PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors in Coronary Heart Disease Patients: The TELEWEAR-CR study protocol.
AUTHORS	Antoniou, Varsamo; Xanthopoulos, Andrew; Giamouzis, Gregory; Davos, Constantinos; Batalik, Ladislav; Stavrou, Vasileios; Gourgoulianis, Konstantinos; Kapreli, Eleni; Skoularigis, John; Pepera, Garyfallia

VERSION 1 – REVIEW

REVIEWER	Xu, Linqi Jilin University
REVIEW RETURNED	26-Feb-2022

GENERAL COMMENTS	This paper presents the protocol for a parallel-group, single-blind RCT to determine the effect of cardiac telerehabilitation compared with center-based CR, using heart rate monitors and accelerometers for patients with coronary artery diseases. This study will add to the evidence which exists regarding optimal strategies for cardiac telerehabilitation. The research presented is relevant, structured and according to the guidelines to authors. Here I would like to offer some places for improvement and more clarity as below: Abstract: 1. P 2 line 42, “This study will investigate the efficacy and safety of”, The aim of the study in different parts of the manuscript has been written (slightly) differently. It would be good if the authors state the aim of the study consistently throughout the manuscript. 2. P 2 line 50, A total of 124 coronary disease patients (instead of One hundred and twenty four coronary disease patients) will be randomized at a 1:1 ratio into two groups. 3. P3 line 5-7, “as obtained from cardiopulmonary exercise testing (CPET) for 60’’, three times/ week”, please state

	what ‘ 60’’ ‘ is. 4. Minor error: P3 line 54, “ Telelerehabilitation” should be “Telerehabilitation”. Background: Background are well written and appropriate. It would be good if the authors state the aim of the study consistently throughout the manuscript. For example, on P6 13-16, for the secondary outcomes “Whilst possible effects in physical activity, training adherence, anxiety and stress management, safety and cost – effectiveness are considered as secondary aims”, however, on P19 45-50, “Secondary outcomes will be the physical activity level, safety, health related quality of life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence and cost effectiveness”. Methods: 1. Well done including good involvement of patients. 2. P9 line 12-18, Provide more information on who will be responsible for providing information and recruiting the patients. 3. Intervention development is well described as are various clinical trial components such as sample size and randomization. 4. P11 line 35, could “one hundred and twenty four eligible” be changed into “a total of 124”? 5. P11 line 51, what is “ Primer”? Do you mean “Primary”? 6. P12 line 26-30, “including 3 training sessions of 60’/week”, do you mean 60 min/week? Could you please modify them throughout the manuscript? 7. “ Through risk stratification and pre – exercise assessment only low and moderate cardiac risk patients will be included in the study groups”, only low and moderate patients will be recruited, so it may cause a selection bias, maybe you could state it in the limitation section. Tables: General comment: In both Tables 1, 4 and 5 the text is difficult to read. Improve on the quality of these tables.

REVIEWER	Snoek, Aernout Isala Medical Center, sportsmedicine
REVIEW RETURNED	02-Mar-2022

GENERAL COMMENTS	The authors describe the study protocol of an extensive RCT in a relevant field in which participation rates of an effective treatment (cardiac rehabilitation) is limited. Their aim to use remote technologies is needed to increase participation rates and limit health care costs. They explain clearly what this study adds to the field. No new insights. It's about validating older findings (i.e. Fit@home) as suggested by reference 32 and 34.. Review Checklist: 2 The abstract is judged as not acurate, balanced and complete. Can the auhtors explain why the abstract mentions a CPET test OR a 6MWT and the method section mentions a CPET AND a 6MWT? Which one is correct? Will al participants receive a CPET? Moreover I read in the abstract that the patients will be training at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 60'', three times/ week and table 4 describes a different filling of the 60 minutes. Maybe this should be changed in the abstract. 6 The outcomes are clearly defined. Maybe the authors can add to the adherence section which percentage they find adherent or non adherent. Am I correct that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period"? This difference would be strange. I can imagine that the control group will also be wearing the Actigraph for only 12 weeks?

REVIEWER	Falter, Maarten UHasselt—Hasselt University, Cardiovascular Research
REVIEW RETURNED	11-Mar-2022

GENERAL COMMENTS	Comments I thank the authors for letting me review this protocol article about a new telerehabilitation intervention using wearables. General • This looks like a very ambitious trial in which only highly motivated, fit and digitally literate patients can participate: o Only age 40-70 o Only RER ≥1,15 o Having to be able to work with 3 types of wearables (Polar chest strap, Polar wrist watch, and Actigraph belt-worn step counter) and being compliant to all three. o Other strict inclusion and exclusion criteria • Please realise that the population you will see will be a very selected population and will not reflect the total coronary artery disease population. This is of course a choice of the investigator, but please address these issues in this manuscript. In the current version one cannot state that cardiac rehabilitation in general in Greece will be improved, but rather in a selected group there may be

	added benefits. Please clearly explain why certain inclusion and exclusion criteria were put forward and explain what implications this might have on the study results. Where possible please provide data from your centre (how many patients reach RER ≥1,15) and from literature (how many patients with CAD are 40-70 years old, how high is digital literacy or how many percent of patients were able to participate in telerehabilitation trials). • For this latter point see: o Brouwers, R. W. M., Brini, A., Kuijpers, R. W. F. H., Kraal, J. J., & Kemps, H. M. C. (2021). Predictors of non-participation in a cardiac telerehabilitation programme: a prospective analysis. European Heart Journal - Digital Health, ztab105. https://doi.org/10.1093/ehjdh/ztab105 o Falter, M., Scherrenberg, M., Kindermans, H., Kizilkilic, S., Kaihara, T., & Dendale, P. (2021). Willingness to participate in cardiac telerehabilitation: results from semi-structured interviews. European Heart Journal - Digital Health. https://doi.org/10.1093/ehjdh/ztab091 o Snoek, J. A., Prescott, E. I., Van Der Velde, A. E., Eijsvogels, T. M. H., Mikkelsen, N., Prins, L. F., Bruins, W., Meindersma, E., González-Juanatey, J. R., Peña-Gil, C., González-Salvado, V., Moatemri, F., Iliou, M. C., Marcin, T., Eser, P., Wilhelm, M., Van'T Hof, A. W. J., & De Kluiver, E. P. (2021). Effectiveness of Home-Based Mobile Guided Cardiac Rehabilitation as Alternative Strategy for Nonparticipation in Clinic-Based Cardiac Rehabilitation among Elderly Patients in Europe: A Randomized Clinical Trial. JAMA Cardiology, 6(4), 463–468. https://doi.org/10.1001/jamacardio.2020.5218 Abstract • Primary outcome CPET or 6MWT: when will CPET be used and when 6MWT, as the results are known to not be comparable (maximal versus submaximal exercise). Methods • Why is there an age restriction of 40-70 years old? It is often used in trials like these but 70 years old is relatively young in a cardiovascular population, so there needs to be thorough argumentation for these criteria. It is demonstrated that digital literacy has more to do with educational level and/or smartphone ownership than age per se, see: o Thimo, M., Christian, B., Tabea, G., Judith, P., Prisca, E., & Matthias, W. (2021). Patient interest in mHealth as part of cardiac rehabilitation in Switzerland. Swiss Medical Weekly, 151(17–18), 1–6. https://doi.org/10.4414/smw.2021.20510 • "Heart failure" is a very general and broad exclusion criterion. Please define what will be considered heart failure, and please consider why you would exclude all heart failure patients from the trial. Stable heart failure with good exercise capacity and coronary artery disease would be good candidates to participate in such a trial. • Please in general consider to limit inclusion and exclusion criteria: in the research in telerehabilitation it could be argued that we are beyond the point to prove that it does "something", we know that it can be effective. In trials like these we are at a point that a broad population needs to be able to participate. TELE-CR group • This looks like a very intense protocol, with 3 wearable sensors and patients having to submit all the data themselves.

	o Please already here in the protocol address feasibility: in how many percent of patients do you think this will realistically work? Is there any data about similar trials? Outcome measures: • CPET: If a participant fails to achieve RER ≥ 1.15 he/she will be excluded o This is again a major exclusion criterion as certainly not all patients achieve RER. o Please in this protocol already report the current number of coronary artery disease patients in your centre that reached RER ≥ 1.15. This will give a realistic number of the percentage of participants that you will be able to include.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Linqi Xu, Jilin University
Comments to the Author:
Comments are attached below.

Reviewer: 2
Dr. Aernout Snoek, Isala Medical Center
Comments to the Author:
The authors describe the study protocol of an extensive RCT in a relevant field in which participation rates of an effective treatment (cardiac rehabilitation) is limited. Their aim to use remote technologies is needed to increase participation rates and limit health care costs. They explain clearly what this study adds to the field. No new insights. It's about validating older findings (i.e. Fit@home) as suggested by reference 32 and 34..

Response: Thank for your comment. Though, our study is standing out from other similar studies, previously implemented. Participants in the telerehabilitation group will receive exercise sessions that will be implemented in groups of up to 5 participants at the same time, through videoconferencing platforms. Additionally, telerehabilitation exercise sessions will be supervised, monitored and guided in real time by specialized in cardiac rehabilitation therapists. The wearable sensors will be used for the real time evaluation of the volume and the safety of the ongoing telerehabilition exercise sessions (monitoring of the heart rate and exercising within the individually prescribed heart rate zones). Furthermore, the wearable sensors will be used for the final evaluation of the efficiency of the intervention implementation. These parameters make our study really unique.

Review Checklist:
2 The abstract is judged as not accurate, balanced and complete. Can the authors explain why the abstract mentions a CPET test OR a 6MWT and the method section mentions a CPET AND a 6MWT? Which one is correct? Will all participants receive a CPET?
Response: Thank you for your comment. The abstract was corrected, as it is CPET and 6MWT. All participants, from both groups, will receive CPET in all assessment points.

Moreover I read in the abstract that the patients will be training at 70% of
their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET)
for 60'', three times/ week and table 4 describes a different filling of the 60 minutes. Maybe this should be changed in the abstract.
Response: Thank you for your comment. It was corrected.

6 The outcomes are clearly defined. Maybe the authors can add to the adherence section which percentage they find adherent or non-adherent.
Response: Thank you for your comment. The participants' categorization, according to adherence rates, was defined.

Am I correct that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period"? This difference would be strange. I can imagine that the control group will also be wearing the Actigraph for only 12 weeks?
Response: Thank you for your comment. Both the telerehabiliation group and the control group will be wearing the Actigraph only during the 12 week intervention period.

Reviewer: 3
Dr. Maarten Falter, UHasselt—Hasselt University
Comments to the Author:
Comments
I thank the authors for letting me review this protocol article about a new telerehabilitation intervention using wearables.

General
• This looks like a very ambitious trial in which only highly motivated, fit and digitally literate patients can participate:
o Only age 40-70
o Only RER ≥1,15
o Having to be able to work with 3 types of wearables (Polar chest strap, Polar wrist watch, and Actigraph belt-worn step counter) and being compliant to all three.
o Other strict inclusion and exclusion criteria
• Please realise that the population you will see will be a very selected population and will not reflect the total coronary artery disease population. This is of course a choice of the investigator, but please address these issues in this manuscript. In the current version one cannot state that cardiac rehabilitation in general in Greece will be improved, but rather in a selected group there may be added benefits. Please clearly explain why certain inclusion and exclusion criteria were put forward and explain what implications this might have on the study results. Where possible please provide data from your centre (how many patients reach RER ≥1,15) and from literature (how many patients with CAD are 40-70 years old, how high is digital literacy or how many percent of patients were able to participate in telerehabilitation trials)
• For this latter point see:
o Brouwers, R. W. M., Brini, A., Kuijpers, R. W. F. H., Kraal, J. J., & Kemps, H. M. C. (2021). Predictors of non-participation in a cardiac telerehabilitation programme: a prospective analysis. European Heart Journal - Digital Health, ztab105. https://doi.org/10.1093/ehjdh/ztab105
o Falter, M., Scherrenberg, M., Kindermans, H., Kizilkilic, S., Kaihara, T., & Dendale, P. (2021). Willingness to participate in cardiac telerehabilitation: results from semi-structured interviews. European Heart Journal - Digital Health. https://doi.org/10.1093/ehjdh/ztab091
o Snoek, J. A., Prescott, E. I., Van Der Velde, A. E., Eijsvogels, T. M. H., Mikkelsen, N., Prins, L. F., Bruins, W., Meindersma, E., González-Juanatey, J. R., Peña-Gil, C., González-Salvado, V., Moatemri, F., Iliou, M. C., Marcin, T., Eser, P., Wilhelm, M., Van'T Hof, A. W. J., & De Kluiver, E. P. (2021). Effectiveness of Home-Based Mobile Guided Cardiac Rehabilitation as Alternative Strategy for Nonparticipation in Clinic-Based Cardiac Rehabilitation among Elderly Patients in Europe: A Randomized Clinical Trial. JAMA Cardiology, 6(4), 463–468. https://doi.org/10.1001/jamacardio.2020.5218
Response: Thank for your comment. We have already changed the age related criteria to adults

above 18 years old and the RER≥1.10, so as to broaden the potential participants in our study sample. Though, we have to mention that unfortunately cardiac rehabilitation is underutilized in Greece and not provided by the Greek national health system. The recruiting hospital is a public hospital. There is no official data on the percentage of patients reaching RER≥1.15. But as I have mentioned we have already changed that criteria. The digital literacy and the participation rates in telerehabilitation intervention have been added in the manuscript.

Abstract
• Primary outcome CPET or 6MWT: when will CPET be used and when 6MWT, as the results are known to not be comparable (maximal versus submaximal exercise).
Response: Thank you for your comment. It is clarified above that functional capacity will be assessed both by CPET and 6MWT for all study participants, evaluating both its maximal and submaximal values.

Methods
• Why is there an age restriction of 40-70 years old? It is often used in trials like these but 70 years old is relatively young in a cardiovascular population, so there needs to be thorough argumentation for these criteria. It is demonstrated that digital literacy has more to do with educational level and/or smartphone ownership than age per se, see:
o Thimo, M., Christian, B., Tabea, G., Judith, P., Prisca, E., & Matthias, W. (2021). Patient interest in mHealth as part of cardiac rehabilitation in Switzerland. Swiss Medical Weekly, 151(17–18), 1–6. https://doi.org/10.4414/smw.2021.20510
Response: Thank you for your comment. We have changed the target group to adults>18 years old. Though, the results from an ongoing systematic review of ours show that most cardiac telerehabilitation studies have been implemented in a cardiac population of a mean age of 50-70 years old. So our initial choice for the age related inclusion criteria was based on the results of our systematic review and not on the basis of the study participants' expected digital literacy.

• "Heart failure" is a very general and broad exclusion criterion. Please define what will be considered heart failure, and please consider why you would exclude all heart failure patients from the trial. Stable heart failure with good exercise capacity and coronary artery disease would be good candidates to participate in such a trial.
Response: Thank you for your comment. Response: Thank you for your comment. Most of HF patients have coexisting comorbid conditions and they differ from the way they are managed in CR programs. This is the reason, we prefer in this project to get focused only in CHD patients. Moreover, there are some studies in the literature relating to CR remodeling in HF patients, however there aren't any CHD in the same field we search.

• Please in general consider to limit inclusion and exclusion criteria: in the research in telerehabilitation it could be argued that we are beyond the point to prove that it does "something", we know that it can be effective. In trials like these we are at a point that a broad population needs to be able to participate.
Thank for your comment. We have already changed the age criteria (adults>18 years old) and the respiratory exchange ratio (RER)≥1.10. Additionally the choice of an urban university hospital as the study participants' recruiting center offers the opportunity to a low-privileged part of the Greek cardiac population to have access to cardiac rehabilitation services.

TELE-CR group
• This looks like a very intense protocol, with 3 wearable sensors and patients having to submit all the data themselves.
o Please already here in the protocol address feasibility: in how many percent of patients do you think this will realistically work? Is there any data about similar trials?

Thank for your comment. We expect more than 70% of the participants in the telerehabilitaion group to be able to successfully transit and monitor the data derived from the wearable sensors. Patients will all be guided in person for at least three training sessions in the hospital rehabilitation facilities on how to use and upload the recorded data. Additionally, a family member, that will be assisting the patient during the intervention, will be also receiving the same education on the use of the wearable sensors. Data from previous similar interventions reveal encouraging results, concerning the use of digital technology within older aged participants.
See: Batalik L, Dosbaba F, Hartman M, Batalikova K, Spinar J. Benefits and effectiveness of using a wrist heart rate monitor as a telerehabilitation device in cardiac patients: A randomized controlled trial. Medicine 2020;99:e19556-e19556. doi: 10.1097/MD.0000000000019556

Outcome measures:
• CPET: If a participant fails to achieve RER ≥ 1.15 he/she will be excluded
o This is again a major exclusion criterion as certainly not all patients achieve RER.
Response: Thank you for your comment. Participants will be excluded if he/she fails to achieve RER≥ 1.10.

o Please in this protocol already report the current number of coronary artery disease patients in your centre that reached RER ≥ 1.15. This will give a realistic number of the percentage of participants that you will be able to include.
Response: Thank you for your comment. It needs to be mentioned that cardiac rehabilitation is almost absent from the Greek national health system. Thus there is scarce data on the number of cardiac patients.

VERSION 2 – REVIEW

REVIEWER	Snoek, Aernout Isala Medical Center, sportsmedicine
REVIEW RETURNED	23-Mar-2022

GENERAL COMMENTS	The authors describe the study protocol of an extensive RCT in a relevant field in which participation rates of an effective treatment (cardiac rehabilitation) is limited. Their aim to use remote technologies is needed to increase participation rates and limit health care costs. They explain clearly what this study adds to the field. The abstract is judged as not accurate. I read in the abstract that the patients will be training at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 60'', three times/ week and table 4 describes a different filling of the 60 minutes. The exact training is far more extensive as explained in table 4 and 5. Why do the authors only mention the aerobic cardio training in the abstract and don't mention the strength training? I have concerns about the study design. Not only the form (centre based or home based) is different, but also the training content of the centre based and TELE-CR aerobic training. I have some concerns about how well it is possible to reach and stay at the 70% of maximal heart rate with the exercises mentioned in table 5. This looks like an interval training instead of the endurance training in the centre based exercise program. How do the authors make sure that only the form (centre based or home based) is different and not the

	training content (interval vs endurance; intensity) Page 11 line 57: Primary instead of Primery The authors state at page 12 (intervention) that the participants will exercise with an intensity of 70% of their maximal heart rate, as assessed during baseline CPET and the 6MWT. I don't see how the 6MWT will be used to determine the 70%. Page 16 and 17: Am I correct that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period"? This difference would be strange. I can imagine that the control group will also be wearing the Actigraph for only 12 weeks? Authors response: Thank you for your comment. Both the telerehabiliation group and the control group will be wearing the Actigraph only during the 12 week intervention period. --> In the text at page 16 and 17 it is stated that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period" Please correct. Page 19: Is it really necessary to exclude a patient when he or she doesn't reach a RER of 1.1? I would suggest to be less strict.

REVIEWER	Falter, Maarten UHasselt—Hasselt University, Cardiovascular Research
REVIEW RETURNED	01-Apr-2022

GENERAL COMMENTS	No additional comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2 Dr. Aernout Snoek, Isala Medical Center Comments to the Author:

The authors describe the study protocol of an extensive RCT in a relevant field in which participation rates of an effective treatment (cardiac rehabilitation) is limited. Their aim to use remote technologies is needed to increase participation rates and limit health care costs. They explain clearly what this study adds to the field.

The abstract is judged as not accurate. I read in the abstract that the patients will be training at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 60'', three times/ week and table 4 describes a different filling of the 60 minutes. The exact training is far more extensive as explained in table 4 and 5. Why do the authors only mention the aerobic cardio training in the abstract and don't mention the strength training?

Response: Thank for your comment. Strengthening and balance training was added in the abstract

I have concerns about the study design. Not only the form (centre based or home based) is different, but also the training content of the centre based and TELE-CR aerobic training. I have some concerns about how well it is possible to reach and stay at the 70% of maximal heart rate with the exercises mentioned in table 5. This looks like an interval training instead of the endurance training in the centre based exercise program. How do the authors make

sure that only the form (centre based or home based) is different and not the training content (interval vs endurance; intensity)

Response: Thank for your comment. The chosen exercises for aerobic training in the TELE-CR group won't be performed in an interval type of mode. On the contrary the alteration between the different exercises will be continuous and without intervals for resting. Moreover, the TELE-CR participants will be asked to continuously check their heart rate levels through their sport watch; thus leading them to raise or lower the intensity of their ongoing aerobic training according to their prescribed optimal training heart rate zone. Furthermore, it needs to be mentioned that the TELE-CR exercise program will be monitored and guided in real time by a physical therapist via videoconferencingplatforms.

Page 11 line 57: Primary instead of Primery

Response: Thank for your comment. It was corrected.

The authors state at page 12 (intervention) that the participants will exercise with an intensity of 70% of their maximal heart rate, as assessed during baseline CPET and the 6MWT. I don't see how the 6MWT will be used to determine the 70%.

Response: Thank for your comment. 6MWT was removed from the sentence.

Page 16 and 17: Am I correct that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period"? This difference would be strange. I can imagine that the control group will

also be wearing the Actigraph for only 12 weeks? Authors response: Thank you for your comment. Both the telerehabiliation group and the control group will be wearing the Actigraph only during the 12 week intervention period.

--> In the text at page 16 and 17 it is stated that the intervention group will be wearing the Actigraph "during the 12 week intervention period" and the control group will be using it "during the entire study period" Please correct.

Response: Thank for your comment. It was corrected.

Page 19: Is it really necessary to exclude a patient when he or she doesn't reach a RER of 1.1? I would suggest to be less strict.

Response: Thank for your comment. The choice of RER>1.1 was made for safety reasons for the TELE-CR group to minimize the chances of the occurrence of any adverse events during home-based exercise implementation.

VERSION 3 – REVIEW

REVIEWER	Snoek, Aernout Isala Medical Center, sportsmedicine
REVIEW RETURNED	13-Apr-2022

GENERAL COMMENTS	The authors describe the study protocol of an extensive RCT in a relevant field in which participation rates of an effective treatment (cardiac rehabilitation) is limited. Their aim to use remote technologies is needed to increase participation rates and limit health care costs. They explain clearly what this study adds to the field