-Time - India (SMART-India) – a community-based screening and referral study

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Smartphone ***M***onitoring for ***A***trial fibrillation in ***R***eal-***T***ime - **India** (**SMART-India**) – a community-based screening and referral study

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Conflict of Interest: DDM discloses equity stakes or consulting relationships with Flexcon, Inc., Bristol-Myers Squibb, Inc., Mobile Sense, Inc., ATRIA, Inc., and Boston Biomedical Associates, Inc. He has also received research funding from Sanofi Aventis, Inc, Otsuka Pharmaceuticals, Inc, Philips Healthcare, Inc, Biotronik, Inc., and Pfizer, Inc.

ABSTRACT

INTRODUCTION: Atrial fibrillation (AF), the world's most common arrhythmia, often goes undetected and untreated in low-resource communities, including India, where AF epidemiology is undefined. AF is an important risk factor for stroke, which plagues an estimated 1.6 million Indians annually. As such, early detection of AF and management of high-risk patients is critically important to decrease stroke burden in individuals with AF. This study aims to describe the epidemiology of AF in Anand District, Gujarat India, characterize the clinical profile of individuals who are diagnosed with AF, and determine the performance of two mobile technologies for community-based AF screening.

METHODS: This observational study builds on findings from a previous feasibility study and leverages two novel technologies as well as an existing community health program to perform door-to-door AF screening for 2,000 people from 60 villages of Anand District, Gujarat, India using local health workers. A single-lead EKG and a pulse-based app is used to screen each individual for AF 3 times over a period of 5 days. Participants with suspected arrhythmias are followed-up by study cardiologist who makes final diagnoses. Participants diagnosed with AF are initiated on treatment as based on current anticoagulation guidelines and clinical reasoning.

ANALYTICAL PLAN: Age and sex-stratified prevalence of AF in the Anand District will be calculated for sample and estimated for Anand distribution using survey design weights. Sociodemographic and clinical factors associated with AF will be evaluated using multivariable regression methods. Performance of each mobile technology in detecting AF will be evaluated using a 12-lead EKG interpretation as the gold-standard.

ETHICS AND DISSEMINATION: This protocol was approved separately by the Institutional Review Board of University of Massachusetts Medical School and the Human Research Ethics Committee at Charutar Arogya Mandal. The findings of this study will be disseminated through peer-reviewed journals and scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The SMART-India study represents an innovative screening and referral paradigm for persons living in low-resource settings who may have an undetected chronic disease.
- This study highlights the importance of conducting a feasibility study and engaging local community partners prior to undertaking more broad- based population screening efforts.
- Serial screening and rigorous clinical follow-ups, which include continuous monitoring using a holter device increases the chances of identifying paroxysmal AF events. By contrast, most AF screening programs described in the literature rely on a single-point screening.
- Our efforts to characterize the clinical profile of participants diagnosed with AF are limited by the cross-sectional design of our study which prohibit us from drawing casual inferences.

1. BACKGROUND

1.1 Clinical and Public Health Significance

Although atrial fibrillation (AF) is the world's most common serious heart rhythm problem, it often goes undetected and untreated, particularly in low-resource settings like India.[1–5] As such, little is known about the epidemiology of AF in India.[1–3,5] However, it is estimated that 5 million Indians have AF, based on aging of the Indian population and limited data showing that the Indian population is increasingly affected by AF risk factors, including hypertension, diabetes mellitus, and coronary heart disease.[6] The importance of AF to Indian public health is underscored by an ongoing stroke epidemic, with an estimated 1.6 million Indians experiencing a stroke in 2015.[7,8] AF is a major risk factor for stroke, conferring a 5-fold higher risk among affected individuals compared with those free from the arrhythmia, suggesting that AF has become a major public health concern in India.[8–10]

Public health programs for the routine surveillance of AF or other risk factors for stroke are sparse in India. A small proportion of Indian residents have access to routine cardiovascular care or prompt stroke treatment, and this subgroup is disproportionately clustered in urban and metropolitan cities. In light of the limited access to, and out-of-pocket costs associated with, stroke treatment, AF screening and treatment represent an appealing method for primary stroke prevention in rural India.[7] Targeted AF screening has been employed successfully in high-income countries, such as the United Kingdom and Australia,[11–13] but there are no major systematic efforts to screen for AF in low and middle-income countries. Furthermore, oral anticoagulation to prevent stroke is an effective therapy for patients with AF, but solutions are needed to assist those with limited means to pay for this treatment.[5,14–16] Another major barrier to AF screening has been the resource intensiveness of performing conventional 12-lead electrocardiography (ECG) to diagnose AF.[17] For these and other reasons, the importance of developing new, affordable, medical devices for AF screening that could be deployed in India was emphasized by an NHLBI Expert panel and at the 2008 Hyderabad workshop.[5]

In this manuscript, we present an innovative community-based study called ***S***martphone ***M***onitoring for ***A***trial fibrillation in ***R***eal-***T***ime - **India** (**SMART-India**). Our approach deploys two novel smart device-based arrhythmia analysis technologies for AF screening using an

existing network of community-health workers in rural western India, medical professionals and provincial health leaders, and builds on a foundational feasibility assessment conducted in Gujarat, India. The SMART-India study is supported by our interdisciplinary Indo-US research team that has an ongoing collaboration between investigators with a proven track-record of conducting community-based technology research in India.[18]

1.2 ATRIAL FIBRILLATION SCREENING TECHNOLOGY:

Single-lead ECG device: Kardia's FDA approved Alivecor device records a single-lead ECG signal from the user for 30 seconds. Participants place two or three fingers of their right and left hands on the two electrodes on the Alivecor device. Finger contact activates the recording of bipolar lead 1 and the signal is transmitted from the device to the iPhone by frequency modulation of an ultrasound signal.[19] An automated algorithm, developed to interpret one's cardiac rhythm, produces noise-filtered traces and a computer-averaged complex for arrhythmia diagnosis based on two criteria: p-wave absence and R-R interval irregularity. The developers of Alivecor device reported a sensitivity of 0.98 and specificity of 0.97 for the detection of AF against the gold-standard 12-lead ECG in the controlled developmental environment.[19]

Pulse-based ANAND app: Our team has developed a novel pulse-based approach for detecting arrhythmias that does not require additional hardware. This experimental Automated Novel Atrial fibrillation Noninvasive Detection application (ANAND), named after our study site in India), uses an algorithm to identify pulse complexity and irregularity. Participants are asked to hold the mobile phone in their hand, with their right first or second finger over the standard camera and lamp. The flashlight illuminates the finger and the pulse waveform is recorded for up to 2 minutes, with 30 seconds being needed in most cases to complete a rhythm analysis. The ANAND algorithm performs two calculations to approximate a person's cardiac rhythm: 1) root mean square of successive difference of RR intervals to quantify variability between RR peaks and 2) Shannon entropy (or Turning Point Ratio) to characterize the complexity of variability between two consecutive segments of 14 RR peaks.[20,21] The results from this automated algorithm's calculation on the waveform are classified as normal sinus rhythm, possible AF, or indeterminate. Our group has evaluated a prototype of this application in a clinical environment and compared its performance against a manually adjudicated ECG reading, with the ANAND prototype demonstrating a sensitivity of 0.97 and a specificity of 0.94 for the detection of AF.[20]

Table 1: Findings from the feasibility study and corresponding modifications in the SMART-India study

Theme	Findings	Modification
Sampling Strategy	- Recruiting an equal distribution of participants across the different age-sex stratum was difficult - Approaching households in a random fashion to recruit participants resulted in a bias towards selection of middle-aged female and older participants who were more likely to be present at home and available for screening	Use of census data to recruit an age- and sex-representative sample through stratified sampling to mitigate potential selection bias
Motion Artifact	- Participants found it difficult to maintain steady hands while placing their fingers on the Alivecor case without additional support - Participants found 2-minute screening period to be too long to maintain steady hands	- Use of clipboards to stabilize participants' hands - Shorter recording time: 60 sec (Alivecor) and 90 sec (ANAND)
Screening Protocol	- A single time-point screening underestimated true AF prevalence (owing to paroxysmal AF) - Five screenings in a week were time-consuming and led to participant attrition	Three screenings over the course of five days to account for paroxysmal events and prevent study attrition
Data Management	- Research staff had difficulties uploading ECG tracings for adjudication in a timely manner - Questionnaires in the field could not be entered using smartphones and tablets due to poor internet connectivity	- Development of a web platform to assist with sharing of de-identified ECG recordings - Use of an offline smartphone-based app

1.3. Feasibility study:

In mid-2015, a feasibility study was undertaken in rural western India to screen for AF using the two smartphone-based technologies: 1) the Alivecor device and 2) the ANAND app. Our primary objective for this study was to help identify the potential barriers and facilitators for conducting AF screening on a larger, more diverse and representative sample.

Our field staff for each village consisted of two undergraduate medical students who were trained in collecting field observation notes (appendix A), a research coordinator, two social workers who were trained in administering questionnaires and using mobile technology to screen for AF, and a local village health worker to help identify residents of the given village who meet

the eligibility criteria. We screened a total of 354 participants aged 50 years and above across 6 villages in Anand district in Gujarat. Each participant in this pilot study was screened for 2 minutes using both technologies for 5 consecutive days. Data was collected over a 6-week period. Key findings from field observation notes and in-depth interviews of the field staff are described in Table 1. The sample prevalence of AF using the clinician's adjudication of single-lead ECG recordings from the Alivecor device was found to be 5.1% (95% CI 2.7-8.7).[22]

1.4. Community based approach:

Our approach builds on a long-standing collaboration between the University of Massachusetts Medical School and Charutar Arogya Mandal (CAM), a tertiary care hospital and medical college in rural western India.[18] This collaboration, which we have called Research and Advocacy for Health in India (RAHI: Hindi word for pathfinder), is grounded in extensive interactions with local Indian communities. As we have described elsewhere,[18] the research priorities of our collaboration and our studies are informed by community health needs assessments. The subsequent collaborative research plans are designed based on a dynamic process that incorporates feedback collected through iterations of community engagement activities. We discussed our findings from the feasibility study with the Community Extension Department at CAM, local community health workers, and CAM clinical staff. Based on their feedback, we decided to leverage an existing CAM program called SPARSH (Shree Krishna Hospital Programme for Advancement of Rural and Social Health; Hindi word for touch) to facilitate the community-based screening for AF(more details in Section 7).

SPARSH is a 5-year joint project by CAM's Community Extension Department and Shree Krishna Hospital that is focused on non-communicable diseases. The ultimate goal of the SPARSH program is to develop a 3-tier healthcare system that reaches local villages at the grassroots level. A total of 60 villages from the administrative district of CAM are enrolled in the SPARSH program. In this program, local village health workers, representing the first tier of three are used to identify and register patients through an annual household survey, monthly camps, and standardized screening programs. These patients are then referred to the remote extension centers, representing the second tier of the SPARSH program, where a medical officer assesses, educates, and prescribes necessary treatment. Additionally, if a medical officer determines that further work-up is required, the patient is referred to the Shree Krishna Hospital,

third tier, located at the main CAM campus. At the time of implementation of the SMART-India study, this three-tier referral system was not in place and, therefore, SMART-India relied exclusively on the census collected by village health workers as part of their annual household survey.

2. METHODS/DESIGN

2.1 Objectives

Box 1 lists the primary objectives of the SMART-India study. These objectives are informed by the feasibility study, AF screening technology, and community-based approach.

Box 1: Study Aims for SMART-India

Aim 1 Describe the epidemiology of AF in Anand District, Gujarat, India: Screen 2,000 residents of Gujarat to describe the age- and sex-stratified prevalence of AF.

Aim 2 Characterize the profile of individuals who are diagnosed with AF: Compare clinical findings, quality of life, and risk factors of participants who are diagnosed with AF with those who do not have AF.

Aim 3 Determine the performance of 2 mobile technologies for community-based AF screening: Determine the sensitivity, specificity, and discriminative ability of the Alivecor and ANAND's automated AF detection algorithm to the gold-standard 12-lead ECG as well as interpretation by a trained clinician.

2.2 STUDY OVERVIEW:

Figure 1 provides an overview of the SMART-India study protocol from the perspective of prospective participants.

2.2 Study design

The SMART-India study is a cross-sectional screening of 2,000 adult men and women 45 years and older from 60 villages participating in the SPARSH program paired with a clinical follow-up of all participants with abnormal screenings. Each participant is screened three times over the course of five days to account for potential paroxysmal AF presentation.

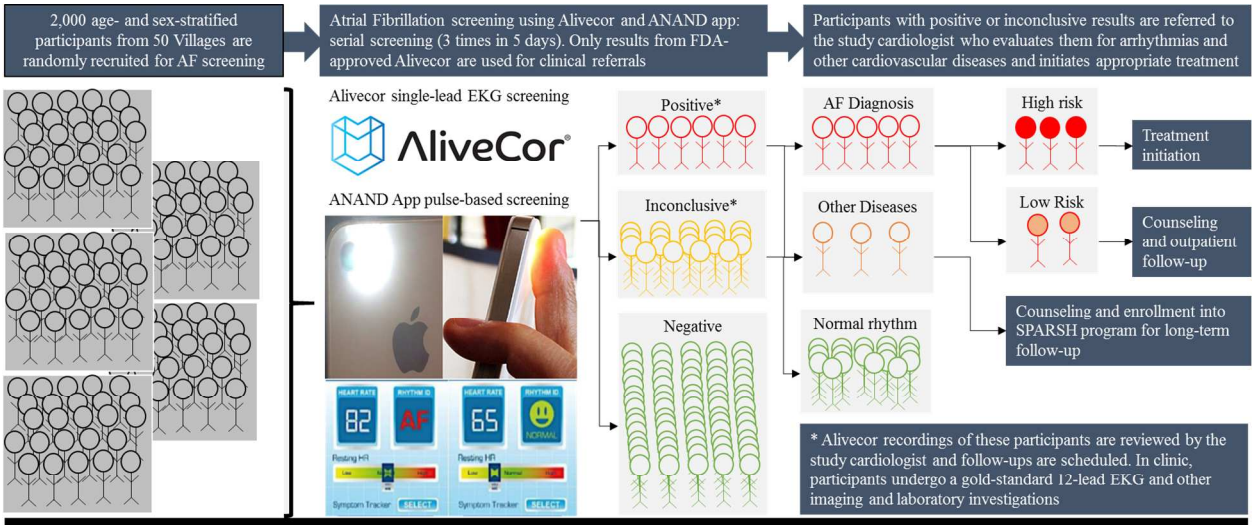

Figure 1: An overview of SMART-India study protocol for community-based screening of Atrial Fibrillation and referral for clinical follow-up in rural western India

2.3 Ethics approval

The SMART-India study was reviewed and approved by ethical boards from the University of Massachusetts Medical School (IRB# H00008089) and Charutar Arogya Mandal (HREC# IEC/HMPCMCE/70/Faculty/15/160/16).

2.4 Staff training

The SMART-India study is supported by four field workers, one clinical coordinator, one project supervisor, and 50 village health workers. The field workers and clinical coordinator received two weeks of training in the use of smartphones and devices to administer questionnaires to surveyed individuals and perform screening for AF. Additionally, the five staff members worked with the investigators to develop standardized operating procedures for their tasks. Following training, the five team members collaborated with the study investigators to organize a one-hour orientation for the 60 village health workers (Figure 2). Training provided the village health workers with information about the study, their roles and introduction to the rest of the study team. During the orientation, village health workers indicated that navigating the village to identify participants listed in the roster would be the primary time constraint. Thus, we divided the four field workers into two teams and proceeded with simultaneous screenings in two separate villages to enhance efficiency. One of the Indian co-investigators on the team fulfilled the role of project supervisor.

2.5 Questionnaire translation and testing

We use standardized questionnaires to collect information about participants' demographic characteristics, lifestyle risk factors, past medical history, family history, physical activity, medication, AF related symptoms, and healthcare usage at the time of the first screening (Table 2). Additionally, we administer an exit survey to ascertain participants' feedback about the screening technology and a clinical follow-up survey to assess participants' quality of life and cardiovascular-related factors. All questionnaires were translated to Gujarati and interpreted by several volunteers representing a wide range of literacy (i.e. attending physician, healthcare worker, research coordinator, village health worker, and community representative). The interpretations of questions and responses were back-translated and compared with the original questionnaire in English. Common themes for discordance between the original and back-translated forms were identified and used to modify the original questionnaire to accommodate the cultural context. This process was repeated until there was convergence between the two versions. All translations were done by certified professional translator services in Gujarat, India.

2.6 Data management

Figure 3 describes the data management strategy for SMART-India study. Based on our prior experience, we use the Magpi platform to administer questionnaire-based surveys to the participants. Magpi allows for offline data collection in smartphones and tablets through a user-friendly app and uploads collected data to a secure server once the device connects to the Internet. The files from the AF screening apps (Alivecor and ANAND) are downloaded to a PC from the phones using iTunes. Results from the automated algorithm of AF screening apps and all abnormal Alivecor ECG tracings are uploaded to REDCap. Additionally, all data emerging from the clinical follow-up, except for questionnaire-based surveys, are uploaded to REDCap. REDCap is used because it allows for file uploads and can create reports that are helpful during the adjudication process.

Post-screening activities: On each of the final two days (Day 4 and 5) of screening, field workers travel back to CAM to complete data entry and upload all abnormal (possible AF/unclassified) ECG files to RedCAP. All Alivecor and ANAND files are downloaded from the phones using iTunes. All Alivecor PDFs are renamed with patient IDs and separated into normal results versus AF/Unclassified results. All AF/Unclassified files are uploaded to Redcap and flagged for adjudication. The field workers create a weekly report to summarize recruitment and results of screening and distribute it with the team (Appendix C). All of the ANAND and Alivecor files are uploaded to a secure server to support ad-hoc analyses for measuring the performance of the two screening methods. Ultimately all data are exported to STATA for statistical analyses (Figure 3).

2.9. CLINICAL FOLLOW-UPS

Our protocol for clinical follow-ups evolved over time based on feedback from the research team. The primary impetus behind the change in approach was a higher than expected number of screenings that are classified as inconclusive and the resultant backlog of follow-up visits needed to understand these inconclusive readings. In order to facilitate prompt clinical visits for high-

risk participants, we introduced a triaging step (Section 8.3) after reviewing the clinical charts and final diagnosis for the first 50 participants that were followed up in clinic.

Scheduling follow-ups: The clinical coordinator schedules all follow up visits with village health workers. One day prior to the visit, the clinical coordinator informs the cardiac and extension departments about the number of participants and which village health workers are coming. The clinical coordinator prints out the abnormal ECGs and paper clinical forms to prepare for the follow up visit.

Follow-up protocol: The clinical coordinator meets the village health workers and participants at the hospital and escorts them to the cardiac center. Once at the cardiac center, the clinical coordinator conducts further AF screening using the Alivecor device and ANAND app using the same methodology as in the field. Subsequently, all participants receive a 12-lead ECG. The study cardiologist reviews all of the ECG recordings (field and clinical visit) and determines whether or not to pursue additional clinical work-up. While waiting for the cardiologist's interpretation, the clinical coordinator administers the follow up survey in Magpi, recorded vital information as measured by the nurse (height, weight, blood pressure, heart rate, O2 saturation, temperature), and verified the participants' medical history. The cardiologists' clinical decision-making is described in Figure 5. If the cardiologist interprets all ECG recordings of the participant as showing normal sinus rhythm, no additional studies are ordered. . If the cardiologist diagnosed the participant as having definite AF in any of the ECG, either in any of the screening ECG or in-office ECG, additional laboratory investigations are performed to inform clinical decision-making about initiation of anticoagulation and management plan (Figure 5). If AF was suspected on any of the screening ECG but a diagnosis of definite AF could not be made due poor quality of ECG tracings from screening app, multiple atrial or ventricular premature complexes, or a normal sinus rhythm on the 12-lead ECG, the cardiologist orders 24 hour Holter monitoring to look for paroxysmal AF events or other abnormalities. Two dimensional Echocardiography is performed in all participants diagnosed with AF and in those having symptoms and/or ECG abnormalities that warrants for an echocardiographic examination. Decision to initiate anticoagulation is taken based on CHA2DS2-VASc score.[23] All of the clinical data including medications is abstracted by the clinical coordinator using clinical research forms.

Modifications for follow-up scheduling: A preliminary inspection of clinical follow-ups found that the majority are due to an "Inconclusive" finding of Alivecor ECG recording based on Kardia's automated algorithm. Specifically, 44 out of the first 50 follow-ups are of participants whose screening was inconclusive. Out of these 44 participants, 41 were found to have normal sinus rhythm after the study cardiologist interpreted field and 12-lead clinical ECGs. Additionally, two of the remaining three participants were found to have benign, non-AF arrhythmias. Based on these findings, we modified our follow-up protocol by having the study cardiologist triage the single-lead ECG recordings from the field prior to the participants' clinical follow ups to prioritize high-risk patients and rule out false positive recordings.

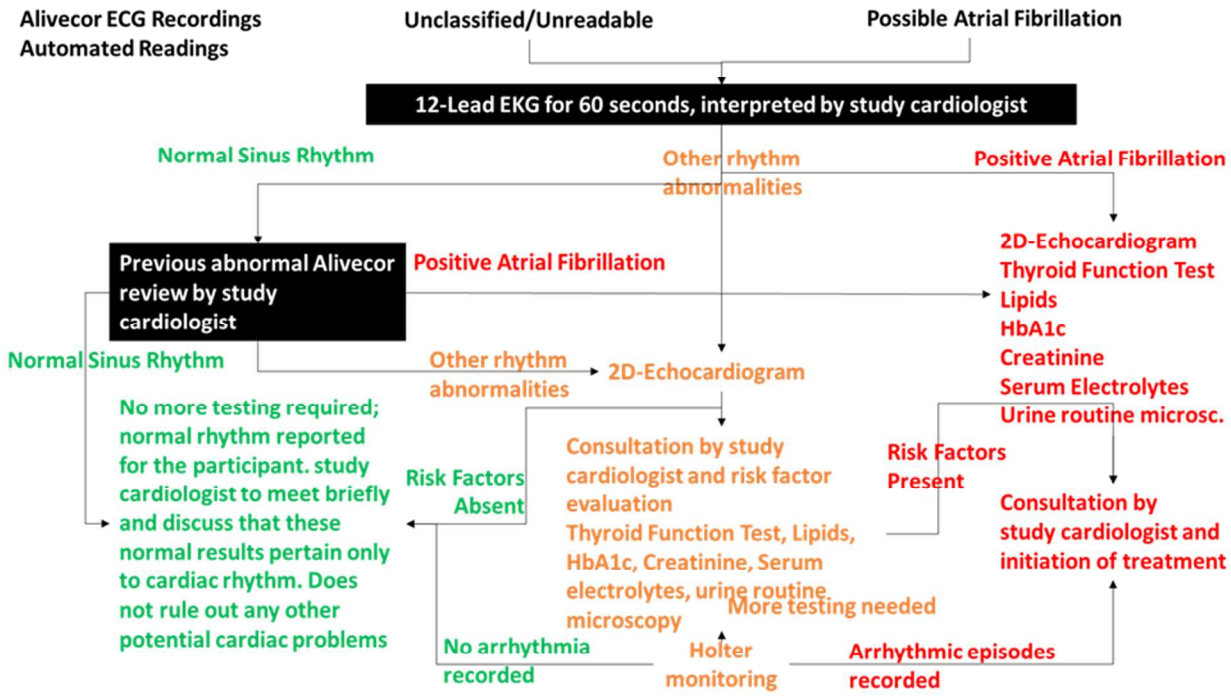

Figure 5: A flowchart describing the clinical decision-making of the study cardiologist for participants following up in clinic for abnormal screening results during SMART-India study

2.10. DATA ADJUDICATION

All interpretations of ECG recordings determined as AF or abnormal by the Alivecor automated algorithm are reviewed by a separate team of trained clinicians through a standardized adjudication process. Two resident-level physicians independently review each abnormal Alivecor generated ECG recording using REDCap and enter their interpretation as either: 1) normal sinus rhythm, 2) AF, or as an 3) other arrhythmia (free text). In the event of disagreement between the two reviewers, a fellow level physician reviews the ECG recording.

2.11. ANALYTICAL PLAN

Aim 1: AF Epidemiology: The gold-standard of cardiologist verified diagnoses of AF will be used to calculate the age and sex-stratified prevalence of AF in the study sample. Population estimates will be derived from the sample prevalence using survey weights constructed using the census collected by the SPARSH program and the Government of India sponsored census in 2011. Three separate calculations will be performed to describe the overall prevalence of AF and separately for those with valvular and non-valvular AF.

Aim 2: Profile of patients likely to have AF: Distribution of covariates (Table 1) across group of participants diagnosed with AF will be compared to those who were not diagnosed with AF to determine associated risk factors. Sensitivity analyses will be performed to rule out differences between the group of participants who were not diagnosed with AF but were followed up clinically in comparison to those who were never followed up. If meaningful differences are identified in our sensitivity analyses, distribution of covariates will be assessed across the three different groups of participants. Additionally, among those participants who are followed up clinically, differences in the distribution of clinical factors between the group of AF-positive and AF-negative participants will be assessed. For sociodemographic and clinical risk factors, multivariable regression techniques will be used to identify their conditional effects after accounting for other covariates. Lastly, among the participants who were followed up clinically, the effects of AF will be estimated by comparing differences in the quality of life score (SF-12, Table 1) between groups of participants who are diagnosed for AF vs those who do not have AF. Potential confounders will be identified based on a-priori knowledge (age, sex, socio-economic status) and an examination of bivariate association of sociodemographic factors with AF and quality of life.

Aim 3: Performance of AF-screening technology: Sensitivity, specificity, and discriminative ability (ROC curve analyses) with 95% confidence bands will be used to measure the performance of our AF-screening technology. In-field performance of AF-screening technology will be used by comparing results from the ANAND and Alivecor automated algorithms with adjudicated interpretations of the Alivecor ECG recordings. The clinical performance of AF-screening technology will be assessed by comparing results from the automated algorithms from both technologies with results from the gold standard 12-lead ECG.

3. -DISCUSSION

The SMART-India study represents an innovative screening and referral paradigm for persons living in low-resource settings who may have an undetected chronic disease. Our study also highlights the importance of conducting a feasibility study and engaging local community partners prior to undertaking more broad- based population screening efforts. Findings from this study will provide greater insights into the silent burden of AF in rural Indian communities and help identify potential targets for intervention to modify the ongoing epidemic of stroke in India. Further work is needed to build on the SMART-India study and build a nexus of providers that can help triage high-risk patients and further enhance the efficiency of a referral system for persons with suspect chronic disease, including cardiovascular disease. Leveraging existing community-based programs, such as SPARSH, can help achieve this ambitious, but feasible, goal.

Contributors' Statement:

Apurv Soni: Soni conceptualized, designed, and implemented the study in India. Soni drafted the initial manuscript, and approved the final manuscript as submitted.

Sunil Karna: Karna contributed to the design and implementation of the study in India. Karna contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Harshil Patel: Patel contributed to the design and implementation of the study in India. Patel contributed to the drafting of the initial manuscript, and approved the final manuscript as submitted.

Nisha Fahey: Fahey conceptualized, designed, and implemented the study in India. Fahey, contributed to the drafting of the initial manuscript, and approved the final manuscript as submitted.

Shyamsundar Raithatha: Raithatha contributed to the conceptualization, design and implementation of the study in India. Raithatha contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Anna Handorf: Handorf contributed to the design of the study. Handorf contributed to the drafting and formatting of the manuscript, and approved the final manuscript as submitted.

John Bostrom: Bostrom contributed to the design and implementation of the study in India. Bostrom contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Syed Bashar: Bashar contributed to the implementation of the study in India. Bashar contributed to the editing of the manuscript, and approved the final manuscript as submitted.

Kandarp Talati: Talati contributed to the design and implementation of the study in India. Talati contributed to the drafting of the initial manuscript, and approved the final manuscript as submitted.

Ravi Shah: Shah contributed to the design and implementation of the study in India. Shah contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Robert Goldberg: Goldberg conceptualized and designed the study in India. Goldberg contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Sunil Thanvi: Thanvi conceptualized, designed, and implemented the study in India. Thanvi provided input to the analyses, contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Ajay Phatak: Phatak conceptualized and designed the study in India. Phatak contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Jeroan Allison: Allison conceptualized and designed the study in India and supported its implementation. Allison contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Ki Chon: Chon supported the implementation of the study in India. Allison contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Somashekhar Nimbalkar: Nimbalkar conceptualized and designed the study in India and supported its implementation. Nimbalkar contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

David McManus: McManus conceptualized and designed the study in India and supported its implementation. McManus contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

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Village:_____ Date:_____

Feasibility Study: Using Mobile Devices to Screen for Atrial Fibrillation in Rural India
Passive Field Observation Guide

Category	'Objective' observation	'Subjective' thoughts, comments
Physical setting (describe layout of where screening is taking place		
Approach by the Research Coordinator (tone, who responds, single v. multiple)		
Response by the participant(s) (appearance of engagement, eye contact)		
Informed Consent Form (response by the participant for the paperwork, gestures)		
Personal space RC-Participant (is the research coordinator in participant's personal space/ is the participant? Body language?)		
Personal space others (are bystanders invading in the personal space, are there attempts by coordinator to create distance)		
Questionnaire (Tone of RC, nonverbal communication between the two)		

Village:_____ Date:_____

About how long from informed consent form to screening for A-Fib?		
Using Mobile Phone Technology? (responses by participant, bystanders, management by RC)		
How long does the whole process take?		
Describe problems observed and problem-solving techniques		
Describe evidence of teamwork		
Overall tone of exchange during departure		
Insights: what stands out for you from what you observed? (take brief notes, expand later)		

SMART-India Recruitment Form

Date:

Villlage Name : Number:

Age	Approached	Enrolled
	Male	
40-55	Not Available	
	Refused	
56-65	Not Available	
	Refused	
65+	Not Available	
	Refused	
	Female	
40-55	Not Available	
	Refused	
56-65	Not Available	
	Refused	
65+	Not Available	
	Refused	

SMART-India Tracking Form

Village: _____ Number: ___

#	ID#	Age	Sex	Visit	Date	Alivecor Time	Alivecor AF	Alivecor HR	ANAND Time	ANAND AF	ANAND HR	Glucose	Sys BP	Dia BP	# try	Home?
1			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
2			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
3			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
4			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
5			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
6			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
7			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
8			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N

SMART-India
Weekly Report

Weekly Report: Week of
Village # and Name:
Research Coordinators:

Recruitment Report						
	Male			Female		
Age	Approached*	Refused	Enrolled	Approached*	Refused	Enrolled
40-55						
56-65						
65+						
Total						
% Response Rate (overall)(enrolled/approached) x 100:						
% Response Rate (refusal) (enrolled/(enrolled+refused)) x 100:						
* Includes not available + refused						

Alivecor Results			
	Normal	Inconclusive	AF-Positive
Total			

Number of Screenings Completed		
3	2	1

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		~~(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found~~
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		~~(*b*) Describe any methods used to examine subgroups and interactions~~
		~~(*c*) Explain how missing data were addressed~~
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		~~(*e*) Describe any sensitivity analyses~~
~~**Results**~~		
~~Participants~~	~~13*~~	~~(a) Report numbers of individuals at each stage of study—eg numbers potentially~~

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Study Protocol for Smartphone Monitoring for Atrial fibrillation in Real-Time - India (SMART-India) – a community-based screening and referral program

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Study Protocol for ***S***martphone ***M***onitoring for ***A***trial fibrillation in ***R***eal-***T***ime - **India** (**SMART-India**) – a community-based screening and referral program

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Conflict of Interest: DDM discloses equity stakes or consulting relationships with Flexcon, Inc., Bristol-Myers Squibb, Inc., Mobile Sense, Inc., ATRIA, Inc., and Boston Biomedical Associates, Inc. He has also received research funding from Sanofi Aventis, Inc, Otsuka Pharmaceuticals, Inc, Philips Healthcare, Inc, Biotronik, Inc., and Pfizer, Inc.

ABSTRACT

INTRODUCTION: Atrial fibrillation (AF), the world's most common arrhythmia, often goes undetected and untreated in low-resource communities, including India, where AF epidemiology is undefined. AF is an important risk factor for stroke, which plagues an estimated 1.6 million Indians annually. As such, early detection of AF and management of high-risk patients is critically important to decrease stroke burden in individuals with AF. This study aims to describe the epidemiology of AF in Anand District, Gujarat India, characterize the clinical profile of individuals who are diagnosed with AF, and determine the performance of two mobile technologies for community-based AF screening.

METHODS: This observational study builds on findings from a previous feasibility study and leverages two novel technologies as well as an existing community health program to perform door-to-door AF screening for 2,000 people from 60 villages of Anand District, Gujarat, India using local health workers. A single-lead EKG and a pulse-based app is used to screen each individual for AF 3 times over a period of 5 days. Participants with suspected arrhythmias are followed-up by study cardiologist who makes final diagnoses. Participants diagnosed with AF are initiated on treatment as based on current anticoagulation guidelines and clinical reasoning.

ANALYTICAL PLAN: Age and sex-stratified prevalence of AF in the Anand District will be calculated for sample and estimated for Anand distribution using survey design weights. Sociodemographic and clinical factors associated with AF will be evaluated using multivariable regression methods. Performance of each mobile technology in detecting AF will be evaluated using a 12-lead EKG interpretation as the gold-standard.

ETHICS AND DISSEMINATION: This protocol was approved separately by the Institutional Review Board of University of Massachusetts Medical School and the Human Research Ethics Committee at Charutar Arogya Mandal. The findings of this study will be disseminated through peer-reviewed journals and scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The SMART-India study represents an innovative screening and referral paradigm for persons living in low-resource settings who may have an undetected chronic disease.
- This study highlights the importance of conducting a feasibility study and engaging local community partners prior to undertaking more broad- based population screening efforts.
- Serial screening and rigorous clinical follow-ups, which include continuous monitoring using a holter device increases the chances of identifying paroxysmal AF events. By contrast, most AF screening programs described in the literature rely on a single-point screening.
- Our efforts to characterize the clinical profile of participants diagnosed with AF are limited by the cross-sectional design of our study which prohibit us from drawing casual inferences.

1. BACKGROUND

1.1 Clinical and Public Health Significance

Although atrial fibrillation (AF) is the world's most common serious heart rhythm problem, it often goes undetected and untreated, particularly in low-resource settings like India.[1–5] As such, little is known about the epidemiology of AF in India.[1–3,5] However, it is estimated that 5 million Indians have AF, based on aging of the Indian population and limited data showing that the Indian population is increasingly affected by AF risk factors, including hypertension, diabetes mellitus, and coronary heart disease.[6] The importance of AF to Indian public health is underscored by an ongoing stroke epidemic, with an estimated 1.6 million Indians experiencing a stroke in 2015.[7,8] AF is a major risk factor for stroke conferring a 5-fold higher risk among affected individuals compared with those free from the arrhythmia, suggesting that AF has become a major public health concern in India.[8–10]

Public health programs for the routine surveillance of AF or other risk factors for stroke are sparse in India. A small proportion of Indian residents have access to routine cardiovascular care or prompt stroke treatment, and this subgroup is disproportionately clustered in urban and metropolitan cities. In light of the limited access to, and out-of-pocket costs associated with, stroke treatment, AF screening and treatment represent an appealing method for primary stroke prevention in rural India.[7] Targeted AF screening has been employed successfully in high-income countries, such as the United Kingdom and Australia,[11–14] but there are no major systematic efforts to screen for AF in low and middle-income countries. Furthermore, oral anticoagulation to prevent stroke is an effective therapy for patients with AF, but solutions are needed to assist those with limited means to pay for this treatment.[5,15–17] Another major barrier to AF screening has been the resource intensiveness of performing conventional 12-lead electrocardiography (ECG) to diagnose AF.[18] For these and other reasons, the importance of developing new, affordable, medical devices for AF screening that could be deployed in India was emphasized by an NHLBI Expert panel and at the 2008 Hyderabad workshop.[5]

In this manuscript, we present an innovative community-based study called ***S***martphone ***M***onitoring for ***A***trial fibrillation in ***R***eal-***T***ime - **India** (**SMART-India**). Our approach deploys two novel smart device-based arrhythmia analysis technologies for AF screening using an

existing network of community-health workers in rural western India, medical professionals and provincial health leaders, and builds on a foundational feasibility assessment conducted in Gujarat, India. The SMART-India study is supported by our interdisciplinary Indo-US research team that has an ongoing collaboration between investigators with a proven track-record of conducting community-based technology research in India.[19]

1.2 Atrial Fibrillation Screening Technology:

Single-lead ECG device: Kardia's FDA approved Alivecor device records a single-lead ECG signal from the user. Participants place two or three fingers of their right and left hands on the two electrodes on the Alivecor device. Finger contact activates the recording of bipolar lead 1 and the signal is transmitted from the device to the iPhone by frequency modulation of an ultrasound signal.[20] An automated algorithm, developed to interpret one's cardiac rhythm, produces noise-filtered traces and a computer-averaged complex for arrhythmia diagnosis based on two criteria: p-wave absence and R-R interval irregularity. The developers of Alivecor device reported a sensitivity of 0.98 and specificity of 0.97 for the detection of AF against the gold-standard 12-lead ECG in the controlled developmental environment.[20]

Pulse-based ANAND app: Our team has developed a novel pulse-based approach for detecting arrhythmias that does not require additional hardware. This experimental Automated Novel Atrial fibrillation Noninvasive Detection application (ANAND), named after our study site in India, builds on our previous US-based algorithm to identify pulse complexity and irregularity.[21,22] Participants are asked to hold the mobile phone in their hand, with their right first or second finger over the standard camera and lamp. The flashlight illuminates the finger and the pulse waveform is recorded for up to 2 minutes, with 30 seconds being needed in most cases to complete a rhythm analysis. The ANAND algorithm performs two calculations to approximate a person's cardiac rhythm: 1) root mean square of successive difference of RR intervals to quantify variability between RR peaks and 2) Shannon entropy (or Turning Point Ratio) to characterize the complexity of variability between two consecutive segments of 14 RR peaks.[22,23] The results from this automated algorithm's calculation on the waveform are classified as normal sinus rhythm, possible AF, or indeterminate. The preceding prototype for ANAND app was tested in a clinical environment and compared its performance against a manually adjudicated ECG reading demonstrating a sensitivity of 0.97 and a specificity of 0.94

for the detection of AF.[23] This ANAND app is not commercially available and differs from the early prototype in two main aspects: a shorter duration of pulse recording and optimized threshold for RR variability and Shannon entropy based on data collected from our feasibility study.[24]

Table 1: Findings from the feasibility study and corresponding modifications in the SMART-India study

Theme	Findings	Modification
Sampling Strategy	- Recruiting an equal distribution of participants across the different age-sex stratum was difficult - Approaching households in a random fashion to recruit participants resulted in a bias towards selection of middle-aged female and older participants who were more likely to be present at home and available for screening	Use of census data to recruit an age- and sex-representative sample through stratified sampling to mitigate potential selection bias
Motion Artifact	- Participants found it difficult to maintain steady hands while placing their fingers on the Alivecor case without additional support - Participants found 2-minute screening period to be too long to maintain steady hands	- Use of clipboards to stabilize participants' hands - Shorter recording time: 60 sec (Alivecor) and 90 sec (ANAND)
Screening Protocol	- A single time-point screening underestimated true AF prevalence (owing to paroxysmal AF) - Five screenings in a week were time-consuming and led to participant attrition	Three screenings over the course of five days to account for paroxysmal events and prevent study attrition
Data Management	- Research staff had difficulties uploading ECG tracings for adjudication in a timely manner - Questionnaires in the field could not be entered using smartphones and tablets due to poor internet connectivity	- Development of a web platform to assist with sharing of de-identified ECG recordings - Use of an offline smartphone-based app

1.3. Feasibility Study

In mid-2015, a feasibility study was undertaken in rural western India to screen for AF using the two smartphone-based technologies: 1) the Alivecor device and 2) the ANAND app. Our primary objective for this study was to help identify the potential barriers and facilitators for conducting AF screening on a larger, more diverse and representative sample.

Our field staff for each village consisted of two undergraduate medical students who were trained in collecting field observation notes (appendix A), a research coordinator, two social workers who were trained in administering questionnaires and using mobile technology to screen for AF, and a local village health worker to help identify residents of the given village who meet the eligibility criteria. We screened a total of 354 participants aged 50 years and above across 6 villages in Anand district in Gujarat. Each participant in this pilot study was screened for 2 minutes using both technologies for 5 consecutive days. Data was collected over a 6-week period. Key findings from field observation notes and in-depth interviews of the field staff are described in Table 1. The sample prevalence of AF using the clinician's adjudication of single-lead ECG recordings from the Alivecor device was found to be 5.1% (95% CI 2.7-8.7).[25]

1.4. Community Based Approach

Our approach builds on a long-standing collaboration between the University of Massachusetts Medical School and Charutar Arogya Mandal (CAM), a tertiary care hospital and medical college in rural western India.[19] This collaboration, which we have called Research and Advocacy for Health in India (RAHI: Hindi word for pathfinder), is grounded in extensive interactions with the local Indian communities. As we have described elsewhere,[19] the research priorities of our collaboration and our studies are informed by community health needs assessments. The subsequent collaborative research plans are designed based on a dynamic process that incorporates feedback collected through iterations of community engagement activities. We discussed our findings from the feasibility study with the Community Extension Department at CAM, local community health workers, and CAM clinical staff. Based on their feedback, we decided to leverage an existing CAM program called SPARSH (Shree Krishna Hospital Programme for Advancement of Rural and Social Health; Hindi word for touch) to facilitate the community-based screening for AF.

SPARSH is a 5-year joint project by CAM's Community Extension Department and Shree Krishna Hospital that is focused on non-communicable diseases. The ultimate goal of the SPARSH program is to develop a 3-tier healthcare system that reaches local villages at the grassroots level. A total of 60 villages from the administrative district of CAM are enrolled in the SPARSH program. In this program, local village health workers, representing the first tier of three are used to identify and register patients through an annual household survey, monthly

camps, and standardized screening programs. These patients are then referred to the remote extension centers, representing the second tier of the SPARSH program, where a medical officer assesses, educates, and prescribes necessary treatment. Additionally, if a medical officer determines that further work-up is required, the patient is referred to the Shree Krishna Hospital, third tier, located at the main CAM campus. At the time of implementation of the SMART-India study, this three-tier referral system was not in place and, therefore, SMART-India relied exclusively on the census collected by village health workers as part of their annual household survey.

2. METHODS/DESIGN

2.1 Objectives

Box 1 lists the primary objectives of the SMART-India study. These objectives are informed by the feasibility study, AF screening technology, and community-based approach.

Box 1: Study Aims for SMART-India

Aim 1 Describe the epidemiology of AF in Anand District, Gujarat, India: Screen 2,000 residents of Gujarat to describe the age- and sex-stratified prevalence of AF.

Aim 2 Characterize the profile of individuals who are diagnosed with AF: Compare clinical findings, quality of life, and risk factors of participants who are diagnosed with AF with those who do not have AF.

Aim 3 Determine the performance of 2 mobile technologies for community-based AF screening: Determine the sensitivity, specificity, and discriminative ability of the Alivecor and ANAND's automated AF detection algorithm to the gold-standard 12-lead ECG as well as interpretation by a trained clinician.

2.2 Study Design

Figure 1 provides an overview of the SMART-India study protocol from the perspective of prospective participants. The SMART-India study is a cross-sectional screening of 2,000 adult men and women 45 years and older from 60 villages participating in the SPARSH program paired with a clinical follow-up of all participants with abnormal screenings. Each participant is

screened three times over the course of five days to account for potential paroxysmal AF presentation.

2.3 Staff Training

The SMART-India study is supported by four field workers, one clinical coordinator, one project supervisor, and 50 village health workers. The field workers and clinical coordinator received two weeks of training in the use of smartphones and devices to administer questionnaires to surveyed individuals and perform screening for AF. Additionally, the five staff members worked with the investigators to develop standardized operating procedures for their tasks. Following training, the five team members collaborated with the study investigators to organize a one-hour orientation for the 60 village health workers. Participants from 50 villages took part in this study, while volunteers from the other ten villages had participated in the feasibility study described earlier. Training provided the village health workers with information about the study, their roles and introduction to the rest of the study team. During the orientation, village health workers indicated that navigating the village to identify participants listed in the roster would be the primary time constraint. Thus, we divided the four field workers into two teams and proceeded with simultaneous screenings in two separate villages to enhance efficiency. One of the Indian co-investigators on the team fulfilled the role of project supervisor.

2.4 Questionnaire Translation and Testing

We use standardized questionnaires to collect information about participants' demographic characteristics, lifestyle risk factors, past medical history, family history, physical activity, medication, AF related symptoms, and healthcare usage at the time of the first screening (Table 2). Additionally, we administer an exit survey to ascertain participants' feedback about the screening technology and a clinical follow-up survey to assess participants' quality of life and cardiovascular-related factors. All questionnaires were translated to Gujarati and interpreted by several volunteers representing a wide range of literacy (i.e. attending physician, healthcare worker, research coordinator, village health worker, and community representative). The interpretations of questions and responses were back-translated and compared with the original questionnaire in English. Common themes for discordance between the original and back-

translated forms were identified and used to modify the original questionnaire to accommodate the cultural context. This process was repeated until there was convergence between the two versions. All translations were done by certified professional translator services in Gujarat, India.

Table 2: Data collected using standardized questionnaires during enrollment, final screening, and follow-up time points for SMART-India Study

Enrollment	Sociodemographic characteristics	Age, sex, household size, education level, occupation, caste, religion, marital status
	Financial status	Household income, perceived income, perceived expenditures
	Healthcare	Healthcare use, healthcare seeking behavior, healthcare expenditures
	Lifestyle	Smoking, non-smoking tobacco, alcohol, expenditures on lifestyle activities
	Physical activity	Mild, moderate, and high levels of activity using International Physical Activity Questionnaire
	Cardiovascular symptoms	Palpitations, irregular heartbeats, skipped heartbeats, dizziness,
	Medical history	Valvular heart disease, coronary heart disease, obstructive lung disease, myocardial infarction, hypertension, diabetes mellitus, hypercholesterolemia, heart failure, stroke, transient ischemic attack, systemic embolism, anemia, internal bleeding (intracranial, GI, or other), chronic kidney disease, congenital heart disease
Exit	Technology access	Cell phone ownership, cell phone with camera, smartphone use, internet usage, internet use to find health information
	ANAND usability	Time-consuming, operational ease, understandability of results
Follow-up	Quality of life	Physical and Mental composite score using SF-12
	Need for assistance	Recreational activities, traveling, shopping, preparing or eating meals, day-to-day activities, medication management, financial management

2.5 Data Management

Figure 2 describes the data management strategy for SMART-India study. Based on our prior experience, we use the Magpi platform to administer questionnaire-based surveys to the participants. Magpi allows for offline data collection in smartphones and tablets through a user-friendly app and uploads collected data to a secure server once the device connects to the Internet. The files from the AF screening apps (Alivecor and ANAND) are downloaded to a PC from the phones using iTunes. Results from the automated algorithm of AF screening apps and all abnormal Alivecor ECG tracings are uploaded to REDCap. Additionally, all data emerging from the clinical follow-up, except for questionnaire-based surveys, are uploaded to REDCap. REDCap is used because it allows for file uploads and can create reports that are helpful during the adjudication process.

2.6 Sample Size Calculations

Based on our calculations, a sample size of 1, 823 persons is required to estimate the prevalence of AF with 1% error assuming the a priori prevalence of AF to be 5% based on our feasibility study. The resultant stratum size of 300 people can estimate the subpopulation prevalence of 5% with a 95% confidence interval of 2.8 – 8.1%. An effective screening tool maximizes sensitivity to avoid false negative findings. Assuming a 5% prevalence of AF, a sample size of 2,000 participants (5% AF rate, n=100) or more is necessary to obtain a satisfactory confidence band for 90% sensitivity for study Aim 3 (Table 3). Considering the extent of resources available, the study team decided to screen 2,000 adult men and women 45 years and older to accomplish the aims outlined in Box 1.

Table 3. 95% Confidence Interval for Sensitivity and Specificity by Number of Participants (assume 5% prevalent atrial fibrillation)

# Participants	500	1000	**2000**	5000
Sensitivity (0.9)	0.69-0.97	0.78-0.97	**0.82-0.95**	0.86-0.93
Specificity (0.9)	0.87-0.93	0.88-0.92	**0.89-0.91**	0.89-0.91

2.7 Community Based Screening:

Pre-screening preparation: One week prior to screening, field workers for study Teams A and B contact the respective village health workers to inform them of the screening plan. Both teams develop an age- and sex-stratified recruitment roster for their respective villages based on the census provided by the SPARSH program. In total, six strata are defined for the combination of age (40—55, 56-65, and 65+ years) and sex (male and female) categories. Teams print out recruitment and screening tracking forms (Appendix B) and charge the smart-phones and ortable power-banks for use during the week.

Screening protocol: Recruitment and enrollment occurs on days one and two of the screening process. The two study teams accompany their respective village health workers to enroll 21 willing participants in their respective villages on a daily basis. Each participant are screened using the Alivecor device for 1 minute, with the Alivecor device placed on the clipboard (Figure 3), followed by the Anand app for 1 minute 30 seconds. Results are recorded in the tracking form. If the participant is screened for either unclassified or unreadable heart rhythm on Alivecor, two more attempts are made to obtain either a normal or possible AF automated reading. Following this screening process, each participant completes the enrollment questionnaire that is entered directly into the Magpi database by the field assistants. Village health workers perform random blood glucose testing and measured the blood pressure of all participants. On day three, both field teams attempt to screen all 42 participants using the Alivecor device and ANAND app. A successful follow-up, number of attempts required, and whether or not the screening occurred at home is recorded in the tracking form. On days four and five, the third screening for AF is again split into two days. If a participant is not available on day three, field workers approach them on both days to perform a total of three screenings over five days. Thus all participants are screened one and two days apart, unless they are unavailable during their follow-up screening. After the final screening was completed, the field workers administer an exit survey, and data is entered directly into Magpi forms. The results of all screenings are recorded on paper and entered into REDCap along with the Alivecor ECG recordings for those who have an abnormal finding.

Post-screening activities: On each of the final two days (Day 4 and 5) of screening, field workers travel back to CAM to complete data entry and upload all abnormal (possible AF/unclassified) ECG files to RedCAP. All Alivecor and ANAND files are downloaded from

the phones using iTunes. All Alivecor PDFs are renamed with patient IDs and separated into normal results versus AF/Unclassified results. All AF/Unclassified files are uploaded to Redcap and flagged for adjudication. The field workers create a weekly report to summarize recruitment and results of screening and distribute it with the team (Appendix C). All of the ANAND and Alivecor files are uploaded to a secure server to support ad-hoc analyses for measuring the performance of the two screening methods. Ultimately all data are exported to STATA for statistical analyses (Figure 2).

2.8. Clinical Follow-Ups

Our protocol for clinical follow-ups evolved over time based on feedback from the research team. The primary impetus behind the change in approach was a higher than expected number of screenings that are classified as inconclusive and the resultant backlog of follow-up visits needed to understand these inconclusive readings. In order to facilitate prompt clinical visits for high-risk participants, we introduced a triaging step (Section 8.3) after reviewing the clinical charts and final diagnosis for the first 50 participants that were followed up in clinic.

Scheduling follow-ups: The clinical coordinator schedules all follow up visits with village health workers. One day prior to the visit, the clinical coordinator informs the cardiac and extension departments about the number of participants and which village health workers are coming. The clinical coordinator prints out the abnormal ECGs and paper clinical forms to prepare for the follow up visit.

Follow-up protocol: The clinical coordinator meets the village health workers and participants at the hospital and escorts them to the cardiac center. Once at the cardiac center, the clinical coordinator conducts further AF screening using the Alivecor device and ANAND app using the same methodology as in the field. Subsequently, all participants receive a 12-lead ECG. The study cardiologist reviews all of the ECG recordings (field and clinical visit) and determines whether or not to pursue additional clinical work-up. While waiting for the cardiologist's interpretation, the clinical coordinator administers the follow up survey in Magpi, recorded vital information as measured by the nurse (height, weight, blood pressure, heart rate, O2 saturation, temperature), and verified the participants' medical history. The cardiologists' clinical decision-making is described in Figure 4. If the cardiologist interprets all ECG recordings of the

participant as showing normal sinus rhythm, no additional studies are ordered. If the cardiologist diagnosed the participant as having definite AF in any of the ECG, either in any of the screening ECG or in-office ECG, additional laboratory investigations are performed to inform clinical decision-making about initiation of anticoagulation and management plan (Figure 4). If AF was suspected on any of the screening ECG but a diagnosis of definite AF could not be made due poor quality of ECG tracings from screening app, multiple atrial or ventricular premature complexes, or a normal sinus rhythm on the 12-lead ECG, the cardiologist orders 24 hour Holter monitoring to look for paroxysmal AF events or other abnormalities. Two dimensional Echocardiography is performed in all participants diagnosed with AF and in those having symptoms and/or ECG abnormalities that warrants for an echocardiographic examination. Decision to initiate anticoagulation is taken based on CHA_2DS_2-VASc score.[26] All of the clinical data including medications is abstracted by the clinical coordinator using clinical research forms.

Modifications for follow-up scheduling: A preliminary inspection of clinical follow-ups found that the majority are due to an "Inconclusive" finding of Alivecor ECG recording based on Kardia's automated algorithm. Specifically, 44 out of the first 50 follow-ups are of participants whose screening was inconclusive. Out of these 44 participants, 41 were found to have normal sinus rhythm after the study cardiologist interpreted field and 12-lead clinical ECGs. Additionally, two of the remaining three participants were found to have benign, non-AF arrhythmias. Based on these findings, we modified our follow-up protocol by having the study cardiologist triage the single-lead ECG recordings from the field prior to the participants' clinical follow ups to prioritize high-risk patients and rule out false positive recordings.

2.9. Data Adjudication

All interpretations of ECG recordings determined as AF or abnormal by the Alivecor automated algorithm are reviewed by a separate team of trained clinicians through a standardized adjudication process. Two resident-level physicians independently review each abnormal Alivecor generated ECG recording using REDCap and enter their interpretation as either: 1) normal sinus rhythm, 2) AF, or as an 3) other arrhythmia (free text). In the event of disagreement between the two reviewers, a fellow level physician reviews the ECG recording.

2.10. Analytical Plan

Aim 1: AF Epidemiology: The gold-standard of cardiologist verified diagnoses of AF will be used to calculate the age and sex-stratified prevalence of AF in the study sample. Population estimates will be derived from the sample prevalence using survey weights constructed using the census collected by the SPARSH program and the Government of India sponsored census in 2011. Three separate calculations will be performed to describe the overall prevalence of AF and separately for those with valvular and non-valvular AF.

Aim 2: Profile of patients likely to have AF: Distribution of covariates (Table 1) across group of participants diagnosed with AF will be compared to those who were not diagnosed with AF to determine associated risk factors. Sensitivity analyses will be performed to rule out differences between the group of participants who were not diagnosed with AF but were followed up clinically in comparison to those who were never followed up. If meaningful differences are identified in our sensitivity analyses, distribution of covariates will be assessed across the three different groups of participants. Additionally, among those participants who are followed up clinically, differences in the distribution of clinical factors between the group of AF-positive and AF-negative participants will be assessed. For sociodemographic and clinical risk factors, multivariable regression techniques will be used to identify their conditional effects after accounting for other covariates. Lastly, among the participants who were followed up clinically, the effects of AF will be estimated by comparing differences in the quality of life score (SF-12, Table 1) between groups of participants who are diagnosed for AF vs those who do not have AF. Potential confounders will be identified based on a-priori knowledge (age, sex, socio-economic status) and an examination of bivariate association of sociodemographic factors with AF and quality of life.

Aim 3: Performance of AF-screening technology: Sensitivity, specificity, and discriminative ability (ROC curve analyses) with 95% confidence bands will be used to measure the performance of our AF-screening technology in-field and in-clinic (Table 4). In-field performance of AF-screening technology will be used by comparing results from the ANAND and Alivecor automated algorithms with the gold-standard of adjudicated interpretations of the Alivecor ECG recordings. The clinical performance of AF-screening technology will be assessed

by comparing results from the automated algorithms from both technologies with results from the gold standard 12-lead ECG.

Table 4: Validation strategy to assess performance of Atrial Fibrillation screening technology		
Phase	Screening Technology	Gold-Standard
In-Field	ANAND automated algorithm Alivecor automated algorithm	Clinical adjudication of Alivecor recording from the same day
In-Clinic	ANAND automated algorithm Alivecor automated algorithm	Clinical interpretation of 12-lead EKG from the same day

3. LIMITATIONS AND STRENGTHS

It is important to consider that this study screens people of villages from rural Indian region who live in villages enrolled in SPARSH program, that is focused on addressing non-communicable diseases and its risk factors. Therefore, the participants recruited in this study may underrepresent the true burden of AF risk factors present in rural Indian population. Additionally, ascertainment of certain lifestyle related AF risk factors is based on self-report, which is prone to underreporting. Mobile technologies are used to perform multiple AF screening to account for potentially paroxysmal nature of AF. This approach, albeit superior to single time point screening, is vulnerable to missing AF. However, we attempt to partially address this limitation by obtaining a 24 hour Holter recording for participants who experience rhythm abnormalities on Alivecor or 12-lead EKG but may not be classified as AF.

4. DISCUSSION

The SMART-India study represents an innovative screening and referral paradigm for persons living in low-resource settings who may have an undetected chronic disease. Our study also highlights the importance of conducting a feasibility study and engaging local community

partners prior to undertaking more broad- based population screening efforts. Findings from this study will provide greater insights into the silent burden of AF in rural Indian communities and help identify potential targets for intervention to modify the ongoing epidemic of stroke in India. The potential public health impact of the SMART-India study is particularly noteworthy in light of a recent white paper on AF screening which reported that AF detected during a screening procedure is not a benign condition and carries a sufficient risk of stroke.[14] Further work is needed to build on the SMART-India study and build a nexus of providers that can help triage high-risk patients and further enhance the efficiency of a referral system for persons with suspect chronic disease, including cardiovascular disease. Leveraging existing community-based programs, such as SPARSH, can help achieve this ambitious, but feasible, goal.

5. ETHICS AND DISSEMINATION:

The SMART-India study was reviewed and approved by ethical boards from the University of Massachusetts Medical School (IRB# H00008089) and Charutar Arogya Mandal (HREC# IEC/HMPCMCE/70/Faculty/15/160/16). The primary outcomes of this study will be disseminated through annual scientific conferences and three separate peer-reviewed publications, one corresponding to each objective. Additionally, the authors will share data with ongoing coalition efforts to better understand global epidemiology of AF and to guide the development of more robust AF screening programs in resource limited settings.

Figure Legends:

Figure 1: An overview of SMART-India study protocol for community-based screening of Atrial Fibrillation and referral for clinical follow-up in rural western India

Figure 2: An overview of data management for SMART-India study. Questionnaire data is collected using Magpi platform, screening files are imported through iTunes, and clinical forms as well as abnormal recordings are stored in REDCap.

Logo credit: Magpi Inc (www.home.magpi.com); Alivecor (www.Alivecor.com); Adobe Reader (www.acrobat.adobe.com); iTunes (www.apple.com/itunes); REDCap (www.project-redcap.org); Stata (www.stata.com)

Figure 3: A field worker is collecting single-lead ECG recording from a SMART-India participant. The participant is asked to place her fingers on the Alivecor device that is supported by a clipboard to minimize motion-noise artifact. The participant approved the use of this picture and provided consent for its use.

Figure 4: A flowchart describing the clinical decision-making of the study cardiologist for participants following up in clinic for abnormal screening results during SMART-India study

Contributors' Statement:

Apurv Soni: Soni conceptualized, designed, and implemented the study in India. Soni drafted the initial manuscript, and approved the final manuscript as submitted.

Sunil Karna: Karna contributed to the design and implementation of the study in India. Karna contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Harshil Patel: Patel contributed to the design and implementation of the study in India. Patel contributed to the drafting of the initial manuscript, and approved the final manuscript as submitted.

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Shyamsundar Raithatha: Raithatha contributed to the conceptualization, design and implementation of the study in India. Raithatha contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Anna Handorf: Handorf contributed to the design of the study. Handorf contributed to the drafting and formatting of the manuscript, and approved the final manuscript as submitted.

John Bostrom: Bostrom contributed to the design and implementation of the study in India. Bostrom contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

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Ravi Shah: Shah contributed to the design and implementation of the study in India. Shah contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

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Sunil Thanvi: Thanvi conceptualized, designed, and implemented the study in India. Thanvi provided input to the analyses, contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Ajay Phatak: Phatak conceptualized and designed the study in India. Phatak contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Jeroan Allison: Allison conceptualized and designed the study in India and supported its implementation. Allison contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

Ki Chon: Chon supported the implementation of the study in India. Allison contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

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David McManus: McManus conceptualized and designed the study in India and supported its implementation. McManus contributed to the drafting of the manuscript, and approved the final manuscript as submitted.

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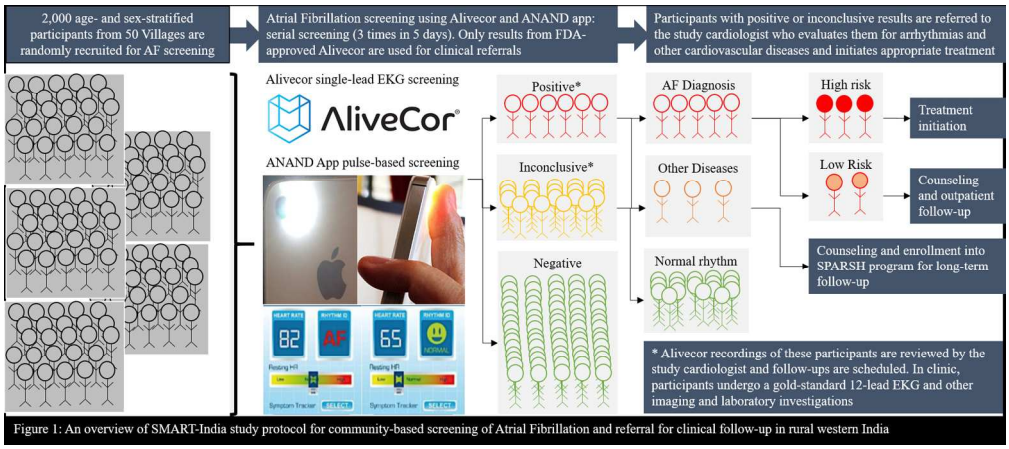

Figure 1: An overview of SMART-India study protocol for community-based screening of Atrial Fibrillation and referral for clinical follow-up in rural western India

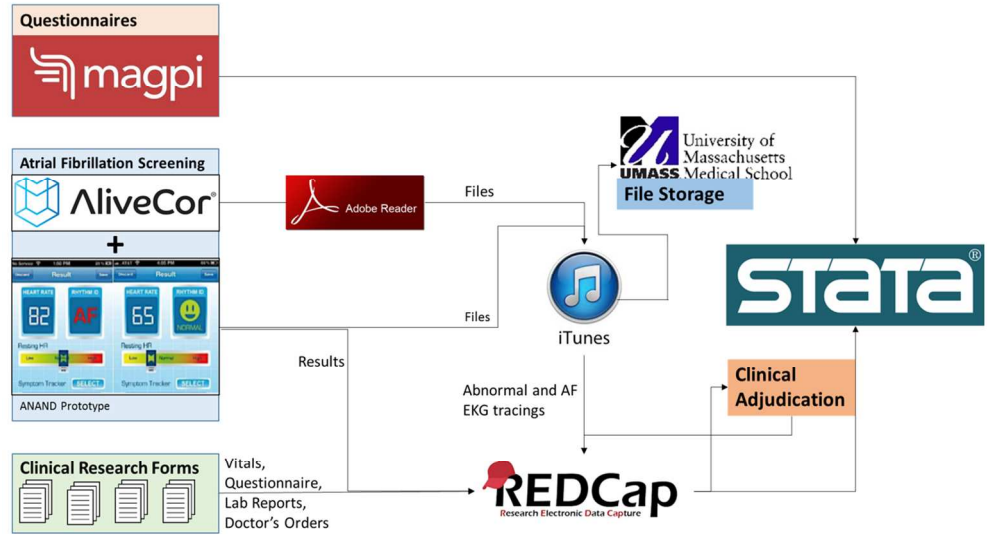

Figure 3: An overview of data management for SMART-India study. Questionnaire data is collected using Magpi platform, screening files are imported through iTunes, and clinical forms as well as abnormal recordings are stored in REDCap.
Logo credit: Magpi Inc (www.home.magpi.com); Alivecor (www.Alivecor.com); Adobe Reader (www.acrobat.adobe.com); iTunes (www.apple.com/itunes); REDCap (www.project-redcap.org); Stata (www.stata.com)

Figure 2: An overview of data management for SMART-India study. Questionnaire data is collected using Magpi platform, screening files are imported through iTunes, and clinical forms as well as abnormal recordings are stored in REDCap.
Logo credit: Magpi Inc (www.home.magpi.com); Alivecor (www.Alivecor.com); Adobe Reader (www.acrobat.adobe.com); iTunes (www.apple.com/itunes); REDCap (www.project-redcap.org); Stata (www.stata.com)

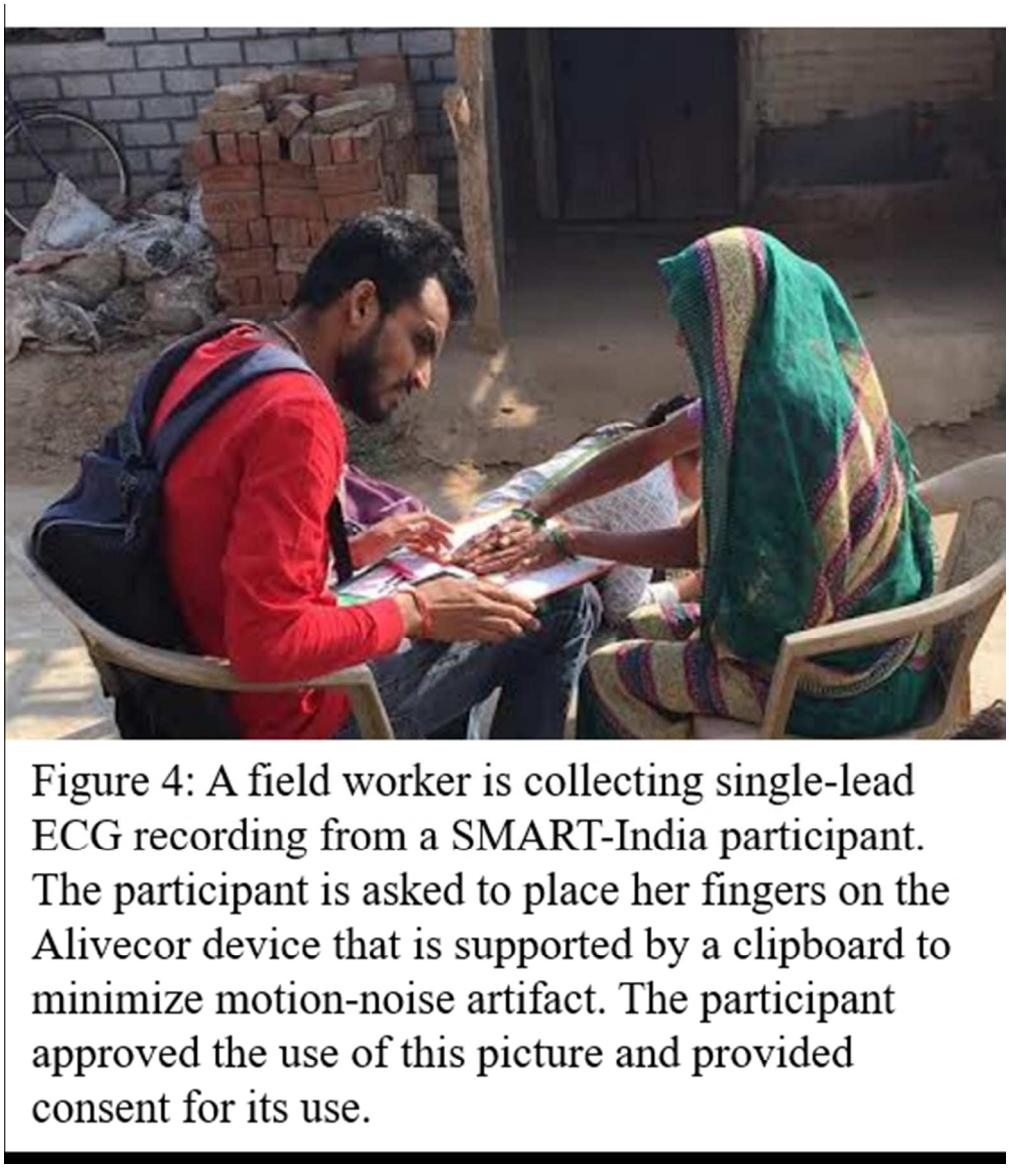

Figure 4: A field worker is collecting single-lead ECG recording from a SMART-India participant. The participant is asked to place her fingers on the Alivecor device that is supported by a clipboard to minimize motion-noise artifact. The participant approved the use of this picture and provided consent for its use.

Figure 3: A field worker is collecting single-lead ECG recording from a SMART-India participant. The participant is asked to place her fingers on the Alivecor device that is supported by a clipboard to minimize motion-noise artifact. The participant approved the use of this picture and provided consent for its use.

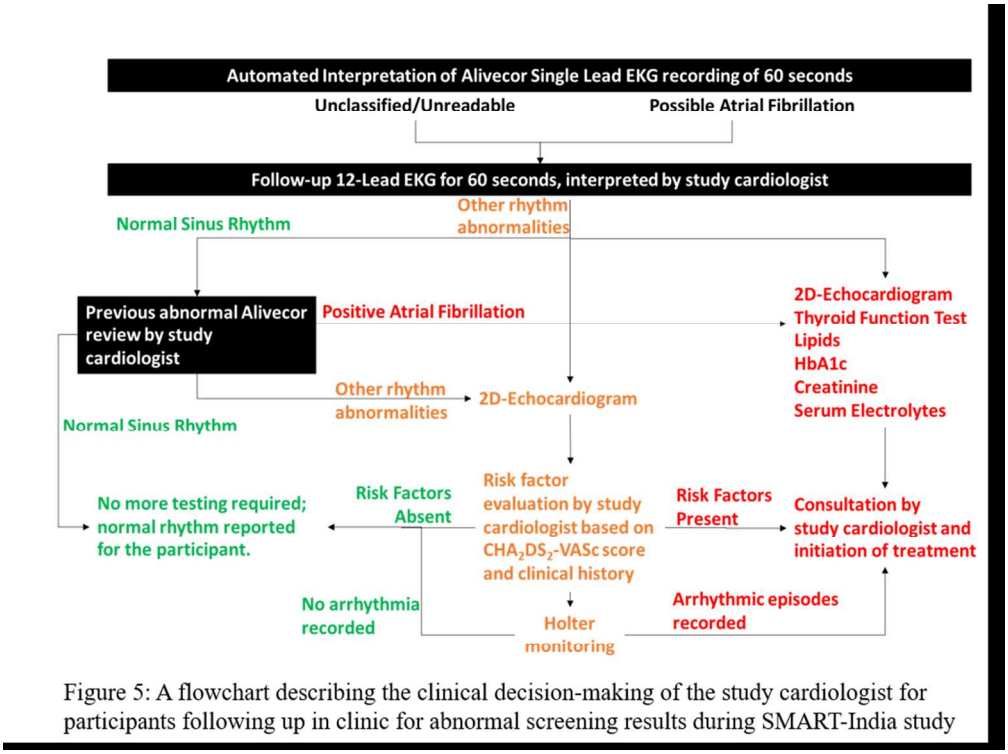

Figure 5: A flowchart describing the clinical decision-making of the study cardiologist for participants following up in clinic for abnormal screening results during SMART-India study

Figure 4: A flowchart describing the clinical decision-making of the study cardiologist for participants following up in clinic for abnormal screening results during SMART-India study

Village:_____ Date:_____

Feasibility Study: Using Mobile Devices to Screen for Atrial Fibrillation in Rural India
Passive Field Observation Guide

Category	'Objective' observation	'Subjective' thoughts, comments
Physical setting (describe layout of where screening is taking place		
Approach by the Research Coordinator (tone, who responds, single v. multiple)		
Response by the participant(s) (appearance of engagement, eye contact)		
Informed Consent Form (response by the participant for the paperwork, gestures)		
Personal space RC-Participant (is the research coordinator in participant's personal space/ is the participant? Body language?)		
Personal space others (are bystanders invading in the personal space, are there attempts by coordinator to create distance)		
Questionnaire (Tone of RC, nonverbal communication between the two)		

Village:_____ Date:_____

About how long from informed consent form to screening for A-Fib?		
Using Mobile Phone Technology? (responses by participant, bystanders, management by RC)		
How long does the whole process take?		
Describe problems observed and problem-solving techniques		
Describe evidence of teamwork		
Overall tone of exchange during departure		
Insights: what stands out for you from what you observed? (take brief notes, expand later)		

SMART-India Recruitment Form

Date:

Villlage Name : Number:

Age	Approached	Enrolled
	Male	
40-55	Not Available	
	Refused	
56-65	Not Available	
	Refused	
65+	Not Available	
	Refused	
	Female	
40-55	Not Available	
	Refused	
56-65	Not Available	
	Refused	
65+	Not Available	
	Refused	

SMART-India Tracking Form

Village: _____ Number: ___

#	ID#	Age	Sex	Visit	Date	Alivecor Time	Alivecor AF	Alivecor HR	ANAND Time	ANAND AF	ANAND HR	Glucose	Sys BP	Dia BP	# try	Home?
1			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
2			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
3			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
4			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
5			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
6			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
7			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N
8			M	1	/	:	N /AF/ IC		:	N / AF/MN						
				2	/	:	N /AF/ IC		:	N / AF/MN						Y / N
			F	3	/	:	N /AF/ IC		:	N / AF/MN						Y / N

SMART-India
Weekly Report

Weekly Report: Week of
Village # and Name:
Research Coordinators:

Recruitment Report						
	Male			Female		
Age	Approached*	Refused	Enrolled	Approached*	Refused	Enrolled
40-55						
56-65						
65+						
Total						
% Response Rate (overall)(enrolled/approached) x 100: % Response Rate (refusal) (enrolled/(enrolled+refused)) x 100:						
* Includes not available + refused						

Alivecor Results			
	Normal	Inconclusive	AF-Positive
Total			

Number of Screenings Completed		
3	2	1

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		~~(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found~~
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Pages 4-7
Objectives	3	State specific objectives, including any prespecified hypotheses Page 8
Methods		
Study design	4	Present key elements of study design early in the paper Pages 8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Pages 8-16
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Pages 8-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Pages 9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Pages 9-12
Bias	9	Describe any efforts to address potential sources of bias Page 13
Study size	10	Explain how the study size was arrived at Page 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Pages 15-16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Pages 15-16
		~~(*b*) Describe any methods used to examine subgroups and interactions~~
		~~(*c*) Explain how missing data were addressed~~
		(*d*) If applicable, describe analytical methods taking account of sampling strategy N/A
		~~(*e*) Describe any sensitivity analyses~~
~~**Results**~~		
~~Participants~~	~~13*~~	~~(a) Report numbers of individuals at each stage of study—eg numbers potentially~~

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 16-17
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.