PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of a Pharmacist-delivered Discharge and Follow-up Intervention for Patients with Acute Coronary Syndromes in Qatar: A Study Protocol for a Randomized Controlled Trial
AUTHORS	Zidan, Amani; Awaisu, Ahmed; Kheir, Nadir; Mahfoud, Ziyad; Kaddoura, Rasha; AlYafei, Sumaya; El Hajj, Maguy

VERSION 1 - REVIEW

REVIEWER	Joppe Tra VU University Medical Center, the Netherlands
REVIEW RETURNED	20-Apr-2016

GENERAL COMMENTS	I would like to congratulate you with a well designed study and well written study protocol. The study addresses a major problem in ACS care and uses an appropriate intervention. In my opinion, there is some room for improvement: - the size of the problem (current medication adherence) is unclear. The reported adherence rates on page 7, line 17 are missing a time frame (six months after discharge? one year? two years?) and the number of patients. The manuscript that is referred to is a poster, which is not generally accessible; describing more details would therefore be recommended; - what is the role of the cardiologist in the control, usual care and intervention arms of the study? Cardiologists should also address secondary prevention medication, although there could usually be more attention for this; - in the description of the setting (Heart Hospital in Qatar), the number of ACS patients per year and system for imbursement of secondary prevention medication (as a potential reason for non-adherence) should be included to facilitate comparison to other countries; - this study could benefit from the experiences in previous studies on clinical pharmacists interventions in the field of ACS, e.g. Bailey et al. 2007 An intervention to improve secondary prevention of coronary heart disease. Arch Intern Med 2007;167:586-590; - the references need some revision (e.g. reference 28 contains to first author); - in the study protocol, it is not described how contra-indications are handled in the study results. In addition, the contra-indications should be predefined as much as possible; - patients are allocated to the usual care or intervention arms of the study by means of their allocation to treatment teams A-D a. However, it is not described by what method patients are allocated to these teams (computer generated sequence? by a triage nurse based on capacity of the team?). In addition, allocation to the control arm of the study is the time of discharge (weekends/evenings = control arm); this is not random.

	- because the intervention and usual care treatment teams work in the same hospital, there is a risk of contamination between these two arms. What measures will be taken to prevent that? - the allocation of patients to treatment teams potentially requires multilevel statistical models, because differences between teams might occur. A statistician should carefully look at both the method of patient allocation to the study arms, and potential correction of the statistical models for the treatment teams; - for significant differences in mortality, large numbers of patients are required; with 125 patients per study arm, this is not very likely. - the study is described as receiving no funding, but in the intervention arm additional control visits will be scheduled, the intervention pharmacists are trained, the study results will be analysed, etc; who pays for all this if the study is not funded? - the study protocol should contain some more information about the limitations of the study, e.g. single centre, (partial) non-random allocation of patients, etc. Hopefully, these suggestions will help you in improving the study description. I wish you all the best with performing this commendable study.

REVIEWER	Rony Zeenny, Pharm.D., BCPS-AQ ID Lebanese American University - School of Pharmacy Lebanon
REVIEW RETURNED	02-May-2016

GENERAL COMMENTS	Congratulations for designing and implementing such a protocol. I would be very much interested to read the results once they are out. I have minor comment related to the typos and grammar mistakes in the texts and the graph, in addition to the incomplete sentences in some places of the text. I would recommend that that this paper be copy-edited.Good luck.

REVIEWER	Pourrat Xavier Hospital clinical pharmacist Trousseau hospital CHRU de Tours 2 bd Tonnellé 37044 Tours cedex
REVIEW RETURNED	02-Jun-2016

GENERAL COMMENTS	I would like to congratulate Zidam Amani for this pertinent subject and the easy way for reading this article. The intervention is well described and pertinent according to that can be expected from a clinical pharmacist in an education program. Nevertheless the topic and the demonstration are difficult to lead and I feel anxious to the intervention to be effective. In fact this study is a prospective controlled randomized trial and single centre as described by the author. But after reading I think that large biases do exist in the protocol. Concerning the method First: the recruitment, 1/It must be noticed if patients are those discharged after the first ACS or all patients with the diagnose of ACS? 2/the RAs will check the file to identify potential participants.

	In my point of view all patients have to be included and only the ones that do not match with criteria have to be excluded; the analysis is in IT. Also those that will not be discharged to home will be excluded - in my country all patients with ACS have to go to a recovery centre perhaps it is specific... but author have to explain it. Second, It said that 3 arms will be drawn a/control b/UC and c/ intervention. Patients in the control are those discharged during WE or at night. In fact (and I hope) that standard clinical pharmacy practice are done to them (med reconciliation at admission, med review…) also nurse and physicians have meeting with them in fact in my point of view the only difference between control and UC is the med reconciliation at discharge…In addition, patients will be allocated to UC or intervention according to the treatment team A, B, C or D. In fact I am not sure that way is randomization. All 4 teams have to take in charge patients with or with not intervention. I think that a cluster study (1 for a, b, c and d) in a stepped wedge way would have be better for implementing this intervention. Concerning the intervention, patients will have a meeting with the PC at discharge and also at M1 and M2. In previous studies it was demonstrated that this kind of intervention is effective if it is repeated every 2 months, once it is stopped patients are likely to be non-observant [JAMA. 2006 Dec 6;296(21):2563-71. Epub 2006 Nov 13 this article have to be read and included]. Some statistics have to be detailed by authors for feasibility (2015 number of patients concern by the intervention, % of discharge during nights and/or WE, mean length stay…). Concerning the outcomes: I am wondering if patient can not go to another hospital in Qatar? Also I would take in account and/or separate the plan and non-plan hospitalizations and separated those without a link to cardiology –ophthalmic for expl or cancer…- but for orthopaedic a broken HIP may du to a fall linked to drug side-effect, so authors have to explain their choice. For the observance/adherence rate by self-medication is not reproductive…I think that only the PDC would be enough. If authors explain how they will evaluate the adherence to CAD treatment also a discussion must be done for other treatment that can be linked to CAD (other ant-hypertensive, drugs for renal impairment…). If they demonstrate to improve PDC for CAD it would be pity to decrease PDC for other pathology. Concerning the data analysis: I am not specialist but it looks to fit with the practices

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer's comment:
I would like to congratulate you with a well-designed study and well written study protocol.

Authors' response:
Thank you so much for your positive feedback. The authors greatly appreciate it.

Reviewer's comment:
The study addresses a major problem in ACS care and uses an appropriate intervention. In my

opinion, there is some room for improvement:
- the size of the problem (current medication adherence) is unclear. The reported adherence rates on page 7, line 17 are missing a time frame (six months after discharge? one year? two years?) and the number of patients. The manuscript that is referred to is a poster, which is not generally accessible; describing more details would therefore be recommended.

Authors' response:
We concur with the reviewer's comments. The time frame and the number of ACS patients included in the pilot study were now added. This pilot study was presented at a national university based conference, but has not yet been published as a peer-reviewed article. The magnitude of non-adherence to secondary prevention medications in patients post ACS as published in international literature has been described in details in previous paragraphs. Please see text below:

"The medication taking behavior of the quadruple evidence-based secondary prevention medications was previously assessed in a cohort of 31 ACS outpatients at HH. The self-reported continuation rates for secondary prevention medications six months after the last hospital discharge decreased from 100% to 77% for β-blockers, 90% to 79% for ACE inhibitors, 100% to 97% for statins, and 84% to 52% for dual antiplatelet therapy"

Reviewer's comment:

- What is the role of the cardiologist in the control, usual care and intervention arms of the study? Cardiologists should also address secondary prevention medication, although there could usually be more attention for this;

Authors' response:
The role of cardiologists is similar across all the study arms and the study does not require any modification of the usual care delivered by cardiologists at Heart Hospital in Qatar. This care entails the usual cardiologist's specialist care including: post-discharge care, education and counseling, and prescribing of secondary prevention medications. This has now been clarified in the Methodology under the section of "study arms". Please see text below:
"The usual care delivered by cardiologists is similar across all the study arms and no modification of level of care was required by the present study."

Reviewer's comment:
- In the description of the setting (Heart Hospital in Qatar), the number of ACS patients per year and system for imbursement of secondary prevention medication (as a potential reason for non-adherence) should be included to facilitate comparison to other countries;

Authors' response:
Thank you to the reviewer for the important comments. This now has now been addressed in the revised version of the manuscript. In Qatar, imbursement of secondary prevention medications is unlikely to be considered a reason for non-adherence, because it is largely covered by the government. Please see text below which has now been added to the manuscript:
"Around 3000 patients are admitted to the HH due to ACS annually. These patients receive their secondary prevention and other medications from the hospital outpatient pharmacy with a nominal charge of about QR 150 per prescription refill."

Reviewer's comment:
- This study could benefit from the experiences in previous studies on clinical pharmacists interventions in the field of ACS, e.g. Bailey et al. 2007 An intervention to improve secondary prevention of coronary heart disease. Arch Intern Med 2007;167:586-590;

Authors' response:
The authors greatly appreciate your recommendation and we have now added this study in the protocol as reference number 40. However, the major distinction between our study and Bailey et al. is that ours has a more focus on patient education.

Reviewer's comment:
- the references need some revision (e.g. reference 28 contains no first author);

Authors' response:
This has been addressed. Please check revised references.

Reviewer's comment:
- In the study protocol, it is not described how contra-indications are handled in the study results. In addition, the contra-indications should be predefined as much as possible;

Authors' response:
This has now been addressed. The contraindications are already predefined and are at the disposal of the intervention pharmacists. Please see also the text below:
"------providing recommendations for alternatives in case of contraindications to any of the secondary prevention medications as per evidence-based guidelines."

Reviewer's comment:
- Patients are allocated to the usual care or intervention arms of the study by means of their allocation to treatment teams A-D. However, it is not described by what method patients are allocated to these teams (computer generated sequence? by a triage nurse based on capacity of the team?). In addition, allocation to the control arm of the study is the time of discharge (weekends/evenings = control arm); this is not random.

Authors' response:
These valuable comments have been taken into consideration. The allocation of patients to the different teams is usually done by the triage nurse based on the capacity of the teams as described by the reviewer. We also agree that the allocation of the participants to the control arm is not random. Unavoidably, this is the most feasible and natural way of randomization given the nature of practice in our setting. For instance, we are unable to influence the practice of discharging patients over weekends or in the evenings.

Reviewer's comment:
- Because the intervention and usual care treatment teams work in the same hospital, there is a risk of contamination between these two arms. What measures will be taken to prevent that?

Authors' response:
We concur with the reviewer's comments. However, the usual care pharmacists and the intervention

pharmacists work in different clinical wards which makes interaction between them very minimal. In addition, the intervention pharmacists don't usually interact with patients in the usual care team and the same applies for the usual care pharmacists and intervention patients. In case of any pharmacist shortage and the intervention pharmacist had to cover for the usual care pharmacist team or vice versa, any recruited patients from these teams will be excluded from the study to prevent any contamination.

Reviewer's comment:
- The allocation of patients to treatment teams potentially requires multilevel statistical models, because differences between teams might occur. A statistician should carefully look at both the method of patient allocation to the study arms, and potential correction of the statistical models for the treatment teams;

Authors' response:
Thank you for pointing this potential pharmacist team effect. We adjusted the statistical analysis plan in order to assess the potential clustering effect within pharmacist teams. Please check added text below:
"------In addition, the primary outcome will be adjusted for the possible clustering effect within each team using mixed effects regression analysis-------"

Reviewer's comment:
- For significant differences in mortality, large numbers of patients are required; with 125 patients per study arm, this is not very likely.

Authors' response:
We agree with the reviewer's comments. We determined the power analysis (sample size) based on the other outcome measure. However, given the current resources available for the study and with only 3 intervention pharmacists in the study, we will not be able to recruit more than 125 patients per arm.

Reviewer's comment:
- The study is described as receiving no funding, but in the intervention arm additional control visits will be scheduled, the intervention pharmacists are trained, the study results will be analysed, etc; who pays for all this if the study is not funded?

Authors' response:
Thank you for your comment. The study was originally funded by an internal grant from Qatar University. However, due to the financial constraints, this grant has been terminated along with several other grants at the university. This explains our statement regarding the unavailability of funding for the project. Before its termination, the grant covered the training of pharmacists, the cost of follow-up phone calls, the cost of pill containers, and the salary of research assistants. Please check added text below:
"------The work was previously supported by Qatar University Internal Grant number QUUG-CPH-CPH-14/15-2."

Reviewer's comment:
- The study protocol should contain some more information about the limitations of the study, e.g. single centre, (partial) non-random allocation of patients, etc.

Authors' response:
Thank you so much for your comments. The limitations of the study have been added to the methods part of the study protocol. Please check added text below:

Limitations
"The study is not without limitations. True randomization of participants is not possible. Participants are allocated to the 3 arms by the triage nurse based on the capacity of the different teams. However, this is the most feasible and natural way of randomization given the nature of practice in our setting. Further, the study involves only one hospital in Qatar; so, the study results may not be generalizable to other centers in the country. Yet Heart Hospital is the main center that offers cardiac services to Qatar's population which makes this limitation less concerning."

Reviewer's comment:
Hopefully, these suggestions will help you in improving the study description. I wish you all the best with performing this commendable study.

Authors' response:
Thank you so much for your valuable feedback. We hope that these changes have addressed the concerns raised by the reviewer.

Reviewer: 2

Reviewer's comment:

Congratulations for designing and implementing such a protocol. I would be very much interested to read the results once they are out. I have minor comment related to the typos and grammar mistakes in the texts and the graph, in addition to the incomplete sentences in some places of the text. I would recommend that that this paper be copy-edited. Good luck.

Authors' response:

Thank you so much to the reviewer for the valuable feedback. The paper has been copy edited and typos and mistakes have been corrected. These suggestions are highly appreciated.

Reviewer: 3

Reviewer's comment:
I would like to congratulate Zidam Amani for this pertinent subject and the easy way for reading this article. The intervention is well described and pertinent according to that can be expected from a clinical pharmacist in an education program.
Nevertheless the topic and the demonstration are difficult to lead and I feel anxious to the intervention to be effective.
In fact this study is a prospective controlled randomized trial and single center as described by the author. But after reading I think that large biases do exist in the protocol.

Authors' response:

Thank you so much for your valuable feedback.

Reviewer's comment:
Concerning the method
First: the recruitment,
1/It must be noticed if patients are those discharged after the first ACS or all patients with the diagnose of ACS?

Authors' response:

Thank you for your valuable feedback. All patients with the diagnosis of ACS will be considered in the study. This has been clarified in the manuscript.
The following text has been added:

"----regardless of whether it is their first ACS attack or not"

Reviewer's comment:
2/the RAs will check the file to identify potential participants. In my point of view all patients have to be included and only the ones that do not match with criteria have to be excluded; the analysis is in IT. Also those that will not be discharged to home will be excluded - in my country all patients with ACS have to go to a recovery center perhaps it is specific... but author have to explain it.

Authors' response:
The authors concur with the reviewer's comments in relation to identification of potential participants. The study research assistants will visit the study sites regularly. Any patients who meet the study inclusion criteria will be approached by the research assistants. Please check revised manuscript.

"Trained research assistants (RAs) will identify potential participants through reviewing the HH 's medical records according to the study inclusion and exclusion criteria. The RAs will approach identified participants, provide them with information about the study, and obtain written informed consent, including permission to access the patient's medical records."

Concerning the recovery center, only a minority of ACS patients at Heart Hospital are discharged to a nursing home or a cardiac rehabilitation center as deemed necessary by the treating team.

Reviewer's comment:
Second, It said that 3 arms will be drawn a/control b/UC and c/ intervention. Patients in the control are those discharged during WE or at night. In fact (and I hope) that standard clinical pharmacy practice are done to them (med reconciliation at admission, med review…) also nurse and physicians have meeting with them in fact in my point of view the only difference between control and UC is the med

reconciliation at discharge…In addition, patients will be allocated to UC or intervention according to the treatment team A, B, C or D. In fact I am not sure that way is randomization. All 4 teams have to take in charge patients with or with not intervention.
I think that a cluster study (1 for a, b, c and d) in a stepped wedge way would have be better for implementing this intervention.

Authors' response:
Thank you to the reviewer for the very valuable comments. Pharmacists will not interact with patients in the control arm as they are not usually available on weekends or after hours, The discharge nurse and physician will perform the medication review or reconciliation if needed. As stated earlier, we agree that the allocation of participants to the three arms is not truly random. Unavoidably, this is the most feasible and natural way of randomization given the nature of practice in our setting. For example: one of the intervention pharmacists is on team A so by default any recruited patients allocated to team A has to be in the intervention arm unless he or she is discharged during weekends or after hours in the latter case he or she will be allocated to the control arm.

Reviewer's comment:
Concerning the intervention, patients will have a meeting with the PC at discharge and also at M1 and M2. In previous studies it was demonstrated that this kind of intervention is effective if it is repeated every 2 months, once it is stopped patients are likely to be non-observant [JAMA. 2006 Dec 6;296(21):2563-71. Epub 2006 Nov 13 this article have to be read and included].

Authors' response:
Thank you for your comment. We do agree with the reviewer's comments. However, given the limited study resources and lack of pharmacist time, it will not be feasible to extend the follow up of participants in the intervention arm beyond 8 weeks after discharge. As advised, the proposed article has been added to the list of the references.

Reviewer's comment:
Some statistics have to be detailed by authors for feasibility (2015 number of patients concern by the intervention, % of discharge during nights and/or WE, mean length stay…).

Authors' response:
This information has now been added to the manuscript. Please see added text below:

"Approximately 250 to 300 patients are admitted per month to HH with ACS of which 10 to 15% are discharged on weekends or after the clinical pharmacist's working hours. On average, ACS patients may stay at the hospital for 72 to 96 hours. The recruitment phase of the study is over 12 months. If the research assistants recruit 3 participants in each arm every week, the estimated sample size of 125 patients per arm would be achieved in 42 weeks."

Reviewer's comment:
Concerning the outcomes: I am wondering if patient can not go to another hospital in Qatar? Also I would take in account and/or separate the plan and non-plan hospitalizations and separated those without a link to cardiology –ophthalmic for expl or cancer…- but for orthopaedic a broken HIP may be due to a fall linked to drug side-effect, so authors have to explain their choice.

Authors' response:
Thank you for your comment. Heart Hospital is the major hospital that offers cardiac care to ACS patients in Qatar. It is the only cardiac specialized hospital in the country. Hospital services are offered to patients for very minimal charges so it is unlikely that cardiac patients would visit another hospital in case of any cardiac adverse events. We strongly agree with the reviewer's comment regarding outcomes. Yes, the causes of emergency department visits and hospitalization will be divided into cardiac and non-cardiac-related causes in the outcome measure forms. The forms can be at the disposal of reviewers if needed.

Reviewer's comment:
For the observance/adherence rate by self-medication is not reproductive…I think that only the PDC would be enough. If authors explain how they will evaluate the adherence to CAD treatment also a discussion must be done for other treatment that can be linked to CAD (other ant-hypertensive, drugs for renal impairment…). If they demonstrate to improve PDC for CAD it would be pity to decrease PDC for other pathology.

Authors' response:
Thank you for your comment. Evaluating adherence using PDC alone would not be enough because of the shortcomings related to the electronic pharmacy prescription refill records. We do totally concur with the reviewer that adherence to CAD medications and to other cardiac related medications such as anti-hypertensives and dyslipidemia medications will be assessed.

Reviewer's comment:
Concerning the data analysis: I am not specialist but it looks to fit with the practices

Authors' response:
Thank you for your comment and we have an experienced biostatistician in our team who will ensure appropriate statistical analyses

VERSION 2 – REVIEW

REVIEWER	Joppe Tra VU University Medical Centre, the Netherlands
REVIEW RETURNED	20-Aug-2016

GENERAL COMMENTS	First of all I would like to praise you for the improvements made to this important paper. The majority of the feedback has been processed excellently and the paper now provides all the required information. However, there are three issues that need the authors' attention. 1) Additional relevant information was included in the introduction, however, this has lead to a diminished structure of the introduction. Please restructure the introduction in order to prevent duplicate information. For example, in paragraph one it is described that prescription of, and adherence to secondary prevention medication after cardiovascular disease can reduce mortality, heart failure, risk of recurrent myocardial infarction and stroke. Subsequently, this is repeated in paragraphs two and four, albeit in a different context. In addition, the part about the Heart Hospital can be merged with the information provided under the heading of 'study site'. Restructuring the introduction would greatly benefit the current version of this paper.

	2) In the allocation procedure, patients are directed to an intervention team or to a usual care team by a triage nurse, based on the capacity of the teams. Patients discharged outside the clinical pharmacists' working hours are all allocated to the control arm. However, a study using such an allocation procedure can not be considered a randomized controlled trial, The design appears to be a combination between a cluster randomized trial (allocation to four teams randomized as intervention team or usual care team) and a cohort study (the patients outside the clinical pharmacists' working hours). This needs to be adjusted throughout the study protocol (including the summary) and more clearly described in the paragraph on page 10, in consultation with the experienced biostatistician in the team. 3) The standard of written English in the improved sections of the paper is suboptimal; these parts qualify for language editing. After these three issues are resolved, all feedback has been throroughly processed. I wish the authors all the best in carrying out this very relevant and important study.

REVIEWER	Rony Zeenny, Pharm.D., BCPS-AQ ID Lebanese American University Lebanon
REVIEW RETURNED	23-Aug-2016

GENERAL COMMENTS	The authors have complied with all previous comments and i have no further input. Congratulations on a work well-done.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer's comment:

First of all I would like to praise you for the improvements made to this important paper. The majority of the feedback has been processed excellently and the paper now provides all the required information. However, there are three issues that need the authors' attention.

1) Additional relevant information was included in the introduction, however, this has led to a diminished structure of the introduction. Please restructure the introduction in order to prevent duplicate information. For example, in paragraph one it is described that prescription of, and adherence to secondary prevention medication after cardiovascular disease can reduce mortality, heart failure, risk of recurrent myocardial infarction and stroke. Subsequently, this is repeated in paragraphs two and four, albeit in a different context. In addition, the part about the Heart Hospital can be merged with the information provided under the heading of 'study site'. Restructuring the introduction would greatly benefit the current version of this paper.

Authors' response:

Thank you so much for your feedback. The introduction section of the manuscript has been restructured and all the reviewer's comments have been taken into consideration. Please check the revised version of the manuscript.

Reviewer's comment:

2) In the allocation procedure, patients are directed to an intervention team or to a usual care team by a triage nurse, based on the capacity of the teams. Patients discharged outside the clinical pharmacists' working hours are all allocated to the control arm. However, a study using such an allocation procedure can not be considered a randomized controlled trial, The design appears to be a combination between a cluster randomized trial (allocation to four teams randomized as intervention team or usual care team) and a cohort study (the patients outside the clinical pharmacists' working hours). This needs to be adjusted throughout the study protocol (including the summary) and more clearly described in the paragraph on page 10, in consultation with the experienced biostatistician in the team.

Authors' response:

Thank you so much for your comment. After consultations with the study biostatistician and other experienced clinical trial experts, we cannot consider the study design as a cluster randomized trial. Typically, in a cluster randomized trial, groups of participants called clusters (as opposed to individual participants) are randomized into intervention and control groups. First, the clusters are randomly assigned into the treatment and the control groups, then all patients belonging to each cluster would receive the treatment allocation to that cluster. This is not applicable to our case. In our study, individual patients are randomly assigned to usual care or intervention arms. While we do appreciate and respect the reviewer's opinion regarding the suggested blended experimental-observational design, we confirmed that the study should be explicitly described as an experimental (interventional: e.g. RCT) design or an observational (e.g. cohort study) design. Nevertheless, in terms of data analysis, we will assess the possible effect of pharmacists on the comparison between the arms. Please check the section related to data analysis below. Further, in concert with the reviewer's concerns, we agree to highlight the major limitations associated with our "natural randomization" process when compared to the conventional methods used in RCTs. We do believe and hope that these strategies will suffice and address the concerns raised.

"In addition, the primary outcome will be adjusted for the possible clustering effect within each team using mixed effects regression analysis. Also the secondary outcomes of all-cause mortality and adherence will be analyzed in a similar manner."

Reviewer's comment:

3) The standard of written English in the improved sections of the paper is suboptimal; these parts qualify for language editing.

Authors' response:

English language has been edited in the improved sections of the paper as suggested by the

reviewer.

Reviewer's comment:

After these three issues are resolved, all feedback has been thoroughly processed. I wish the authors all the best in carrying out this very relevant and important study.

Authors' response:

Thank you so much for your positive feedback. The authors greatly appreciate it.

Reviewer: 2

Reviewer's comment:

The authors have complied with all previous comments and i have no further input.
Congratulations on a work well-done.

Authors' response:

Thank you so much for your positive feedback