PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and cost-effectiveness of a virtual community of practice to improve the empowerment of patients with ischaemic heart disease: study protocol of a randomised controlled trial.
AUTHORS	GONZALEZ-GONZALEZ, ANA ISABEL; Perestelo-Pérez, Lilisbeth; Koatz, Débora; Ballester, Marta; Pacheco-Huergo, Valerial; Ramos-García, Vanesa; Torres-Castaño, Alezandra; Rivero-Santana, Amado; Toledo-Chávarri, Ana; Valcárcel-Nazco, Cristina; Mateos-Rodilla, Juana; Obaya-Rebollar, Juan Carlos; García-García, Javier; Díaz-Sánchez, Santiago; Morales-Cobos, Luis; Bosch-Fontcuberta, Josep María; Vallejo-Camazón, Nuria; Rodríguez-Almodovar, Ana; del Castillo, José Carlos; Muñoz-Balsa, Marcos; del Rey-Granado, Yolanda; Garrido-Elustondo, Sofía; Tello-Bernabé, María-Eugenia; Ramírez-Puerta, Ana Belén; Orrego, Carola

VERSION 1 – REVIEW

REVIEWER	Guiqing Yao Department of Health Science University of Leicester England
REVIEW RETURNED	18-Mar-2020

GENERAL COMMENTS	This is a nice written protocol paper. The study is clearly planned and easy to follow. I only have few queries. 1. Please clarify whether the intervention is defined as VCoP plus the usual care or VCoP alone? 2. The paragraph of the cost-effectiveness analyses seems not clear. The authors stated that “the accepted analytical methods by the scientific community will be followed (lines 398-399)”. However an analyses method (non-parametric bootstrap) has been given at the end of that session (line 412). It would be better if the paragraph is re-organised starting from stating the study perspective, followed by what the resource usage will be covered and how often they will be collected, how they will be costed, how the EQ-5D-5L will be translated to utility scores and which tariff will be used, how the analyses will be done and what the health economic outcomes are then how those will be presented. 3. The author stated two study perspectives for the economic evaluations: the National Health System and the societal perspective. The formal included only direct health cost, and latter included indirect associated with the costs of loss of productivity. More details here would be helpful. How and what the costs associated with the intervention should be included and stated clearly. 4. Societal cost only included productivity loss. What about the personal time spending on the VCoP? This could be considered as an opportunity costs foregone not doing alternative. Therefore

	should be included in the study. 5. The authors stated that the short-term costs in development and implemental of the VCoP will be included. This is not clear to me whether they will record such costs for their study records or planning to include in the cost effectiveness analyses. Please remember research cost should be separated from the cost effectiveness analyses. 6. How often the resource usage questionnaire will be collected and through what ways (online or postal)? Has the resource usage questionnaire been designed? If yes, please include in the appendix. Minor points: Line 147, Did “secondary variables “refer to “secondary outcomes”? If so, the baseline social demographic variables should be separated from the other outcome variables. Line 303 "use VCoP”. Please give details on what will be included. Did this referring time in using the VCoP? Line 325 the author listed the items of health care resources to be collected but not mentioned medication. Will medication be collected? Line 395. “Cost-effectiveness analysis of the VCoP (5 months)”. The cost-effectiveness analyses referred to 5 months? Why this time period has been chosen? Should the cost effectiveness analyses be the same time frame as the main outcome analyses? Line 406, “the costs observed during the follow-up will be included”: please list the observed costs in details.

REVIEWER	Ken Redekop Erasmus University Rotterdam (Erasmus School of Health Policy and Management), The Netherlands
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	I like the idea of publishing the protocol of this study long before the study will be completed. As expected, it is a challenge to anticipate what will ensue during the study and make appropriate plans. I've added some suggestions regarding the ways to improve the documentation of the study design as well as improve the planned study analysis. Abstract One sentence describing a VCoP would improve the usefulness of the abstract and attract more readers. Strengths and limitations of the study (line 162) "Participation in the intervention group will require a minimum level of digital literacy ..." Note that all randomised patients must have a minimum level of digital literacy and not just those in the intervention group. I therefore suggest something like: "Since all randomised patients will be required to have a minimum level of digital literacy, the results of this study may not be generalisable to all patients." or "Since a minimum level of digital literacy will be one of the inclusion criteria, the results of this study may not be generalisable to all patients."

	Also, how will digital literacy be assessed? Usual care group Comparator (line 259) To what extent is current care truly based on the guidelines? While this may be the intention, the reality may be much different. Therefore, proper documentation of what current care looked like will be needed later. Sample size (line 344) and Allocation and blinding (line 363) It is stated that 246 (123 patients per arm) will be needed and that a 20% loss (due to dropout during the study) could be seen. However, later (line 363) it is stated that 246 patients will be randomised. Shouldn't this number be higher given the expected 20% loss? I think that the number would not be 20% greater but 25% greater (1/(1-20%), which would make it n=308. Statistical analysis (line 385) The intention is to perform a multilevel regression analysis, where patients and GPs form the two levels. The value of this approach will depend on the number of GPs and number of patients per GP. What about time of measurement as an additional level? Time of measurement as a covariate and the outcome measure as a dependent variable could be considered. Cost-effectiveness analysis (CEA) (line 396 The main outcome measure will be incremental costs per QALY gained based on the EQ-5D-5L. Some points here: a) In additon to ref 44, the authors could refer to Ramos-Goni et al. (Val Health, 2018), who provided a value set to convert the EQ-5D-5L results into utility (or QOL) values. b) The time horizon to be used in the CEA will be equal to the length of follow-up (i.e., 18 months). Do the authors truly expect to see a difference in QALYs within 18 months? If not, they could consider mentioning additional outcomes here. One options is a second time horizon that is longer (e.g., 10 years, lifetime) in which the the results at the last follow-up are extrapolated. Extrapolation could be based on age, sex, etc as well as the outcome measures. This is not ideal, of course, but it addresses the fact that QALY benefits may appear only the followup period. Another option is to do a cost-consequence analysis in which the results seen with the different outcome measures are discussed together with the differences in costs. c) Good to see that both an NHS and a societal perspective will be applied. Will other costs like the productivity of informal carers, out-of-pocket payments or travel costs be considered? d) The authors should also consider reporting 95%CIs for the incremental costs and effects. Trial status (line 448) Given the coronavirus crisis in Spain (and elsewhere), I imagine that the dates of recruitment and completion will need to be adjusted. Some grammatical errors can be found here and there. Examples include the following: Line 275 (Typo/grammatical error): "researcher's developed" should be "researcher developed" or "researcher-developed". Line 371 (Typo/grammatical error): "analysists" should be "analysts".

REVIEWER	Darsy Darssan The University of Queensland, Australia
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	Some minor comments 1) The title can be improved. VCoP does not exactly mean "virtual intervention ". I suggest avoiding this acronym in the title. Some suggestions below: a) Virtual community practice for ischaemic heart disease patients: study protocol of a randomized controlled trial. b) Checking the effectiveness of virtual community practice in ischaemic heart disease patients: study protocol of a randomized controlled trial. c) Improving patient empowerment for ischaemic heart disease using virtual community practice: study protocol of a randomized controlled trial. 2) Line 138: the word effectiveness is repeated. I think, "we aim to evaluate cost and effectiveness", is sufficient. 3) Line 148: "...knowledge test (.....)". I do not understand the words within the bracket. 4) Line 165: Acronym CoP is not defined before. 5) Lines 172-173: Statistical analysis could reflect on this. Therefore, an analysis account for center effect. You could present or do it as a supplementary analysis or a sensitivity analysis to the center effect. See the next comment. 6) What happens if some centers are small? Therefore, contributing a small sample size to the trial. The study results will be biased toward the self-management support practiced in the bigger centers. I understand it is a limitation you are presenting. Another important point here is that your randomization is not stratified by center. If a center recruit fast you might reach the required sample size without any contribution from the center which is slow in recruiting. 7) Line 222: First sentence need to be checked for grammar. 8) Line 344: "...means of independent means test..". Means mentioned two times here. I suggest the phrase "independent two-sample t-test" instead of "independent means test". 9) Line 389: "...adjusting for baseline scores...". Table 1 shows no data collected at baseline. This line confuses the reader who look at Table 1. 10) Line 394: Any reason for using two statistical software programs (R and PASW) for the analysis? It is called SPSS not PASW anymore. Version 18 is very old and the latest version is 25. I recommend an upgrade to your statistical software program. Is it possible to mention your R version? Looks like you have been using an old version of R as it shows 2014. No excuse for using an old R version, because it is free. 11) Line 395: 5 months. I do not understand why the timeline appears only here.

	12) Table 1, Page 31: What is the difference between Enrollment (before randomization) and baseline? Why Baseline appear here but no data get collected? Is baseline means week 1 or week 0? See the next comment. 13) Figure 1, Page 34: The figure contradicts to Table 1. Here baseline (t=0weeks) happens before the randomization. In Table 1 Baseline is under post-allocation.

VERSION 1 – AUTHOR RESPONSE

Revisions (R) made in response to BMJ Open reviewers' report (Guiqing Yao, Reviewer 1) by query (Q):

Q1 - This is a nice written protocol paper. The study is clearly planned and easy to follow. I only have few queries.

R1 - We would like to thank Reviewer 1 for the positive comments and for reading our manuscript so thoroughly.

Q2 - Please clarify whether the intervention is defined as VCoP plus the usual care or VCoP alone?

R2–We thank Reviewer 1 for this suggestion, and we added the clarification in the text:

- Abstract (Line 150): "TheIntervention and control groups will receive usual care.
- Interventions (Line 279): "Patients allocated to both the intervention and the control group will continue with their usual self- and professional care according to the local guidelines (3-5)."

Q3 - The paragraph of the cost-effectiveness analyses seems not clear. The authors stated that "the accepted analytical methods by the scientific community will be followed (lines 398-399)". However, an analyses method (non-parametric bootstrap) has been given at the end of that session (line 412). It would be better if the paragraph is re-organised starting from stating the study perspective, followed by what the resource usage will be covered and how often they will be collected, how they will be costed, how the EQ-5D-5L will be translated to utility scores and which tariff will be used, how the analyses will be done and what the health economic outcomes are then how those will be presented.

R3–We appreciate this comment very much. In order to fulfil this suggestion and the other comments regarding this issue (see Q4 and Q6), we modified the paragraph of the cost-effectiveness analysis section as follows:

- Methods and analysis – Statistical analysis (lines 448-473): "We will carry out an economic evaluation in which the costs and the results of the VCoP will be compared to the usual care

following the recommendations of the guidelines for the management of patients with IHD (3-5), during the period of the clinical trial. The accepted analytical methods by the scientific community will be followed (48). The analysis will take both the perspective of economic analysis will be that ofthe National Health Service (NHS),including only direct health costs,and the societal perspective, including indirect costs associated with the loss of productivity of patients.Therefore, direct healthcare costs and indirect costs will be included. The direct costs per patient will be calculated based on the use of healthcare resources, and the indirect costs will be estimated focusing on productivity losses due to IHD, applying the human capital approach. In addition to including the short-term costs (development and implementation of the VCoP), the costs observed during the follow-up will be included. The use utilizationof resources will be obtained from a patient self-reported questionnaire described in the outcome section.In addition, information about work absences related to the illness will be requested in this questionnaire. The classic costs estimation approach will be followed multiplying the use of resources by their unit cost. The unit costs will be obtained from the eHealth cost database (Oblikue Consulting) and from Spanish public sources such as rates and PVP. The main outcome measure will be the incremental cost per gained QALY. The utilities for the estimation of the QALYs will be obtained through the EQ-5D-5L questionnaire (44) that will be completed by the patient at the beginning of the study and at each follow-up visit.As a summayrResultsmeasure,of the cost-effectiveness analysis will be summarized asthe incremental cost-effectiveness ratio (ICER)that results from dividing. ICER is the ratio of the differences in costsbetweenchoices by theto the differences ineffectiveness will be usedobserved effects. Non-parametric methods based on bootstrap simulations will be used to calculate confidence intervals in the ICER. The same nonparametric methods will be used to calculate the acceptability curve that represents the probability that each choice will be cost-effective for different cost-effectiveness thresholds. The willingness-to-pay threshold is defined at Euro 25,000/QALY on the basis of the values most recently reported in the Spanish literature (49). Finally, deterministic sensitivity analyses (one, two or several ways) will be carried out in order to assess the impact of the parameters on the cost-effectiveness results of the VCoP."

Q4- The author stated two study perspectives for the economic evaluations: the National Health System and the societal perspective. The formal included only direct health cost, and latter included

indirect associated with the costs of loss of productivity. More details here would be helpful. How and what the costs associated with the intervention should be included and stated clearly.

R4–We added more information for further clarification to the description of the two study perspectives as mentioned in R3.

Q5 - Societal cost only included productivity loss. What about the personal time spending on the VCoP? This could be considered as an opportunity costs foregone not doing alternative. Therefore, should be included in the study.

R5–We thank Reviewer 1 for the suggestion. However, we do not plan to consider opportunity costs in our analysis. We understand that patients will use their free time in VCoP and they will not spend work or productive time, therefore it will not generate a cost for the system.

Q6 - The authors stated that the short-term costs in development and implemental of the VCoP will be included. This is not clear to me whether they will record such costs for their study records or planning to include in the cost effectiveness analyses. Please remember research cost should be separated from the cost effectiveness analyses.

R6 -We added more information for further clarification to the description of the cost-effectiveness analysis as mentioned in R3.

Q7 - How often the resource usage questionnaire will be collected and through what ways (online or postal)? Has the resource usage questionnaire been designed? If yes, please include in the appendix.

R7 – The resource usage questionnaire has been developed in Spanish and is available upon request to the authors. This questionnaire will be administered online at 6, 12 and 18 months from baseline. To make it clearer, we added the following information in the text:

- Methods and analysis – Outcome measures (Lines 354-356): “This information will be collected online from a patient self-reported questionnaire that the research team will elaborate combined with information from the EMR.”
- Table 1 on Schedule of enrolment, interventions, and assessments was modified.

Q8 - Line 147, Did “secondary variables “refer to “secondary outcomes”? If so, the baseline social demographic variables should be separated from the other outcome variables.

R8– We made the changes as suggested:

- Abstract (line152): “Secondary outcomesvariables will include: sociodemographic and clinical variables; knowledge…”

Q9 - Line 303 "use VCoP”. Please give details on what will be included. Did this referring time in using the VCoP?

R9– We have included additional information about what we will include into this outcome:

- Methods and analysis – Outcomes measures (Line 353): “Use of the VCoP:number of logins into the platform”.

Q10 - Line 325 the author listed the items of health care resources to be collected but not mentioned medication. Will medication be collected?

R10 – We did mention we would collect prescribed medications as it appears in the paragraph highlighted by Reviewer 1:

- Methods and analysis – Outcomes measures (lines 348-350): “Use of health care resources: primary care (PC) visits, visits to the emergency department, visits to specialists, number of hospitalizations, lengths of stay, prescribed medications, use of diagnostic tests.”

Q11 - Line 395. “Cost-effectiveness analysis of the VCoP (5 months)”. The cost-effectiveness analyses referred to 5 months? Why this time period has been chosen? Should the cost effectiveness analyses be the same time frame as the main outcome analyses?

R11 - Thank you for letting us know of this confusing issue.This is due to an error in the text. The resources use and cost analysis will be estimated from the information collected at 6, 12 and 18 months.The time horizon of the cost-effectiveness analysis will be 18 months. We removed this timeline in the text and added the corresponding months for the assessment.

- Methods and analysis - Statistical analysis (Line 439): “Cost-effectiveness analysis of the VCoP (56, 12 and 18 months).”

Q12 - Line 406, “the costs observed during the follow-up will be included”: please list the observed costs in details.

R12 –We agree with the suggestion. The observed costs during the follow-up will be those related to the resource use by each patient included in the questionnaire described in the outcomes measures section.

- Methods and analysis - Outcomes measures (Lines 348-350): “Use of health care resources: primary care (PC) visits, visits to the emergency department, visits to specialists, number of hospitalizations, lengths of stay, prescribed medications, use of diagnostic tests.”

Revisions (R) made in response to BMJ Open reviewers’ report (Ken Redekop, Reviewer 2) by query (Q):

Q13 - I like the idea of publishing the protocol of this study long before the study will be completed. As expected, it is a challenge to anticipate what will ensue during the study and make appropriate plans. I've added some suggestions regarding the ways to improve the documentation of the study design as well as improve the planned study analysis.

R13 - We would like to thank Reviewer 2 for the encouraging comments and the helpful suggestions for clarification.

Q14 – Abstract. One sentence describing a VCoP would improve the usefulness of the abstract and attract more readers.

R14– We agree with Reviewer 2 and added a sentence describing the VCoP as follows:

- Abstract (Lines 137): “Virtual Communities of Practice (VCoP)or knowledge-sharing communities…”

Q15 - Strengths and limitations of the study (line 162)"Participation in the intervention group will require a minimum level of digital literacy ..."Note that all randomised patients must have a minimum level of digital literacy and not just those in the intervention group. I therefore suggest something like:"Since all randomised patients will be required to have a minimum level of digital literacy, the results of this study may not be generalisable to all patients." or"Since a minimum level of digital literacy will be one of the inclusion criteria, the results of this study may not be generalisable to all patients."

R15–We thank Reviewer 2 for the suggestion. We have modified the text accordingly:

- Strengths and limitations of the study (lines 181-182):“Since all randomised patients will be requiredParticipation in the intervention group will require a minimum level of digital literacy so, the results could not be generalized to all patients

Q16 - Also, how will digital literacy be assessed?

R16- Digital literacy will be assessed by a short-questionnaire developed by the research team. It is in Spanish and is available upon request to the authors.

Q17 - Usual care group Comparator (line 259). To what extent is current care truly based on the guidelines? While this may be the intention, the reality may be much different. Therefore, proper documentation of what current care looked like will be needed later.

R17– We agree with Reviewer 2 and we will proceed accordingly.

Q18 - Sample size (line 344) and Allocation and blinding (line 363). It is stated that 246 (123 patients per arm) will be needed and that a 20% loss (due to dropout during the study) could be seen. However, later (line 363) it is stated that 246 patients will be randomised. Shouldn't this number be higher given the expected 20% loss? I think that the number would not be 20% greater but 25% greater (1/(1-20%), which would make it n=308.

R18 - The estimated 20% of lost patients was already included in the calculation, but anyway we did not make it correctly. We have corrected it and rewritten the paragraph to explain more clearly the calculation:

- Methods and analysis. Sample size (Lines 367-371): “The necessary number of patients to detect, by means of independent two-sample t-test, an average minimal important difference of 4 points (SD 10) in the PAM questionnaire (12-23) between the intervention and usual care group, is 123 patients per arm. For this calculation we assume an alpha error of 0.05, power of 80% and size is increased by the estimation of a 20% loss.Assuming an alpha error of 0.05 and power of 80%, the necessary number of patients to detect, by means of independent two-sample t-test, an average minimal important difference of 4 points (SD 10) in the PAM questionnaire (12,23) between the intervention and usual care group, is 200 patients (100 per arm). Assuming a 20% loss to follow up, the required sample increases to 250 (125 per arm)”.

Q19 - Statistical analysis (line 385)The intention is to perform a multilevel regression analysis, where patients and GPs form the two levels. The value of this approach will depend on the number of GPs and number of patients per GP. What about time of measurement as an additional level? Time of measurement as a covariate and the outcome measure as a dependent variable could be considered.

R19 - Both Reviewer 2 considerations are correct. We will include time as a fixed factor (with random slope, to account for within-subject correlations) and analyse its interaction with the intervention, with random intercepts for patients. We expect to recruit a sufficient number of professionals (>15) that

justify their inclusion as a random intercept. Anyway, we will calculate the intra-class correlation and compare the results of including them or not.

Q20 - Cost-effectiveness analysis (CEA) (line 396). The main outcome measure will be incremental costs per QALY gained based on the EQ-5D-5L.

Some points here:

Q20a. In addition to ref 44, the authors could refer to Ramos-Goni et al. (Val Health, 2018), who provided a value set to convert the EQ-5D-5L results into utility (or QOL) values.

R20a – We thank Reviewer 2 for the suggestion. Certainly, we will use the Ramos-Goñi algorithm to calculate Spanish utilities values. We added the reference in the text.

Q20b. The time horizon to be used in the CEA will be equal to the length of follow-up (i.e., 18 months). Do the authors truly expect to see a difference in QALYs within 18 months? If not, they could consider mentioning additional outcomes here. One option is a second time horizon that is longer (e.g., 10 years, lifetime) in which the results at the last follow-up are extrapolated. Extrapolation could be based on age, sex, etc as well as the outcome measures. This is not ideal, of course, but it addresses the fact that QALY benefits may appear only the follow-up period. Another option is to do a cost-consequence analysis in which the results seen with the different outcome measures are discussed together with the differences in costs.

R20b – We are very grateful to Reviewer 2 for this comment. We believe that a difference in QALYs could be found considering the depression dimension of the EQ5D. However, we will add a cost-consequence analysis with intermediate measures in which there will be changes at 18 months.

Q20c. Good to see that both an NHS and a societal perspective will be applied. Will other costs like the productivity of informal carers, out-of-pocket payments or travel costs be considered?

R20c – The analyses will take both the perspective of the National Health Service (NHS) and societal perspective; therefore, direct healthcare costs and indirect costs will be included. The direct costs per patient will be calculated based on the use of healthcare resource, and the indirect costs will be estimated focusing on productivity losses due to IHD applying the human capital approach. We added more information about these aspects in the cost-effectiveness analysis section.

- Methods and analysis – Statistical analysis (Lines 451-461): “The analysis will take both the perspective of the National Health Systemand of the social perspective. Therefore, direct healthcare costs and indirect costs will be included. The direct costs per patient will be calculated

based on the use of healthcare resources, and the indirect costs will be estimated focusing on productivity losses due to IHD, applying the human capital approach. In addition to including the short-term costs (development and implementation of the VCoP), the costs observed during the follow-up will be included. The use of resources will be obtained from a patient self-reported questionnaire described in the outcome section.In addition, information about work absences related to the illness will be requested. The classic costs estimation approach will be followed multiplying the use of resources by their unit cost. The unit costs will be obtained from the eHealth cost database (Oblikue Consulting) and from public sources such as rates and PVP."

Q20d.The authors should also consider reporting 95%CIs for the incremental costs and effects.

R20d – We certainly agree with Reviewer 2. We will report a descriptive data analysis (means, medians and standard deviations) of costs and effects as well as we will report their confidence interval.

Q21 - Trial status (line 448). Given the coronavirus crisis in Spain (and elsewhere), I imagine that the dates of recruitment and completion will need to be adjusted.

R21 –We appreciate the observation as we have not been able to start recruiting due to the coronavirus situation. We reflect this in the protocol as follows:

- Trial status (Lines 548-549):"The recruitment of patients in each region will start in March September 2020. The estimated end date of the recruitment for this study isAugustDecember 2020."

Q22 - Some grammatical errors can be found here and there. Examples include the following: Line 275 (Typo/grammatical error): "researcher's developed" should be "researcher developed" or "researcher-developed".

Line 371 (Typo/grammatical error): "analysists" should be "analysts".

R22–We thank Reviewer 2 for identifying these typos. We have corrected them in the text.

Revisions (R) made in response to BMJ Open reviewers' report (DarsyDarssan, Reviewer3) by query (Q):

Q23. The title can be improved. VCoP does not exactly mean "virtual intervention ". I suggest avoiding this acronym in the title. Some suggestions below:

a) Virtual community practice for ischaemic heart disease patients: study protocol of a randomized controlled trial.

b) Checking the effectiveness of virtual community practice in ischaemic heart disease patients: study protocol of a randomized controlled trial.

c) Improving patient empowerment for ischaemic heart disease using virtual community practice: study protocol of a randomized controlled trial.

R24–We would like to thank Reviewer 3 for this suggestion. We have modified the title as follows:

- Title (lines 2-4): “Effectiveness and cost-effectiveness of a virtualintervention (VCoP)community of practice to improve the empowerment of patients with ischaemic heart disease: study protocol of a randomized controlled trial.

Q25 - Line 138: the word effectiveness is repeated. I think, "we aim to evaluate cost and effectiveness", is sufficient.

R25 – We will carry out a full economic evaluation. Cost analysis is only a comparison of costs and cost-effectiveness analysis is a way to examine both the costs and consequences (health outcomes) of one or more interventions. In this sense, we consider appropriate to keep the word “cost-effectiveness”, since this the comparative analysis that we will conduct in our study.

Q26Line 148: "...knowledge test (.....)". I do not understand the words within the bracket.

R26–To make the name of the questionnaire clearer, we have translated it from Brazilian into English:

- Abstract (Lines 152-153): “…(Questionnaire of Cardiovascular Risk Factors Questionário de Fatores de Risco Cardiovascular)…”
- Methods and analysis – Outcome measures (Lines 298-299): “Knowledge about the disease will be assessed through a self-administered online questionnaire based on the Questionário de Fatores de Risco Cardiovascular Questionnaire of Cardiovascular Risk Factors (Q-FARC) (25-27),”

Q27 - Line 165: Acronym CoP is not defined before.

R27–We eliminated the acronym as suggested and substituted it by the term “community”:

- Strengths and limitations of this study (Lines 176-177): VCoP can enhance communication between communityCoP members in different geographic locations and even from different time zones.

Q28 - Lines 172-173: Statistical analysis could reflect on this. Therefore, an analysis account for center effect. You could present or do it as a supplementary analysis or a sensitivity analysis to the center effect. See the next comment.

- R28–We will assess this potential moderator effect by means of a three-way interaction intervention x time x centre.
- Methods and analysis – Statistical analysis (Lines 424-433): "The VCoP effect on the primary and secondary outcomes will be examined by means of multilevel linear regression, with the intervention, measurement time (0, 6, 12, 18 months) and their interaction as fixed effects (along with other potential covariates), random intercepts for patients and GP, and random slope for time, to account for within-subject correlations. We will also analyse the three-way interaction intervention x time x centre, since usual care could vary between centres, leading to differential intervention effects. We expect to recruit a sufficient number of GP to allow their inclusion in the model as a random intercept, but anyway we will perform a sensitivity analysis excluding this component. Between-group differences at each time-point will be compared by means of Wald's χ^2 test."

Q29 - What happens if some centers are small? Therefore, contributing a small sample size to the trial. The study results will be biased toward the self-management support practiced in the bigger centers. I understand it is a limitation you are presenting. Another important point here is that your randomization is not stratified by center. If a center recruit fast you might reach the required sample size without any contribution from the center which is slow in recruiting.
R29– We thank Reviewer 3 for these valuable comments. Given the recruitment strategy this is a potential limitation. We have now included the stratified randomization by centre, but the likelihood of differential recruitment rates will still be present. As commented above, we will assess this potential moderator effect by means of a three-way interaction intervention x time x centre.

- Methods and analysis – Allocation and blinding (Lines 397-399): "The randomisation,stratified by centre, will be central and automatically performed by the online "e-mpodera^2" platform and the assigned group will be communicated to the patient once he or she has entered the platform and completed baseline assessment (Figure 1)."

Q30 - Line 222: First sentence need to be checked for grammar.

R30 – We thank Reviewer 3 and rephrased the sentence:

- Methods and analysis – Setting (Line 233): “The setting forof the intervention armwill be a virtual setting.”

Q31 - Line 344: "...means of independent means test..". Means mentioned two times here. I suggest the phrase "independent two-sample t-test" instead of "independent means test".
R31–We changed the sentence as suggested:

- Methods and analysis (Lines367-368): “by means of independenttwo sample meanst-test”

Q32 -Line 389: "...adjusting for baseline scores...". Table 1 shows no data collected at baseline. This line confuses the reader who look at Table 1.

R32– We thank Reviewer 3 for highlighting this confusion between the text and Table 1. We modified Table 1 accordingly.

Q33 - Line 394: Any reason for using two statistical software programs (R and PASW) for the analysis? It is called SPSS not PASW anymore. Version 18 is very old and the latest version is 25. I recommend an upgrade to your statistical software program. Is it possible to mention your R version? Looks like you have been using an old version of R as it shows 2014. No excuse for using an old R version, because it is free.

R33–We follow Reviewer 3 suggestion and modified the text as follows:

- Methods and analysis – Statistical analysis: (Lines 437-438): “Analyses will be carried out with the statistical software RCore Team 20144.0.2http://www.R-project.org/and PASW Statistics 18.”

Q34 - Line 395: 5 months. I do not understand why the timeline appears only here.

R34–We corrected the mistake as follows:

- Methods and analysis – Statistical analysis (Line 439): “Cost-effectiveness analysis of the VCoP(6, 12 and 18 months).”

Q35 - Table 1, Page 31: What is the difference between Enrolment (before randomization) and baseline? Why Baseline appear here but no data get collected? Is baseline means week 1 or week 0? See the next comment.

R35– We agree with Reviewer 3 this information was not clearly described in the text and table 1. We modified Table 1.

Q36 - Figure 1, Page 34: The figure contradicts to Table 1. Here baseline (t=0weeks) happens before the randomization. In Table 1 Baseline is under post-allocation.

R36– We thank Reviewer 3. We modified Table 1.

Q37 - Editorial requests:

- Please update the trial registry so that both the adherence scale to be used, and the expected start date of the study, are correct.

R37 – The registry was modified accordingly.

VERSION 2 – REVIEW

REVIEWER	Guiqing Yao University of `leicester
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	I am very happy the authors have addressed all my queries.It would be helpful if the authors could make the following two points clear: 1, Line 439: “Cost-effectiveness analysis of the VCoP (6, 12 and 18 months).”. It is still not clear. It should state clearly that the baseline/primary analyses is over 18 months. The bracket (6,12 and 18 months) should be deleted. 2, In the text, the assumption on the time of individual patients spent in VCoP will be their free time therefore no costs will be considered as it could potentially underestimates the costs of the intervention.

REVIEWER	Ken Redekop Erasmus University Rotterdam, The Netherlands
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	The authors seem to have sufficiently addressed at least the most important concerns expressed by the three reviewers. Minor comment regarding grammar. The authors occasionally use the word 'anyway' inappropriately in both the responsed and the paper (e.g., "but anyway we will perform a sensitivity analysis").

REVIEWER	Darsy Darssan School of Public Health, The University of Queensland, Australia.
REVIEW RETURNED	29-Jun-2020

GENERAL COMMENTS	The manuscript changed substantially from the previous version. Authors acted on all the comments I left in my previous review. I have no further comments.

VERSION 2 – AUTHOR RESPONSE

Revisions (R) made in response to BMJ Open reviewers’ report (Guiqing Yao, Reviewer 1) by query (Q):

Q1 - I am very happy the authors have addressed all my queries.It would be helpful if the authors could make the following two points clear:

R1 - We would like to thank Reviewer 1 for all the queries that have allowed the improvement not only of the paper but the study protocol as well.

Q2 - Line 439: “Cost-effectiveness analysis of the VCoP (6, 12 and 18 months).”. It is still not clear. It should state clearly that the baseline/primary analyses is over 18 months. The bracket (6,12 and 18 months) should be deleted.

R2–We appreciate the suggestion and proceeded accordingly as follows:

- Statistical analysis (now line 409): “Cost-effectiveness analysis of the VCoP(6, 12 and 18 months)”
- Statistical analysis (now lines 410-413): “We will carry out an economic evaluation, from baseline to 18-month follow-up, in which the costs and the results of the VCoP will be compared to the usual care following the recommendations of the guidelines for the management of patients with IHD (3–5), during the period of the clinical trial.”

Q3 - In the text, the assumption on the time of individual patients spent in VCoP will be their free time therefore no costs will be considered as it could potentially underestimates the costs of the intervention.

R3–We thank Reviewer 1 for the suggestion. Although we will only consider the costs associated to productivity loss under the social perspective of our cost-effectiveness analysis, we will include as a variable the time spent by the individual patients using the platform and we will analyse it as an opportunity cost. We have included the following paragraphs in the text:

- Statistical analysis (now lines 419-422): “We do not plan to consider opportunity costs in our cost-effectiveness analysis from the social perspective, as we understand that patients will use their free time on the VCoP and therefore they will not spend work or productive time not generating a cost for the system.”
- Outcomes measures (now line 335): “Use of the VCoP: number of logins into the platform and time spent using the platform.”

Revisions (R) made in response to BMJ Open reviewers’ report (Ken Redekop, Reviewer 2) by query (Q):

Q4 - The authors occasionally use the word 'anyway' inappropriately in both the response and the paper (e.g., "but anyway we will perform a sensitivity analysis").

R4 – We thank Reviewer 2 for identifying this grammar error. We have corrected the text by eliminating the word in the paper.

- Methods and analysis - Statistical analysis (lines 400-401): “We expect to recruit a sufficient number of GPs to allow their inclusion in the model as a random intercept, but anyway we will perform a sensitivity analysis as well excluding this component.”