PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol for Smartphone Monitoring for Atrial fibrillation in Real-Time - India (SMART-India) – a community-based screening and referral program
AUTHORS	Soni, Apurv; Karna, Sunil; Patel, Harshil; Fahey, Nisha; Raithatha, Shyamsundar; Handorf, Anna; Bostrom, John; Bashar, Syed; Talati, Kandarp; Shah, Ravi; Goldberg, Robert; Thanvi, Sunil; Phatak, Ajay; Allison, Jeroan; Chon, Ki; Nimbalkar, Somashekhar; McManus, David D

VERSION 1 – REVIEW

REVIEWER	Chiao Wen Lim Cardiology specialist and clinical lecturer, Faculty of Medicine, University Teknologi MARA, Malaysia
REVIEW RETURNED	08-Jun-2017

GENERAL COMMENTS	Study information for participant and consent was not stated in detail. Limitation of observational study did not explore possible under-reporting of illness/risk factors. Enrolment questionnaire relies heavily on participant's lay health belief, their education attainment and understanding of disease. All these factors may lead to under reporting of illness.

REVIEWER	Ben Freedman Heart Research Institute, Charles Perkins Centre, University of Sydney, Sydney Australia
REVIEW RETURNED	18-Jun-2017

GENERAL COMMENTS	This is a very interesting study protocol, that builds on the recently reported pilot study performed by the same authors. The study will produce important and novel information about the prevalence of both unknown and previously known AF in India, using a combination of novel technologies. The strengths are the RAHI collaboration between the US and CAM institutions, and the leverage using the SPARSH epidemiological platform, and the culturally competent translations and local health workers with an adequate referral pathway to institute therapy when appropriate. It will certainly be worthwhile recording how often appropriate therapy is both prescribed, and then adhered to, given the financial and logistic issues in that important outcome in this rural setting in India. I have a number of comments and questions that should be considered in this protocol.

	The technologies to be used are the Alivecor single lead ECG, and smartphone photoplethysmograph. The PULSE SMART paper is quoted, (#20, unpublished), but it has been published last year. How does the ANAND algorithm differ from the PULSE SMART algorithm cited in that paper? Are either apps available as freeware or commercial apps? If so, this should be stated. The Alivecor is to be recorded for 60 seconds, although the commercial app only records for 30 sec. Does this mean 2 x 30 sec recordings will be made? If so this should be stated. Will the ECGs be uploaded to the commercial Alivecor website which will ensure some safe HIPAA compliant storage? The photo of the clipboard being used to reduce motion artefact looks as though it will increase tremor artefact, and the arms are outstretched. It would be better to have the forearms and hands resting on the clipboard to relax the arms, and address this issue. Aim 3 describes that the gold standard is the 12-lead ECG as well as the clinician, whereas in the Fig 5 flowchart and elsewhere in the text, it is obvious that the gold standard is an expert reading of the single lead trace (where that is diagnostic) first, and then the 12-lead recorded only once. The ESC 2016 guidelines state that screening for AF can be performed using a single lead ECG rhythm strip. Also, as much of the AF in the pilot Indian study is paroxysmal, unless the single lead and photoplethysmography are performed simultaneous with the 12-lead, the sens/spec cannot be determined with accuracy without a change in the gold standard. Aim 1 is to determine the prevalence of AF. Will it be possible to determine whether AF found was previously known from the medical records? Agreed there is a large ascertainment bias, especially outside the large urban areas with upper middle class representation, but helpful to know whether any AF was previously known. There are a few caveats to the data. Is the 5 day screening spatially distributed across the 5 days, not clustered on the first 3 days for a group of subjects, which would miss PAF given the findings of the pilot study of distribution of positive traces on day 4 or later. Will there be an adequate sample of older subjects? The mean age of people with newly discovered AF is about 79 in Europeans. How many of the 2000 will be over 75? What would be the CI for AF prevalence in different age ranges eg 45-54, 55-64, 65-74 and 75 and older, given the likely denominator in each of these age ranges? P18: therapy given according to CHADSVASc. One assumes there will be a significant prevalence of rheumatic mitral valve disease, and an echo is mandated, so this should be added and clarified. Is the questionnaire able to capture the BMI and diet? It would be helpful to cite the recent white paper on screening for AF from AF-SCREEN in Circulation May 2017, which is very germane to the protocol, and has some country specific issues described in the online appendix including a brief section on India. Has the trial been registered? This would be ideal to happen pari passu with the publication of the protocol paper

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment:
Study limitations arising from this observational study i.e. under-reporting of illness/risk factors, heavy reliance on participants' lay health belief, and other factors need to be adequately discussed

Response:
We have elaborated on potential limitations of this observational study in the revised discussion section and outlined some steps that were taken to address them.

Reviewer 2

Comment:
How does the ANAND algorithm differ from the PULSESMART algorithm cited in the manuscript. Are either apps available as freeware or commercially?

Response:
We have provided clarification for how this ANAND algorithm differs from the PULSESMART algorithm "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".

Comment:
The Alivecor is to be recorded for 1 minute, although the commercial app only records for 30 seconds.

Response:
We have changed the recording duration in the commercially available app to record for 60 seconds.

Comment:
Aim 3 describes that the gold standard is the 12-lead ECG as well as the clinician but elsewhere gold-standard is an expert reading of the single lead trace. This needs to be clarified

Response:
We have revised our language to limit confusion and added a table to clarify our approach towards validation of mobile technologies for the screening of persons with possible AF. There are two separate validation approaches: in-field and in-clinic. Clinical adjudication of a single-lead tracing is considered as the gold-standard for the validation of screening technologies' performance in the field while the 12-lead ECG is considered as the gold-standard for validation of screening technologies' performance in the clinic setting.

Comment:
Will it be possible to determine whether AF found was previously know from the medical records?

Response:
Previous determination of AF was limited to participant's self-reports because medical records rarely exist and are not standardized across different populations.

Comment:
Is the 5 day screening spatially distributed across the 5 days?

Response:
We have added an explicit description of the spatial distribution of AF screening, “Thus all participants are screened one and two days apart, unless they are unavailable during their follow-up screening

Comment:
Will there be an adequate sample of older subjects?

Response:
Because of our age and sex-stratified sampling, we will have roughly 330 participants in each of the six strata. We have added details of subsample prevalence estimation “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%.”

Comment:
One assumes there will be a significant prevalence of rheumatic mitral valve disease, and an echo is mandated, so this should be added and clarified

Response:
We agree with the reviewer that rheumatic mitral valve disease is an important consideration in this setting and echocardiogram investigation is necessary for further clinical decision-making. We performed a 2D-echocardiogram for all participants where AF was suspected and others for whom the study cardiologist at CAM suspected a possible clinical reason.

Comment:
Is the questionnaire able to capture the BMI and diet

Response:
The BMI of participants who were selected for follow-up was measured by the clinical nurse. Information about dietary practices was not captured by the questionnaires.

Comment:
It would be helpful to cite the recent white paper on screening for AF from AF-SCREEN in circulation

Response:
We agree with the reviewer and have included references to the white paper on AF-Screening “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”

VERSION 2 – REVIEW

REVIEWER	Ben Freedman Heart Research Institute, Charles Perkins Centre, University of Sydney, Sydney Australia

REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	I have looked through the response to reviewers and the changes made, and I am happy to recommend acceptance of the revised manuscript.