## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial |
| **AUTHORS** | Jaén, Irene; Suso-Ribera, Carlos; Castilla, Diana; Zaragoza, Irene; García-Palacios, Azucena; Gómez Palones, Jose Luis |

## VERSION 1 – REVIEW

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| **REVIEWER** | Madelon Peters<br>Maastricht University<br>the netherlands |
| **REVIEW RETURNED** | 18-Sep-2019 |

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| **GENERAL COMMENTS** | The paper describes the protocol of a study on the efficacy of an app and web application to score and review daily pain on pain reductions by medical treatment. The study has been registered and is ongoing.<br><br>The trial is interesting and generally well-designed. I have a few suggestions for the paper that can add to the clarity of presentation, and some questions concerning the design. I will list my suggestions and questions below.<br><br>1. In the abstract, and also later in the paper, it was unclear to me what is meant with the statement that “alarms are created with previously defined undesirable events”. Only after reviewing the supplemental material, it became clear that these undesirable events relate to high pain levels or the occurrence of side effects that persist for a certain (predefined) number of days. It may be helpful to add a little note on this to the text. In the abstract it might be added that physicians receive these alarms and not the patient.<br><br>2. It is somewhat surprising that according to the paper, no data is collected regarding the number of actual occurrences of alarms, whether physicians act upon these alarms , and how often treatment strategies are changed in both groups (whether or not in response to an alarm). The hypothesis is that treatment will be more effective because physicians can change the treatment strategy or dosage because of the alarms. If indeed the app proves effective, some insight into the potential underlying mechanism might be good. Is it indeed because of earlier adaptation of treatment strategy or is it because patient feel more in control, get better insight in when pain occurs or adhere better to treatment regimens? If no data is collected to gain insight in this, this could be mentioned in the discussion as a limitation.<br><br>3. Physicians receive the pain scores of every patient each day. Are they instructed to review these scores, also in the absence of an |

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| | alarm, or only retrospectively when an alarm has occurred? If they are instructed to review daily (or at certain times during treatment) is this monitored, i.e. whether they actually do so? How much time will this cost?<br><br>4. What is the rational for expecting changes on the secondary outcomes like for instance pain catastrophizing and anxiety? Treatment consists of medical interventions not specifically addressing cognitions or emotions. Is the expectation that these outcomes will change as a results of pain reductions?<br><br>5. There are more items in the app (e.g. acceptance, social support) than those used for the present study. Can these items be disabled in the app, or do patients have to fill these out anyway? This might unnecessarily increase patients' burden.<br><br>6. Intention to treat analyses will be used. However, this does not relate to attrition from follow-up assessment. Only patients with complete pre and post test assessment are included. In that sense, it is a completer analysis. ITT relates to whether or not the app is used. One concern might be that if a pain deterioration occurs, patients re requested to stop using the app. Care should be taken to keep these patients in the trial (i.e. obtain post assessment) otherwise this might introduce a bias where patients with the worst response selectively drop out from the experimental condition. The manner in which (potential) drop outs are handled may be described.<br><br>7. The introduction states that "60% of patients after surgery will continue to experience severe chronic pain months and years later" with a reference to a paper of Lavand'homme et al., 2011. What this paper actually says is that the incidence of chronic pain after surgery varies between 15 - 60% , with severe pain occurring in 4 – 10% of patients.<br><br>8. At several places reference 14 is mentioned as a paper describing the development and previous work with the app. I guess this should be reference 15 in the list. I have not systematically checked the number of all references.<br><br>9. A small textual remark: p.6, line 156. Ration should be ratio. |

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| **REVIEWER** | Dr Anita Amorim<br>The University of Sydney, Australia |
| **REVIEW RETURNED** | 23-Sep-2019 |

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| **GENERAL COMMENTS** | Comments:<br>The study described in the manuscript aimed to test the utility of a technology-based solution for pain telemonitoring consisting of a smartphone app for patients and a web application for physicians. Overall, this protocol is well written, the methods are well described, and the outcomes are clear. However, to be considered for publication this manuscript needs to be revised in order to clarify some important aspects. Specific comments are listed below and will hopefully enhance the quality of this study and increase the likelihood of acceptance.<br>Major revisions:<br><br>- The authors are advised to look critically at the first couple of sentences at the second paragraph in their introduction. The way it |

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| | is written it does not differentiate if you're talking about "chronic primary pain" or other chronic pain subgroups or "chronic secondary pain", where pain is secondary to an underlying disease and conceived as a symptom. I believe this paragraph would be strengthened by adding figures regarding the burden of chronic primary pain (e.g. fibromyalgia or nonspecific low-back pain). Please see suggested references below.<br><br>Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA. "Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the: International Classification of Diseases:(: ICD-11:)". Pain. 2019 Jan 1;160(1):19-27.<br><br>Blyth FM, Van Der Windt DA, Croft PR. "Chronic Disabling Pain: A Significant Public Health Problem". Am J Prev Med 2015;49:98–101.<br><br>Vos, Theo, et al. "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." The Lancet 386.9995 (2015): 743-800.<br><br>- My major concern is that previous studies have shown that focusing on pain outcomes daily may bring more harm than help for people with chronic primary pain. Often people that have less disability and seek-less care they tend not to focus on their pain and its limitations and find that frequent monitoring to be more of a hindrance than a help. For those people, even though they live with chronic pain, they learn how to live with it rather than letting the pain control their lives and for this reason, they have less activity limitation and they rely less on medication and usually adopt e healthier lifestyle to self-manage their pain syndrome. On the other hand, people living with chronic pain who present yellow flags, especially for those who with anxiety or depression, they tend to rely on passive treatments and medication and daily pain monitoring can increase pain catastrophising and boost their yellow flags. For instance, a similar study looking at satisfaction of an app for pain monitoring published in 2018 (Jamison RN, Mei A, Ross EL. Longitudinal trial of a smartphone pain application for chronic pain patients: predictors of compliance and satisfaction. Journal of telemedicine and telecare. 2018) showed that those with less activity limitation were less satisfied with the app, they found the frequent monitoring of the app inconvenient. In contrast, people with greater self-reported disability and who demonstrated less mobility were more satisfied with the app. Quite possibly, those who were active throughout the day found the app to be more bothersome. Conversely, those who found the app useful were more focused on their pain, which is probably not helpful. I appreciate that the close monitoring of pain and side effects for people initiating a course of opioid therapy, for example, may be helpful to avoid long term use and complications, however, daily monitoring of people with chronic primary pain may not be the case.<br><br>- As the economic burden of chronic pain is associated with sickness absence, are these patients sick-listed or working? Are you going to measure this variable in the study?<br><br>- The challenge with mobile health technology is to encourage and motivate participants to continue to use an app in order to make |

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| | improvements in their condition. This is particularly important among individuals with chronic illnesses. Programs that demand a lot of time and attention, such as using an app daily twice a day, are less likely to be used. If you are only measuring the Pain monitor app for one month how will you be able to conclude how feasible it would be to implement the use of the pain app over time?<br><br>- How do the authors think the app would improve the overall quality of life for chronic pain patients? How and why the frequent use of the app would be positively correlated with improvement in pain and mood?<br><br>- Please check the references through the whole manuscript, many of them are misreferenced in the text.<br><br>Minor revisions:<br>Introduction<br>- References 9 and 10 are not correct. It should be 10 and 11. The same applies for the following references in the introduction.<br>Methods<br>- Minor error on line 169: Please change it to: “will be offered the possibility…”<br><br>- Reference 14 is incorrect in the text. It should be 15.<br><br>- Minor error on line 214: Delete ‘are’ from the sentence: “Changes in the medication or improvement of disease are do not result in study discontinuation.”<br>Discussion<br>- The first sentence of the discussion should be in the introduction. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Reviewer Name: Madelon Peters
Institution and Country:
Maastricht University
the netherlands
Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below
The paper describes the protocol of a study on the efficacy of an app and web application to score and review daily pain on pain reductions by medical treatment. The study has been registered and is ongoing.

The trial is interesting and generally well-designed. I have a few suggestions for the paper that can add to the clarity of presentation, and some questions concerning the design. I will list my suggestions and questions below.

1. In the abstract, and also later in the paper, it was unclear to me what is meant with the statement that “alarms are created with previously defined undesirable events”. Only after reviewing the supplemental material, it became clear that these undesirable events relate to high pain levels or the occurrence of side effects that persist for a certain (predefined) number of days. It may be helpful to

add a little note on this to the text. In the abstract it might be added that physicians receive these alarms and not the patient.
Answer: Thank you for this suggestion; we have chanched the statement accordingly, both in the abstract and in the paper (line 175). We hope this is clearer now.

2. It is somewhat surprising that according to the paper, no data is collected regarding the number of actual occurrences of alarms, whether physicians act upon these alarms , and how often treatment strategies are changed in both groups (whether or not in response to an alarm). The hypothesis is that treatment will be more effective because physicians can change the treatment strategy or dosage because of the alarms. If indeed the app proves effective, some insight into the potential underlying mechanism might be good. Is it indeed because of earlier adaptation of treatment strategy or is it because patient feel more in control, get better insight in when pain occurs or adhere better to treatment regimens? If no data is collected to gain insight in this, this could be mentioned in the discussion as a limitation.

Answer: We highly appreciate this remark, since we are indeed collecting the aforementioned data about physician responses to alarms and number of alarms. We have added this information in the text (line 340).

3. Physicians receive the pain scores of every patient each day. Are they instructed to review these scores, also in the absence of an alarm, or only retrospectively when an alarm has occurred? If they are instructed to review daily (or at certain times during treatment) is this monitored, i.e. whether they actually do so? How much time will this cost?
Answer: This is an important point, thanks. The physicians do not receive the patient pain scores each day, but they can log into the physician website and chek the sympthomathology of any patients whenever they want to. Physicians only receive the instruction to review the scores when an alarm occurs. In this case, the experimenter who receives the alarms (IJP) sends them the instruction to give an answer to the alarm. After that, the physician that is in the pain unit responds to the alarm and reports the action taken to the experimenter. We do not expect the physicians to check each patient status daily, because this would be very time consuming and, in fact, the use of alarms has this purpose of passive monitoring for the physicians. We will note this in the text in more detail (line 280).

4. What is the rational for expecting changes on the secondary outcomes like for instance pain catastrophizing and anxiety? Treatment consists of medical interventions not specifically addressing cognitions or emotions. Is the expectation that these outcomes will change as a results of pain reductions?
Answer: Yes, as you have mentioned there is evidence to suggest that pain intensity, catastrophizing and anxiety are moderately associated (e.g., Suso-Ribera, García-Palacios, Botella & Ribera-Canudas, 2017; Mortazavi Nasiri, Pakdaman, Dehghani, & Togha, 2017) and that changes in pain severity are related to changes in anxiety and psychological functioning (Nieto, Raichle, Jensen, & Miró, 2012). Therefore, we expect that changes in pain severity in the alarm group might also result in reduced catastrophizing and improved mood as secondary gains. We have explained this better in the text (line 161).

5. There are more items in the app (e.g. acceptance, social support) than those used for the present study. Can these items be disabled in the app, or do patients have to fill these out anyway? This might unnecessarily increase patients' burden.
Answer: Many thanks for this comment. We agree that this could increase patients' burden. However, Pain Monitor has been designed as a preset assessment protocol and it was not possible to make changes in the app for this study. We will include this as a limitation.

6. Intention to treat analyses will be used. However, this does not relate to attrition from follow-up

assessment. Only patients with complete pre and post test assessment are included. In that sense, it is a completer analysis. ITT relates to whether or not the app is used. One concern might be that if a pain deterioration occurs, patients re requested to stop using the app. Care should be taken to keep these patients in the trial (i.e. obtain post assessment) otherwise this might introduce a bias where patients with the worst response selectively drop out from the experimental condition. The manner in which (potential) drop outs are handled may be described.
Answer: Thanks a lot for noticing this. Indeed, the inclusion of an ITT analysis was an error. We meant to perform a completer's analysis, as described in the text. We have corrected this. Additionally, we now described how we expect to detect cases where dropout due to the App occurs. We have set an alarm that is sent to the physicians if a patient fails to repond to the App during 3 consecutive days, so that the physicians can call the patient and further explore the reasons for App use discontinuation. We have now indicated this in the text (line 377).

7. The introduction states that "60% of patients after surgery will continue to experience severe chronic pain months and years later" with a reference to a paper of Lavand'homme et al., 2011. What this paper actually says is that the incidence of chronic pain after surgery varies between 15 - 60% , with severe pain occurring in 4 – 10% of patients.
Answer: Thank you for pointing this out. Indeed, we had deleted part of the initial sentence by mistake. We have modified the text in order to adjust the information to the actual study findings.

8. At several places reference 14 is mentioned as a paper describing the development and previous work with the app. I guess this should be reference 15 in the list. I have not systematically checked the number of all references.
Answer: Thank you for the remark, we have checked all the references.

9. A small textual remark: p.6, line 156. Ration should be ratio.
Answer: Thank you, we have made the change.

Reviewer: 2

Reviewer Name: Dr Anita Amorim
Institution and Country: The University of Sydney, Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Comments:
The study described in the manuscript aimed to test the utility of a technology-based solution for pain telemonitoring consisting of a smartphone app for patients and a web application for physicians. Overall, this protocol is well written, the methods are well described, and the outcomes are clear. However, to be considered for publication this manuscript needs to be revised in order to clarify some important aspects. Specific comments are listed below and will hopefully enhance the quality of this study and increase the likelihood of acceptance.
Major revisions:

- The authors are advised to look critically at the first couple of sentences at the second paragraph in their introduction. The way it is written it does not differentiate if you're talking about "chronic primary pain" or other chronic pain subgroups or "chronic secondary pain", where pain is secondary to an underlying disease and conceived as a symptom. I believe this paragraph would be strengthened by adding figures regarding the burden of chronic primary pain (e.g. fibromyalgia or nonspecific low-back pain). Please see suggested references below.

Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA. “Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the: International Classification of Diseases:(: ICD-11:)”. Pain. 2019 Jan 1;160(1):19-27.

Blyth FM, Van Der Windt DA, Croft PR. “Chronic Disabling Pain: A Significant Public Health Problem”. Am J Prev Med 2015;49:98–101.

Vos, Theo, et al. "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." The Lancet 386.9995 (2015): 743-800.

Answer: Thank you very much for this recommendation. Indeed, further clarification was needed in this regard. We have now added that “We refer here to primary chronic pain, a pain associated with important interference on functioning and/or emotional distress which cannot be better accounted for by any other condition”. We have also mentioned that “Indeed, chronic primary pain (e.g., fibromyalgia or nonspecific low back or neck pain, to name some examples) is imposing a huge burden in our societies as this disease has become one of the leading causes of years lived with disability globally” We have included the proposed references.

- My major concern is that previous studies have shown that focusing on pain outcomes daily may bring more harm than help for people with chronic primary pain. Often people that have less disability and seek-less care they tend not to focus on their pain and its limitations and find that frequent monitoring to be more of a hindrance than a help. For those people, even though they live with chronic pain, they learn how to live with it rather than letting the pain control their lives and for this reason, they have less activity limitation and they rely less on medication and usually adopt e healthier lifestyle to self-manage their pain syndrome. On the other hand, people living with chronic pain who present yellow flags, especially for those who with anxiety or depression, they tend to rely on passive treatments and medication and daily pain monitoring can increase pain catastrophising and boost their yellow flags. For instance, a similar study looking at satisfaction of an app for pain monitoring published in 2018 (Jamison RN, Mei A, Ross EL. Longitudinal trial of a smartphone pain application for chronic pain patients: predictors of compliance and satisfaction. Journal of telemedicine and telecare. 2018) showed that those with less activity limitation were less satisfied with the app, they found the frequent monitoring of the app inconvenient. In contrast, people with greater self-reported disability and who demonstrated less mobility were more satisfied with the app. Quite possibly, those who were active throughout the day found the app to be more bothersome. Conversely, those who found the app useful were more focused on their pain, which is probably not helpful. I appreciate that the close monitoring of pain and side effects for people initiating a course of opioid therapy, for example, may be helpful to avoid long term use and complications, however, daily monitoring of people with chronic primary pain may not be the case.

Answer: Many thanks for this comment. As mentioned, the fact that patients focus on their symptomathology might be harmful for some patients with chronic pain. We completely agree with this and also with the following statement which noted that the use of daily monitoring is most useful after a new treatment onset. Indeed, in our study the Pain Monitor app is not used to monitor pain chronically, but during the first month after the beginning of a new treatment (as suggested by the reviewer). Because this was unclear in the text, we have added the following statement: “Only patients for whom a change in the treatment is planned (e.g., an epidural infiltration or a change in the prescribed medication) will be included in the study (this includes both new and consecutive patients). The reason for doing this is that the utility of the technology is expected to be maximized during the onset of new treatments, as opposed to those cases in which the treatment plan is already well-established.” We have also specified this in detail in the “Inclusion citeria” section.

- As the economic burden of chronic pain is associated with sickness absence, are these patients sick-listed or working? Are you going to measure this variable in the study?

Answer: Patients included in the study include all kinds of job conditions (e.g., active workers, unemployed individuals, or patients on sick leave). We include a measure of this in sociodemographic assessment, both in the paper-and-pencil and in the App assessments. Additionally, we included an item in the pre and post paper-and-pencil and App assessments that refers to the frequency of sickness absence during the past month. Because this was not specifically mentioned in the text, we have included this information (line 289). Thanks again for noticing this.

- The challenge with mobile health technology is to encourage and motivate participants to continue to use an app in order to make improvements in their condition. This is particularly important among individuals with chronic illnesses. Programs that demand a lot of time and attention, such as using an app daily twice a day, are less likely to be used. If you are only measuring the Pain monitor app for one month how will you be able to conclude how feasible it would be to implement the use of the pain app over time?

Answer: Thanks very much for this appointment. We would like to emphasize that the aim in our research is to study the effectiveness of the app use during the implementation of a new pain treatment, so we are interested in assessing pain-related variables and side effects between first and the second consultation, when there is not contact with physician. In addition, since physicians do not currently have time during consultations allocated to resolve alarms, a long-term monitoring service would not be feasible at this stage. Our goal at this point is only to explore whether the inclusion of such a technology is useful for patients in which pain is not well controlled and patients are offered new treatments that can potentially cause side effects or be ineffective. We cannot conclude how feasible the implementation of long-term monitoring would be within the context of the current study. We will now state this more clearly in the text, as follows: “Note that the study goal is not the explore the feasibility of implementing the use of the integrative technology for patient long-term use, but to explore its utility and acceptability when used in the short-term (e.g., during a month) in a critical treatment stage (i.e., after the onset of a new treatment plan, when pain is not well controlled and treatment tolerance is unclear)”.

- How do the authors think the app would improve the overall quality of life for chronic pain patients? How and why the frequent use of the app would be positively correlated with improvement in pain and mood?
Answer: We expect that a better adjustment of medical treatment due to monitoring and responding to alarms generated by patient responses has a positive impact on physical and mental health. There is evidence to suggest that pain severity is associated to another pain related variables as pain interference, catastrophism or mood (e.g., Suso-Ribera, García-Palacios, Botella & Ribera-Canudas, 2017; Mortazavi Nasiri, Pakdaman, Dehghani, & Togha, 2017; Bair, Robinson, Katon, Kroenke, 2003). Thus, if Pain Monitor + web for physician achieve to improve the usual treatment including a decrease of pain intensity and interferece, mood and another pain related variables would be positively correlated. Therefore, we expect that changes in pain-related outcomes might occur as secondary gains of reducing pain severity and minimizing side medication effects. We now indicate this in more detail in the text: “Additionally, we expect that this group of patients will present additional improvements on secondary outcomes, including mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month as secondary gains of reducing pain levels, as suggested in the literature [35]. We also expect that the rapid detection of treatment undesired events will rapidly minimize threats to the patient’s quality of life and mood.”

- Please check the references through the whole manuscript, many of them are misreferenced in the text.
Answer: Thanks for the appreciation. We have checked all the references.

Minor revisions:
Introduction
- References 9 and 10 are not correct. It should be 10 and 11. The same applies for the following references in the introduction.

Answer: Thanks for noticing this. We have checked all the references.

Methods
- Minor error on line 169: Please change it to: “will be offered the possibility…”
Answer: Thank you. We have changed the sentence.

- Reference 14 is incorrect in the text. It should be 15.
Answer: Thank you for the remark. All references have been checked.

- Minor error on line 214: Delete ‘are’ from the sentence: “Changes in the medication or improvement of disease are do not result in study discontinuation.”
Answer: Thank you. We have deleted “are” from the sentence.

Discussion
- The first sentence of the discussion should be in the introduction.
Answer: Thank you for this remark. We have moved this sentence from the discussion to the introduction.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Madelon Peters<br>Maastricht University The Netherlands |
| **REVIEW RETURNED** | 31-Oct-2019 |

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| **GENERAL COMMENTS** | The authors have adequately responded to the concerns raised. I congratulate them with a fine paper. |