PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol
AUTHORS	Rodríguez-Molinero, Alejandro; Hernández-Vara, Jorge; Miñarro, Antonio; Pérez-López, Carlos; Bayes, Àngels; Martínez-Castrillo, Juan Carlos; David A Pérez-Martínez, David

VERSION 1 – REVIEW

REVIEWER	Anne-Louise Cunnington NHS Greater Glasgow and Clyde Scotland
REVIEW RETURNED	23-Oct-2020

GENERAL COMMENTS	Clear research question and of significant scientific interest to all those with Parkinson's and those involved in the care of people with Parkinson's. Would be keen however, to explore why there was not consideration given to a fourth arm that included all modalities i.e. Holter +diary +consultation. In addition medication and exercise programme concordance is not considered. Given the Holter registers falls, a common event in advanced Parkinson's ,often with significant adverse clinical outcomes, it is perhaps shortsighted of the researchers not to include this as an outcome measure. I would also like reassurances regarding the Neurologist-led patient training for completion of the diary with the aforementioned supportive video clips, in terms of timing in relation to clinic visits, repeated at any stage, carer present to assist? Could this be delivered by a trained researcher instead to ensure consistency of reporting? Duration of clinical review, as well as the demographic data, could be valuable.

REVIEWER	Jeroen Habets Maastricht University, The Netherlands
REVIEW RETURNED	26-Nov-2020

GENERAL COMMENTS	Dear authors, I have read your work with great interest, and I appreciate the effort to publish your study protocol. The main points which should be answered are: - The included PD patient population is unclear, and since this is essential for valid interpretation of the Parkinson Holter validation, this should be solved.

	- It is not clear how the Parkinson Holter is used by the neurologist. What are the scores/results they receive from the Parkinson Holter, and is there a advised methodology to interpret and use the resulting scores? This should also include elaboration on the time period of 7 days with regards to the validity and interpretation of the outcome scores of the Parkinson Holter. Dear editor, dear authors, The study protocol submitted by Rodriguez-Molinero et al is of great interest for the Parkinson community scientifically or clinically interested in device-aided, continuous home monitoring. Their group published an impressive line of work recent years on home monitoring for Parkinson's disease, leading to the Parkinson Holter. Here, they present a probably first of its kind clinical validation of the Parkinson Holter. In a randomized, controlled design, they compare the effect on off-time reduction of clinical decision making based on the Parkinson Holter, based on a Hauser motor diary, and without extra information (only patient narrative). This work is both a logical and a necessary next step in the growing field of Parkinson monitoring at home. By conducting this research, they distinguish their validation work from other available commercial devices so far. In case data collection is not completed yet, the article type is suited for BMJ Open's mission. In general, I support their initiative to publish their protocol, to help other researchers design experiments. Comments: First of all, it is not clear whether data collection has started at this point or not. The dates when data collection did start/ is expected to start, and when data collection is expected to end, are missing. This makes it harder to comment, since it is unclear whether protocol changes are possible or not. The main study design is well thought out, and the outcomes fit the objectives and goals of this study. Some major questions remain unanswered regarding the clinical utilization of the Holter in this study, and regarding the intended future clinical utilization which need more elaboration (SPIRIT item no. 10 and 11a). These questions should be clarified to ensure valid and meaningful results towards future clinical implementation. A main critic is the participant description. To understand the exact clinical setting on which the Holter will be validated, it is of interest to know how the inclusion criteria 'motor fluctuations, with at least 2 hours per day in the Off state' was assessed? Also, can the authors explain how they plan to compare the patient populations in the different arms? Since it is not well explained why the participants are visiting the neurologist in the first place, it is difficult to hypothesize what the expected result of the clinical visit is, regardless of which information source is used. The authors chose a monitoring period of 7 days before clinical visit. It would be interesting to know why these 7 days are chosen. Is the Holter expected to perform optimal based on a 7-day-period, and if so based on what, or are the 7 days chosen out of practical reasons? Elaboration on the optimal period of use for the Holter

	would contribute to be able to interpret the upcoming results. In case of negative or positive results, is the period of 7 days the intended instruction to use the Holter, or is this device suited for longer periods of use, and can it be interpreted as a limitation in case of negative results? The latter comment leads to question about the temporal representability of the Holter. And this connects with the next main question: can the authors elaborate on how the Holter informs the neurologist? The different parts of the Holter are of course published in separate publications, but to understand, interpret, and reproduce the intervention validated in this study, essential information is missing. The authors are asked to explain the clinical intervention which is performed with the Holter. What are the data the neurologist gets to perform clinical decision making? Is this based on intra-daily scores, based on daily scores, based on a week score? And did the authors inform/train the clinicians on how to use the Holter? It would be of great interest to add this instruction as a supplemental material.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Anne-Louise Cunnington, Glasgow Royal Infirmary
Comments to the Author:
Q: Clear research question and of significant scientific interest to all those with Parkinson's and those involved in the care of people with Parkinson's.
Would be keen however, to explore why there was not consideration given to a fourth arm that included all modalities i.e. Holter +diary +consultation. In addition medication and exercise programme concordance is not considered.

RESPONSE: Thanks for your comment. Including a fourth arm would have been interesting, but was unfeasible, due to recruitment limitations (we are using more than 40 centers to recruit total patients for the present 3 arms), and budget.

Exercise programs were not considered in the present version of the protocol. Although recruitment is ongoing, we have carefully considered the point raised by the reviewer, and have decided to amend the protocol in order to register prescription of exercise programs in each patient.

Please see changes in “Outcome variables and measurement instruments” section, and Table 1

Q: Given the Holter registers falls, a common event in advanced Parkinson's ,often with significant adverse clinical outcomes, it is perhaps shortsighted of the researchers not to include this as an outcome measure.

RESPONSE: The device is able to detect falls, but this functionality is designed to have some degree of confirmation by the user (otherwise, a significant amount of false positives arise). In this trial, the confirmation by the user was not implemented, so we cannot reliably estimate falls as an outcome. We have now commented on this issue in the discussion.

Please see discussion section, third paragraph

Q: I would also like reassurances regarding the Neurologist-led patient training for completion of the

diary with the aforementioned supportive video clips, in terms of timing in relation to clinic visits, repeated at any stage, carer present to assist? Could this be delivered by a trained researcher instead to ensure consistency of reporting?

RESPONSE: Although the neurologists received specific training on how to instruct the patient in the use of the diary, in this clinical trial no strong restrictions were implemented in terms of patient training by the neurologist. The reason was that the diary is not only an outcome measurement, but also a comparator branch, and as such, it should be used like in clinical practice. However, to guarantee diary quality as an outcome measurement, an independent team reviews all basal and last visit diaries, in terms of completion, duplicities, and consistency between days and with data of the Parkinson's Holter. Those diaries suspected to be wrong filled, are dismissed, and the responsible local investigator is contacted, who decides if the patient is re-trained and the diary repeated, or the patient is excluded, if unable to collaborate with study procedures.

We have provided more details on this in the methodology section.
Please see "procedures" section, 3rd paragraph.

Q: Duration of clinical review, as well as the demographic data, could be valuable.

RESPONSE: Demographic data are collected and will be published along with the results. Medical review duration is not recorded, though it would have been useful. We have recognized it in the limitations section.

Please see discussion section, 7th paragraph

ADDITIONAL COMMENT: please see also a comment made to the editor, regarding an amendment of the study protocol.

We would like to thank Dr. Cunnington for her helpful comments.

Reviewer: 2
Dr. Jeroen Habets, Maastricht University

Comments to the Author:
Dear authors,

Q: I have read your work with great interest, and I appreciate the effort to publish your study protocol. The main points which should be answered are:
- The included PD patient population is unclear, and since this is essential for valid interpretation of the Parkinson Holter validation, this should be solved.
- It is not clear how the Parkinson Holter is used by the neurologist. What are the scores/results they receive from the Parkinson Holter, and is there a advised methodology to interpret and use the resulting scores?
This should also include elaboration on the time period of 7 days with regards to the validity and interpretation of the outcome scores of the Parkinson Holter.
Please see the attached document for my complete review and other comments.

RESPONSE: We thank Dr. Habets, for this summary of the main points raised in the review. As the reviewer attached a more detailed list of comments, we have answered below to the specific

comments of the list.

Q: First of all, it is not clear whether data collection has started at this point or not. The dates when data collection did start/ is expected to start, and when data collection is expected to end, are missing. This makes it harder to comment, since it is unclear whether protocol changes are possible or not.

RESPONSE: We apologize for this omission, we have included now data collection dates. Recruitment is already in course, so major modifications of the protocol are not possible at this point.

We have provided details on the study dates in the paper, please see the “Study setting and duration” section.

Q: The main study design is well thought out, and the outcomes fit the objectives and goals of this study. Some major questions remain unanswered regarding the clinical utilization of the Holter in this study, and regarding the intended future clinical utilization which need more elaboration (SPIRIT item no. 10 and 11a). These questions should be clarified to ensure valid and meaningful results towards future clinical implementation.

RESPONSE: We have added the section entitled “investigational device”, in which the main characteristics of the Parkinson’s Holter are presented. Also we have added two new figures showing the reports the Holter produces, and the information depicted in them.

Please see the new section “Investigational device”, and figures 3 and 4

Q: A main critic is the participant description. To understand the exact clinical setting on which the Holter will be validated, it is of interest to know how the inclusion criteria ‘motor fluctuations, with at least 2 hours per day in the Off state’ was assessed? Also, can the authors explain how they plan to compare the patient populations in the different arms? Since it is not well explained why the participants are visiting the neurologist in the first place, it is difficult to hypothesize what the expected result of the clinical visit is, regardless of which information source is used.

RESPONSE: This is a realistic study in which the Parkinson's Holter will be used in a similar way to how it would be done in clinical practice. Neurologists select patients who are being followed up in their outpatient clinic, in whom ambulatory monitoring of their symptoms could help to adjust the treatment. We have established the criterion that they have at least two daily hours in Off, as a cut-off point for this purpose. Once the neurologist has selected them, and before the baseline visit, the patients fill in a diary for the first time. This diary is reviewed by a team independent of the neurologist, and if the inclusion criterion is not met (2h in Off), the patient is rejected (considered a screening failure). Therefore, neurologists will include in the study patients who had 2 hours in Off, and who, for any circumstance, would benefit from ambulatory monitoring (expected reduction of time on off, expected reduction of dyskinesia, etc.), without the protocol imposing further restrictions in this regard.

We have clarified these points in the paper. Please see the “participants” section, first paragraph and “procedures” section, 4th paragraph.

Q: The authors chose a monitoring period of 7 days before clinical visit. It would be interesting to know why these 7 days are chosen. Is the Holter expected to perform optimal based on a 7-day-period, and if so based on what, or are the 7 days chosen out of practical reasons? Elaboration on the optimal period of use for the Holter would contribute to be able to interpret the upcoming results. In

case of negative or positive results, is the period of 7 days the intended instruction to use the Holter, or is this device suited for longer periods of use, and can it be interpreted as a limitation in case of negative results?

RESPONSE: The Holter requires use for at least 3 days, for self-calibration reasons. It can be used for any period of time equal or greater than three days (also long-term), although the manufacturer recommends a minimum of 7 days, to capture changes in symptoms due to weekend routines. We have chosen this number of days for both the diary arm and the Holter arm, so the information provided by the two monitoring methods will be more comparable.

We have added some of this information to the paper. Please see the last paragraph of the new section “Investigational device”

Q: The latter comment leads to question about the temporal representability of the Holter. And this connects with the next main question: can the authors elaborate on how the Holter informs the neurologist? The different parts of the Holter are of course published in separate publications, but to understand, interpret, and reproduce the intervention validated in this study, essential information is missing. The authors are asked to explain the clinical intervention which is performed with the Holter. What are the data the neurologist gets to perform clinical decision making? Is this based on intra-daily scores, based on daily scores, based on a week score? And did the authors inform/train the clinicians on how to use the Holter? It would be of great interest to add this instruction as a supplemental material.

RESPONSE: We believe that the reviewer has detected a very important deficiency in the article. We, the authors, are so used to the Parkinson’s Holter that we have forgotten to better explain how it is used and what data it shows. As mentioned before, we have added a new section (“investigational device”) to provide information about what the Holter records and how it is used. In addition, we have added figures that show the reports it produces. An explanatory video on the interpretation of the Holter results and the instruction manual were made available to the doctors. These documents are in Spanish, so we think they will not be of aid as supplementary material. However, the reports of the Holter are quite user friendly, so we think the readers will understand the reports depicted in the figures, without any additional instructions.

Please see the new section “Investigational device”, procedures section, fourth paragraph, and figures 3 and 4

ADDITIONAL COMMENT: please see also a comment made to the editor, regarding an amendment of the study protocol.

We sincerely thank Dr. Habets for his detailed and useful review.

VERSION 2 – REVIEW

REVIEWER	Cunnington, Anne-Louise Glasgow Royal Infirmary, Care of Elderly
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	A few typos - I have made some corrections, but unsure if saved. Spell checking advised.

REVIEWER	Habets, Jeroen Maastricht University
REVIEW RETURNED	27-Apr-2021

GENERAL COMMENTS	Dear authors, thank you for your work and clarifying answers. I sincerely want to compliment you with the pioneering work you are doing in this robust clinical validation of a wearable Parkinson monitoring tool. All, except one, questions are answered in your revision. My only remaining comment concerns the usability and instruction of the STAT-ON. You mention the video and the Spanish instruction, but I could not find them in your documents. For my feeling, a English translation of this instruction would massively increase the impact of your work on the community since this instructions and practical implementation are one of the missing links in my opinion. Also, the addition of figure 2 and 3 is very much appreciated to guide the reader to your utilisation of STAT-ON. However, you do not refer yet to both figures in the text. An explanation in the text would be very helpful. Could you include an explanation of the %-time in ON/intermed/OFF state as well? The total of the percentages in figure 2 does not exceed 30% of total time, can you explain how the other time durations were classified? And why, and whether this is important for interpretation? Many thanks, and I am looking forward to learn more from your experiences. Best regards, Jeroen Habets

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 Dr. Anne-Louise Cunnington, Glasgow Royal Infirmary
A few typos - I have made some corrections, but unsure if saved. Spell checking advised.

RESPONSE: Spelling review done. Thanks for your positive review.

Reviewer: 2 Dr. Jeroen Habets, Maastricht University
My only remaining comment concerns the usability and instruction of the STAT-ON. You mention the video and the Spanish instruction, but I could not find them in your documents. For my feeling, a English translation of this instruction would massively increase the impact of your work on the community since this instructions and practical implementation are one of the missing links in my opinion.

RESPONSE: We have uploaded the English version of the user manual as supplementary material.

Also, the addition of figure 2 and 3 is very much appreciated to guide the reader to your utilisation of STAT-ON. However, you do not refer yet to both figures in the text. An explanation in the text would

be very helpful. Could you include an explanation of the %-time in ON/intermed/OFF state as well? The total of the percentages in figure 2 does not exceed 30% of total time, can you explain how the other time durations were classified? And why, and whether this is important for interpretation?

RESPONSE: We have replaced the figures with the reports of another patient, with results that are easier to understand. There is a part of the time monitored, in which the sensor cannot establish the motor status (these are the areas represented in gray, in figure 3). To reach 100% of the monitored time, time in On, time in Off and time in “intermediate” state, should be added to the without motor diagnosis. We have now commented the figures in the text, explaining a bit more the time calculations and interpretation.

Please see “Investigatonal device” section, second paragraph

Many thanks for your helpful review.