ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a feasibility interventional study investigating PAIN in neurorehabilitation through wearabLE SensorS (PAINLESS)
AUTHORS	Moscato, Serena; Orlandi, Silvia; Di Gregorio, Francesco; Lullini, Giada; Pozzi, Stefania; Sabattini, Loredana; Chiari, Lorenzo; La Porta, Fabio

VERSION 1 – REVIEW

REVIEWER	Cerasa, Antonio Institute for Biomedical Research and Innovation National Research Council
REVIEW RETURNED	11-Jun-2023

GENERAL COMMENTS	The objective evaluation of pain disorders in neurological patients is a very huge field of study deserving of future investigation. In this paper, the authors sought to demonstrate the feasibility of developing a new technique for making a differential diagnosis based on physiological signals captured by wearable sensors to determine whether pain is present or not. Reference measurements, study design, wearable recording, and statistical analysis are very well done. I only suggest including a wider framework for improving the overall presentation of this approach. In order to translate it into a clinically meaningful practical application, this kind of approach needed to be presented considering all steps of the technological device: Usability, acceptability, and feasibility. Please provide a new figure discussing these overall steps.

REVIEWER	Castan Delshorts, Alex Institut Guttmann
REVIEW RETURNED	11-Jun-2023

GENERAL COMMENTS	Comments to the Author: The manuscript's description of the process is very thorough. However, there are a few areas in which the manuscript could be improved: Page 1, line 44: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract. Page 1, line 57: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract.

Page 2, line 3: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract.

Page 2, line 11: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract.

Page 4, line 26: How was the sample size used determined? Further explanation for the justification of the sample sizes is needed.

Page 4, lines 36-41: If the study is to be conducted in Italy, with Italian speakers and questionnaires written in Italian, it should be considered as inclusion criteria that the participant has a good written and reading command of the Italian language.

Page 5, lines 29-49: More information on the psychometric properties of the measures should be included in the description of the measures. Also, information on their validity in the specific population to be studied (multiple sclerosis) and also information on the validations of the questionnaires in Italian language or how the translation of the questionnaires into Italian has been carried out.

Page 6, line 8: Further explanation of the use of accelerometer data is needed. It would be necessary to know what kind of data the accelerometer shows, e.g. does it show different intensities of physical activity?

Page 6, line 24: More information about motor neurorehabilitation treatment is needed. Is it a protocolized treatment, and is it always the same?

Page 7, line 18: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

Page 7, line 30: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

Page 7, line 45: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

Page 8, line 22 – page 9, line 24 (Discussion Section): Although the information Discussion Section is well structured, it is necessary to accompany it with references to the scientific literature.

Page 10, line 37: the link in reference 11 is not available.

Figure 1: Nice figure!

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. The objective evaluation of pain disorders in neurological patient is a very huge field of study deserving of future investigation. In this paper, the authors sought to demonstrate the feasibility of developing a new technique for making a differential diagnosis based on physiological signals captured by wearable sensors to determine whether pain is present or not. Reference measurements, study design, wearable recording, and statistical analysis are very well done.

Thank you for your kind appraisal.

2. I only suggest including a wider framework for improving the overall presentation of this approach. In order to translate it into a clinically meaningful practical application, this king od approach needed to be presented considering all steps of the technological devices: usability, acceptability, and feasibility. Please provide a new figure discussing these overall steps.

Thank you for your helpful feedback. With this study, our purpose is to preliminary assess the feasibility of such an approach in terms of digital biomarkers that can be clinically relevant to assess the pain experience. At the same time, we will also collect feedback from patients to have a preliminary understanding of the acceptability of this approach. If the primary aims (feasibility) will be reached, we will conduct a study involving a higher number of participants in which all the steps of the technological devices will be considered.

Based on your interesting suggestion, we have added a sentence in the manuscript at page 5 to make it clearer that we preliminary investigated also the acceptability from the patients of the tools.

Since we did not want to introduce any bias in participants' answers, and since there are no studies similar to this, we decided to employ an unstructured interview approach. The physiotherapist asks a broad question regarding any comments or feedback the participant may have about the study. We record any comments received in a diary. Consequently, in the manuscript, we included a sentence stating, "At the end of the study, a structured interview was conducted, and researchers annotated patients' comments in order to evaluate the acceptability of such new approach."

Reviewer #2

1. The manuscript's description of the process is very thorough. However, there are a few areas in which the manuscript could be improved

Thank you for your constructive feedback.

2. Page 1, line 44: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract [NOTE FROM THE EDITORS: Yes, it is fine to use abbreviations in the abstract)

Thank you for pointing this out, although the Editors suggested that it is fine to use abbreviations in the abstract.

3. Page 1, line 57: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract

Thank you, please see the answer to point 2.

4. Page 2, line 3: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract

Already answered by the editor

5. Page 2, line 11: consult and check with the journal's instructions for authors whether it is allowed to use abbreviations in the abstract

Already answered by the editor

6. Page 4, line 26: how was the sample size used determined? Further explanation for the justification of the sample sizes is needed

In response to this comment, we inserted two references in the main text (Teresi et al. 2022 and Moore et al. 2011).

As reported by Teresi et al. 2022, the sample size for a feasibility study "should be based on practical considerations including participant flow, budgetary constraints, and the number of participants needed to reasonably evaluate feasibility goals". Moreover, as also stated by Moore et al. 2011, "small samples may be appropriate for aims such as pilot-testing a data management system, demonstrating the ability to execute a specific research protocol, or testing the acceptability and adherence to a new online disease management intervention". We choose the sample size based on these considerations. We added a line to explicitly define the reference our choice was made on (page 7).

7. Page 4, lines 36-41: if the study is to be conducted in Italy, with Italian speakers and questionnaires written in Italian, it should be considered as inclusion criteria that the participant has a good written and reading command of the Italian language

We have already added an exclusion criterion including what the reviewer suggested: "Linguistic expression less than 75%. In case of doubt, a simple verbal fluency test (verbal fluency by phonemic category) will be administered before enrollment"

8. Page 5, lines 29-49: More information on the psychometric properties of the measures should bel included in the description of the measures. Also, information on their validity in the specific population to be studied (multiple sclerosis) and also information on the validations of the questionnaires in Italian language or how the translation of the questionnaires into Italian has been carried out.

Thank you for your comment, we are sorry that we did not mention these points in the text. Scales and questionnaires used in this study have already been translated in Italian and there is evidence that they are valid and reliable to detect pain in persons with MS. Thus, we added a new subparagraph, named "Measures' psychometric properties" at Page 5, collecting this kind of information

9. Page 6, line 8: Further explanation of the use of accelerometer data is needed. It would be necessary to know what kind of data the accelerometer shows, e.g. does it show different intensities of physical activity?

We added "three-axis" to "accelerometer data" to better define that the info coming from this sensor is related to the acceleration on the three axes only. The sensor provides raw data about the acceleration expressed in "g" along the three axes, the physical activity can be a derived parameter from the raw data

10. Page 6, line 24: More information about motor neurorehabilitation treatment is needed. Is it a protocolized treatment, and is it always the same?

Thank you for this suggestion. We better specify the type of motor neurorehabilitation treatment by adding a paragraph at page 6 by adding.

11. Page 7, line 18: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

Thank you for the suggestion, we replaced "gold standard" with "state-of-the-art methods"

12. Page 7, line 30: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

We replaced "gold standard" with "state-of-the-art methods"

13. Page 7, line 45: Questionnaire is not a gold standard measurement tool. This sentence should be modified accordingly.

We replaced "gold standard" with "state-of-the-art methods"

14. Page 8, line 22 – page 9, line 24 (Discussion Section): Although the information Discussion Section is well structured, it is necessary to accompany it with references to the scientific literature.

We thank the reviewer for this comment. We added the following references throughout the discussion section to better consolidate the concepts and to be compared with the literature:

- Subramaniam SD, Doss B, Chanderasekar LD, *et al.* Scope of physiological and behavioural pain assessment techniques in children – A review. *Healthc Technol Lett* 2018;**5**:124–9. doi:10.1049/htl.2017.0108

- Werner P, Lopez-Martinez D, Walter S, *et al.* Automatic Recognition Methods Supporting Pain Assessment: A Survey. *IEEE Trans Affect Comput* 2019;**X**:1–1. doi:10.1109/TAFFC.2019.2946774
- Naranjo-Hernandez D, Reina-Tosina J, Roa LM. Sensor Technologies to Manage the Physiological Traits of Chronic Pain: A Review. *Sensors (Basel)* 2020;**20**. doi:10.3390/s20020365
- Gordon DB, Dahl JL, Miaskowski C, *et al.* American Pain Society recommendations for improving the quality of acute and cancer pain management: American Pain Society quality of care task force. *Arch Intern Med* 2005;**165**:1574–80. doi:10.1001/archinte.165.14.1574
- Sinatra R. Causes and Consequences of Inadequate Management of Acute Pain. *Pain Med* 2010;**11**:1859–71. doi:10.1111/j.1526-4637.2010.00983.x
- Moscato S, Lo Giudice S, Massaro G, *et al.* Wrist Photoplethysmography Signal Quality Assessment for Reliable Heart Rate Estimate and Morphological Analysis. *Sensors* 2022;**22**:5831. doi:10.3390/s22155831

15. Page 10, line 37: the link in reference 11 is not available.

Thank you for the report, we replaced the old reference with another one related to the validation of the DN4 questionnaire

16. Figure 1: Nice figure!

We really appreciate the positive comment by the reviewer on the protocol figure

VERSION 2 – REVIEW

REVIEWER	Castan Delshorts, Alex Institut Guttmann
REVIEW RETURNED	28-Jul-2023

GENERAL COMMENTS	The authors have adequately addressed my concerns and the article has been improved with the updates/revisions. Nice work!