PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([http://bmjopen.bmj.com/site/about/resources/checklist.pdf](http://bmjopen.bmj.com/site/about/resources/checklist.pdf)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Protocol for Home-Based SoUtion for Remote Atrial Fibrillation Screening to PrevenT RecurrenT Recurrence StrOke (HUA-TUO AF Trial): A Randomized Controlled Trial |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Wong, Chun Ka; Hai, Jo Jo; LAU, Yuk-Ming; zhou, Mi; LUI, Hin-Wai; Lau, Kui; CHAN, Koon-Ho; MOK, Toi Meng; Liu, Yong; Feng, Yingqing; Tan, Ning; TAM, Weng-Chio; TAM, Kun-Chong; FENG, Xiuhua; ZUO, Ming-Liang; YIN, Li-Xue; TAN, Jing; ZHANG, Wen-Jun; JIANG, Xiaofei; HUANG, Xiaoyu; YE, Jianfeng; Liang, Yan; JIANG, Wei; LEI, Zhen; Huang, Duo; YUE, Wen-Sheng; TAN, Guanming; Yan, BP; EVORA, Mario; Chen, Ji-yan; SIU, Chung-Wah |

VERSION 1 – REVIEW

| REVIEWER | Hespe, Charlotte |
|----------|------------------|
| SCHOOL   | The University of Notre Dame Australia, School of Medicine |
| REVIEW RETURNED | 09-Jul-2021 |

| GENERAL COMMENTS | Thank you for submitting this protocol paper for publication. It is a very interesting study and if successfully completed will provide comprehensive data about BP and AF recurrence in this patient cohort. However I have multiple concerns about the quality of your paper that need to be addressed prior to acceptance for publication. 1. There is no mention of sources of funding for this project. Who is funding the development of the cardiac app that all patients have access to? Who is funding the AF ECG device for the active patient cohort? Who is supplying the home BP machine and how is it being validated? Who is funding the research team who will be monitoring this data during the study? Who is funding the clinicians to review the patient data? There is mention of the Doctor who is responsible for the patient safety but no mention about the actual pathway for patient communications - the protocol states that if AF is detected then they will have a 12 lead ECG within a week but no mention of clinical oversight for dangerous rhythm and how often the 1 lead ECG's will actually be monitored. The protocol also suggests that the patients will have daily monitoring of their BP (which needs to be measured twice daily) and how is the patient to be contacted to adjust the medications and who is responsible for the daily clinical oversight. Although you mention that the medication will be adjusted according to an algorithm, this is not supplied and no mention about how the patient compliance with the algorithm will be recorded. Nor is there any details re what medications the patients will be prescribed / nor how they will be adjusted for this protocol. The protocol does not talk about how the patients will be recruited nor how they will be consented. There is no mention of how the patients will be assisted in adhering to the protocol, which I note is very onerous and requires a lot of |
input and assistance from the patients to collect the data (twice daily for 2 years with BP monitoring, weekly weight and recording of events for ALL patients as well as daily ECG for the active arm). There is no comment about incentives that might be used (and needed) in order to both enrol and engage patients in this onerous study.

There is also no mention of whether patients who do have AF detected (and treated) are then handled with respect to their ongoing clinical care and ongoing data with respect to the study - do they continue to participate as an active or control patient. A lot of these queries could be addressed by a more comprehensive flow chart documenting decision pathways and patient outcomes. I note that there is a complete absence of commentary about the role that BP plays in stroke recurrence, despite the twice daily measures and daily medication adjustments for all patients, and I therefore have to make an assumption that the intensive BP management protocol is the Research teams approach to removing this effect in the study. This needs to be discussed in the protocol. I believe there are significant limitations of this study with respect to the protocol being translatable into the real world. The authors need to address this limitation by discussion around how they anticipate Post Stroke management (due to the intensive requirements for both the patient and the clinician) may be altered by this study. It is proposed by the authors that this is a cheaper approach to detection of AF and stroke prevention but the authors fail to discuss the high daily workload that this study will impose and do not provide economic justification for their approach. Finally, the protocol does not provide any detail about when it is proposed to start and finish, nor if there is going to be any qualitative or economic analysis regarding the ability to replicate it into the real world of clinical practice.

REVIEWER
Mlynarska, Agnieszka
Medical University of Silesia

GENERAL COMMENTS
The work submitted for review is a selective endorsement of the scientific work and presentation of the reliability of the results. The idea for the study is very interesting, however, the results of the work should be published, not just assumptions. After doing the research, I think it will be a very valuable material. However, in this arrangement, the work is unacceptable.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments

thank you for submitting this protocol paper for publication. It is a very interesting study and if successfully completed will provide comprehensive data about BP and AF recurrence in this patient cohort. However I have multiple concerns about the quality of your paper that need to be addressed prior to acceptance for publication.

There is no mention of sources of funding for this project. Who is funding the development of the cardiac app that all patients have access to? Who is funding the AF ECG device for the active patient cohort? Who is supplying the home BP machine and how is it being validated? Who is funding the
Research team who will be monitoring this data during the study? Who is funding the clinicians to review the patient data?

Response: Thank you for raising the important question. The clinical trial is funded by Department of Science and Technology of Sichuan Province, China (2020YFH0183). Standard blood pressure monitor with CE mark is used. Manuscript was updated to include more detailed description.

There is mention of the Doctor who is responsible for the patient safety but no mention about the actual pathway for patient communications - the protocol states that if AF is detected then they will have a 12 lead ECG within a week but no mention of clinical oversight for dangerous rhythm and how often the 1 lead ECG's will actually be monitored.

Response: Thank you for raising the important enquiry. Cardiologists at the remote monitoring center will review all electrocardiogram on a daily basis to verify diagnosis of atrial fibrillation before instructing research staff to call subjects in concern by phone for further arrangement. Malignant rhythm identified by the cardiologist at the remote monitoring center will be managed in liaison with trial center cardiologists responsible for the patient in concern. Manuscript was updated for further elaboration.

The protocol also suggests that the patients will have daily monitoring of their BP (which needs to be measured twice daily) and how is the patient to be contacted to adjust the medications and who is responsible for the daily clinical oversight.

Response: Thank you for raising the important question. Medication adjustment will be confirmed by trial center cardiologists using web-based dashboard. Patient will receive instructions on drug regimen from their smartphone application. Manuscript was amended to improve clarity.

Although you mention that the medication will be adjusted to according to an algorithm, this is not supplied and no mention about how the patient compliance with the algorithm will be recorded. Nor is there any details re what medications the patients will be prescribed / nor how they will be adjusted for this protocol.

Response: Thank you for the valuable comment. The drug titration was designed with reference to American Heart Association/American Stroke Association guidelines. Medications will be prescribed and dispensed through trial hospitals. It is of interest to study the degree of drug compliance on clinical outcome. Nonetheless it is beyond the scope of the current research to include extra measures to quantify actual drug compliance towards prescribed medications. Manuscript was updated to include this important discussion.

The protocol does not talk about how the patients will be recruited nor how they will be consented.

Response: Thank you for the important comment. The recruitment process begins with obtaining written informed consents from all study participants by study staff responsible for recruitment after detailed discussion. Subsequently hardware and software required for the clinical trial will be allocated to each study participants. Education regarding trial protocol will be provided at the recruitment session. The methods section was updated to improve clarity.

There is no mention of how the patients will be assisted in adhering to the protocol, which I note is very onerous and requires a lot of input and assistance from the patients to collect the data (twice daily for 2 years with BP monitoring, weekly weight and recording of events for ALL patients as well as daily ECG for the active arm).
Response: Thank you for valuable comment. In addition to reminders shown on the smartphone application designed for the clinical trial, recruited subjects are also allowed to contact remote monitoring center staff should they require other forms of assistance. We agree with the reviewer that the home-based AF screening strategy require active participation and overall efficacy may be limited by degree of protocol adherence by recruited subjects. Post-hoc analysis on protocol adherence will be performed. This important limitation was added to the limitation section.

There is no comment about incentives that might be used (and needed) in order to both enrol and engage patients in this onerous study.

Response: Thank you for the reminder. Compensation will be paid for trial participation. Manuscript was updated to include this important information.

There is also no mention of whether patients who do have AF detected (and ? treated) are then handled with respect to their ongoing clinical care and ongoing data with respect to the study - do they continue to participate as an active or control patient.

Response: Thank you for raising the important question. This trial is designed to be analyzed using intention-to-treat principle as described in the statistical analysis section. Patients who have atrial fibrillation diagnosed in the follow up period will continue the clinical trial in their allocated groups.

A lot of these queries could be addressed by a more comprehensive flow chart documenting decision pathways and patient outcomes.

Response: Thank you for the suggestion. Figure 3 was updated to provide more details about the trial design.

I note that there is a complete absence of commentary about the role that BP plays in stroke recurrence, despite the twice daily measures and daily medication adjustments for all patients, and I therefore have to make an assumption that the intensive BP management protocol is the Research teams approach to removing this effect in the study. This needs to be discussed in the protocol.

Response: Thank you for the important comment. Further elaboration regarding importance of blood pressure control on stroke prevention was added to the manuscript.

I believe there are significant limitations of this study with respect to the protocol being translatable into the real world. The authors need to address this limitation by discussion around how they anticipate Post Stroke management (due to the intensive requirements for both the patient and the clinician) may be altered by this study. It is proposed by the authors that this is a cheaper approach to detection of AF and stroke prevention but the authors fail to discuss the high daily workload that this study will impose and do not provide economic justification for their approach.

Response: Thank you for the comment. Daily monitoring of the web-based dashboard is performed by mainly by centralized remote monitoring center optimize efficiency. We agree with the review that cost-effective analysis is important to assess applicability of system in real-world use. After completion of trial, post-hoc cost-effectiveness analysis will be performed. Limitation section was updated to include this important discussion.

Finally, the protocol does not provide any detail about when it is proposed to start and finish, nor if there is going to be any qualitative or economic analysis regarding the ability to replicate it into the real world of clinical practice.
Response: Thank you for the important comment. The start date of the randomized controlled trial is intended to be 1st March, 2022 and the end date is after the last recruited subject completed 24 months of follow up. We agree that it would be of interest to perform post-hoc cost-effectiveness analysis to gain further insight into the real world applicability of the remote monitoring system, despite it is not an intended primary or secondary clinical outcome of the clinical trial. Manuscript was updated to add the description.

Reviewer 2 Comments

The work submitted for review is a selective endorsement of the scientific work and presentation of the reliability of the results. The idea for the study is very interesting, however, the results of the work should be published, not just assumptions. After doing the research, I think it will be a very valuable material. However, in this arrangement, the work is unacceptable.

Response: Thank you for the valuable comment. The manuscript was submitted to the Journal under the category study protocol. Results of the randomized controlled trial will be submitted for peer review when it is subsequently available.