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Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial

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Complete List of Authors:	Jaén, Irene; Universitat Jaume I, Basic Psychology, Clinical Psychology and Psychobiology Suso-Ribera, Carlos; Universitat Jaume I Castilla, Diana; Universidad de Zaragoza Zaragoza, Irene; Instituto de Salud Carlos III García-Palacios, Azucena; Universitat Jaume I Gómez Palones, Jose Luis; Hospital General de Castellon
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Authors: Irene Jaén[1,a], Carlos Suso-Ribera[1], Diana Castilla[2,3], Irene Zaragoza[3], Azucena García-Palacios[1,3] and José Luis Gómez Palonés[4]

[1] Universitat Jaume I, Castelló 12007, Spain

[2] Universidad de Zaragoza, Teruel 44003, Spain

[3] CIBER of Physiopathology of Obesity and Nutrition CIBERobn, CB06/03 Instituto de Salud Carlos III, Spain

[4] Hospital General Universitari de Castelló, 12004, Spain

[a] Corresponding author. Universitat Jaume I. Facultad de Ciencias de la Salud. Departamento de Psicología Básica, Clínica y Psicobiología. Avda. Vicente Sos Baynat s/n. Castellón de la Plana E-12071 Spain

ijaen@uji.es

Trial Sponsor: Universitat Jaume I.: Avda. Vicente Sos Baynat, s/n Castellón de la Plana E-12071 Spain; **Telephone:** +34 964 38 74 80; e-mail: ocit@uji.es

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Abstract

Introduction: Chronic pain has become a matter of concern for public health due to its high prevalence and because public costs associated with treatment and disability increase each year. Research suggests that limitations in the traditional assessment of chronic pain patients limit the effectiveness of current medical treatments. The use of technology might serve change patient traditional monitoring into Ecological Momentary Assessments, which might be visualized by physicians live. This study describes a Randomized Control Trial designed 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. The goal of this study will be to explore whether this combination of eHealth and mHealth improves the effectiveness of existing pain treatments.

*Methods and analysis***:** Participants will be 250 patients randomly assigned to one of these two conditions: treatment as usual (TAU) and TAU+app+web. All participants will receive the usual treatment for their pain. Only in the TAU+app+web group alarms will be generated by the Pain Monitor app in the face of previously established undesired events. Physicians will be able to monitor app reports using a web application, which might result in an adjustment of treatment. We anticipate that the use of Pain Monitor plus the therapist web will result in a reduction of pain intensity and side effects of the medication. Improvements on secondary outcomes, namely fatigue, mood, pain interference, rescue medication use, and quality of life, are also expected. Mixed repeated-measure MANOVAs will be conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition.

Ethics and dissemination: Ethical approval from the Hospital General Universitari de Castellon was obtained. The findings will be published in peer-reviewed journals.

Trial registration: NCT03606265. The trial is active and recruitment is ongoing.

Keywords: Chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring.

Strengths and limitations of this study

- To the best of our knowledge, this is the first randomized, controlled clinical trial to test the effectiveness of the implementation of an integrative technology-based solution for chronic pain that provides support to patients and physicians.
- The results obtained from this study may have important implications for the personalization of pain treatments and to enhance the effectiveness and safety of pain interventions.
- A study limitation is that physicians who participate in the investigation are not blinded to the participants' assigned condition since they need to respond to alarms generated by the app.
- An additional shortcoming is that the results will not necessarily be generalizable to all pain patients but only to those who met the eligibility criteria for the study. This excludes patients not using a smartphone with Internet connection (e.g., some older adults).

Introduction

Pain can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1] and can only be understood as an interplay between "sensory, emotional, cognitive, and social components" [2]. Although pain often is acute and disappears as tissues heal, sometimes pain persists for long periods of time and becomes chronic. For instance, it has been reported that 15% of individuals admitted to trauma hospitals due to a severe injury and up to 60% of patients after surgery will continue to experience severe

chronic pain months and years later [3]. In general, a cut-off of 3 to 6 months is used to define the transition from acute/subacute to chronic pain [4].

The aforementioned chronification of pain is becoming a major public health problem across the globe [5]. Specifically, epidemiological studies indicate that the prevalence of this disease in the adult population ranges from 19% to 38% worldwide [6–9]. Furthermore, the increase in life expectancy and the ageing of the population is likely to have an important impact on the number of individuals experiencing chronic pain, since the prevalence of this syndrome boosts dramatically with age [9]. For instance, it is expected that the population of chronic pain individuals will be doubled in 2050 for people older than 65 years and tripled for people over 80 years of age [10].

As a result of the growing concern about this disease, there have been numerous attempts to improve treatments for pain in the past decades. However, recent reviews on the effectiveness of numerous interventions, including medical treatments, psychological therapy, physical rehabilitation, or a combination of these indicate that the effectiveness of existing treatments is, on average, only modest [11–13]. While there might be numerous factors explaining the limited effectiveness of current interventions for pain, including unexplored biomechanical mechanisms or genetic factors, patient characteristics, or therapists' training, some authors have pointed to methodological shortcomings as key elements explaining the modest effectiveness of pain interventions. Specifically, the way assessment is currently performed (i.e., a single measure of pain intensity performed episodically during onsite appointments) has been argued to impact negatively in the ability of existing interventions to achieve more reliable and powerful changes in patient outcomes [14,15]. For instance, a single rate of pain intensity has been shown to be an unreliable measure of pain as this experience can vary dramatically within the same day and across days [16–18]. In addition, pain is frequently assessed retrospectively, which is known to lead to recall bias and to decrease the accuracy of pain ratings [19] and does not allow for timely

responses to undesired events, so these often take place time after the problem occurred [20].

As a consequence of the above, Ecological Momentary Assessment (EMA), which refers to the assessment of pain repeatedly and in real life, has received renewed interest in the past years in the pain literature and is now considered by many as the gold standard method to assess the pain experience [19,21–24]. Traditionally, EMA has been difficult due to the limitations and costs of repeated measurement procedures (i.e., paper diaries or phone calls). However, with the explosion and availability of smartphones, EMA has become easier than ever and immediate communication between the patient and the physician is now a more feasible practice [25].

It has been argued that this change in the assessment paradigm towards ecological daily telemonitoring using apps will improve treatment effectiveness and reduce costs if used to respond to patient reports quickly [14,26]. Indeed, there is evidence to suggest that smartphones are useful tools to be used for the assessment of pain core outcome measures in chronic pain settings [14,27,28]. However, the extent to which this EMA of pain patients can effectively lead to better practices in pain medicine is still unknown.

For this purpose, we developed a technology-based solution that integrated a pain and symptom tracking app for patients and a web for physicians where app-generated alarms are received daily and patient app responses can be monitored in real time. To the best of our knowledge, no study has yet investigated the utility of using such an integrative technology-based solution for remote, ecological monitoring of patient evolution and to adjust treatment in response to app alarms in a randomized controlled trial.

With the previous goal in mind, in the present parallel group, 1:1 superiority trial we will use the *Pain Monitor* app (https://play.google.com/store/apps/details?id=painmonitor.srccode), which was developed by a team of psychologists and an engineer with the collaboration of physicians and nurses and has been recently validated in clinical settings [14], together

with a web for the physicians where app responses and alarms can be tracked in real time to facilitate the professional's decision-making process. As we will explain in more detail in the Methods section, Pain Monitor assesses a number of pain-related outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of pain-related health resources) and the most frequent side effects of medical treatments for pain. In the study, patients will be randomly assigned to a treatment as usual condition (TAU) or to a TAU with the support of the patients' app and the physician's web. We anticipate that the use of the web application linked with the smartphone app (TAU+app+web condition) will improve the effectiveness of usual treatments resulting in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment. 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.

Method

Study design

The current investigation is a randomized superiority clinical trial composed of two parallel groups (1:1 allocation ration): a) TAU and b) TAU+app+web. In the study, participants in the TAU condition receive the usual pain treatment by the physicians working at the pain unit (i.e., pharmacological treatment or infiltration). Participants included in TAU+app+web group receive the usual treatment for their pain plus daily monitoring of their symptoms and pain experience with the Pain Monitor app during one month. In the TAU+app+web condition, alarms are generated in the presence of previously established undesired events, which have been previously determined by the physicians at the pain clinic. Physicians are able to monitor these patients' app reports using a web application created for this purpose (https://monitordolor.dolortic.com/). Thus, phone calls can be conducted in the

presence of alarms in order to change or discontinue the medical treatment when necessary. If the study results indicate that the use of technology leads to better outcomes, participants in the TAU condition will be informed about these findings and will the offered the possibility to use the app after study participation. In the TAU condition only, assessment is performed as usual, that is, using self-report measures administered onsite at the beginning and the end of the study (1 month later).

Neither the physicians nor the patients will be blind to the treatment condition assigned. Physicians will not be blind because they will receive alarms from the TAU+app+web participants only. Patients will not be blind because only those in the TAU+app+web condition will be using technology in addition to usual treatment and because patients in the TAU condition must know that there is no telemonitoring in their condition.

The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All items from the World Health Organization Trial Registration Data Set are showed in the Supplementary file 1. The recruitment started at the end of the same month. SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were followed to design the trial. The participant timeline (i.e., schedule of enrolment, interventions, and assessments) is shown in Figure 1. Recruitment is currently ongoing and is expected to end in November 2019.

Sample

Participants will be 250 consecutive chronic pain patients attending the pain clinic at the Hospital General Universitari de Castello (Spain) for the first time. Required sample size was calculated using *G**Power [29]. Although the a priori calculation resulted in 198 participants, the sample size was increased to 250 considering a dropout rate of 27-30% based on previous studies [30,31]. Thus, 125 participants were assigned to each condition. Randomization of participants was performed by an independent

researcher using a computer-generated sequence with *Randomizer* [32]. Inclusion criteria are shown in Table 1.

Table 1. Inclusion criteria

The patient is over 18 years of age
The patient has a mobile phone with Android operating system (the app is currently only available for Android, which is the operating system used by more than 80% of users in Spain) [33].
The patient has the physical ability to use the application
The patient does not present psychological and/or cognitive alterations or problems with language that make his/her participation difficult
The patient voluntarily wants to participate and signs the informed consent form

In the study, all participants are identified using an alphanumeric code. In the case of participants in the TAU+app+web condition, this code is automatically generated by the app. Thus, the database generated by the app is anonymized and the app only collects the international mobile equipment identity (IMEI). The association between app codes and patient identifiable characteristics is stored locally at the pain clinic. All data storage procedures follow the European law and data protection rules (European Union General Data Protection Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016). In addition, ethical approval from the Hospital General Universitari de Castello was obtained, in accordance with the Declaration of Helsinki. Important protocol modifications will be notified and require the approval of the Ethics Committee of the Hospital General Universitari de Castello. Approved changes will be made public at clinicaltrials.gov. All the participants read and sign an informed consent form before randomization (see Supplementary file 2). Patients who do not agree with the assigned condition, are given the opportunity to be allocated to the preferred

condition, but are not used in the analyses. Any changes to modify the assigned condition are accepted at any time during the study, again resulting in an exclusion from the study. Changes in the medication or improvement of disease are do not result in study discontinuation. Disease worsening is not expected to be associated with the inclusion of the app but, if existent, will result in the discontinuation of app use.

Procedure

The study is conducted at the pain clinic of the Hospital General Universitari de Castelló. The study is advertised by physicians to all consecutive patients attending the pain clinic for the first time. To ensure enrolment, physicians will emphasize the importance of active patient participation in research in general and in self-monitoring in particular. Patients interested in participating are directed to another office where the lead author, I.J., explains the study procedures in more detail and ensures their eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by explaining the utility of the study and by contacting patients when an alarm informing of low app adherence (i.e., more than three consecutive days without response) is received. All participants are provided with an information sheet and sign the informed consent. After participation acceptance, participants are assigned to one of the experimental conditions (TAU or TAU+app+web), which had been previously randomized by an external researcher. All participants then complete a paper-and-pencil assessment protocol in order to control for differences between the two assessment formats (app vs. pen and pencil) and to compare both conditions using the same assessment approach. In addition to this paper-and-pencil evaluation, patients in the TAU+app+web condition download and install the Pain Monitor app into their phones. Once they install the app, they answer to an initial assessment and then complete two measures daily (10 am and 7 pm) during one month (study duration). Finally, an end of study appointment is set (one month later) to conduct the post-

assessment evaluation. Due to difficulties in transportation or availability, the post-assessment intervention can either be completed onsite or via an on-line survey.

Pain monitor

The Pain Monitor app (Figure 2) has been developed by a group of pain psychologists and an engineer, with the collaboration of physicians and nurses specialized in pain care. Pain Monitor is composed of several pain-related items which are to be answered twice a day at preset times (10 am and 7 pm, with a two-hour flexibility) during 30 days. The app content has been previously validated with chronic pain patients at the pain unit of the Vall d'Hebron Hospital [14]. This assessment protocol contains sociodemographic items (i.e., age, sex, and education level, among others) which are evaluated on the first day of app use only, as well as a number of pain-related outcomes that are evaluated daily, which have been selected following recent guidelines on core outcome domains for pain treatments [34,35]. Constructs in the app, including pain intensity, pain interference, anxiety, depression, catastrophizing, social support, acceptance, and coping, among others, are measured with a single item to reduce the burden of daily assessment, each of which was adapted and validated against well-established paper-and-pencil measures [14]. Additionally, the assessment protocol includes a list of side effects created *ad hoc* based on the literature findings on the most frequent adverse effects of pain treatments [36,37], as well as measures of treatment adherence, use of rescue medication, neuropathic characteristics of pain, and use of medical services in the past month. All app items can be found in Supplementary file 3.

The app generates alarms in the presence of predefined events (see Supplementary file 4 for the alarms set in the present study in collaboration with the participating physicians). These alarms are sent to the physicians early in the morning on working days so that they can decide whether an action from their side is required (e.g., calling

the patient and setting an earlier appointment or suggesting a change in the medication). For this study, a website linked to the app was created for the physicians to observe patient alarms and evolution live. Examples of the physician web are presented in Figure 3.

Interventions

Five physicians at the pain clinic of the Hospital General Universitari de Castelló participate in this study. All patients in the study receive the usual treatment for their pain irrespective of their assigned condition. However, a change in treatment might occur in the TAU+app+web condition at the discretion of the physicians in charge of treatment after receiving an alarm and consulting the web page with the graphical representation of patient app responses. As usual, patients in the TAU condition without the app are not contacted by the physicians between appointments. It is important to note that both patients in the TAU only and patients in the TAU+app+web condition are allowed to attend to the emergency services or the family physician in the event of an emergency at any stage of the study due to ethical reasons. At the end of the study, this practice is investigated for each participant in the final assessment.

Assessment plan

All participants in the study fill in a number of questionnaires in a paper-and-pencil format at the beginning and at the end of the study. This assessment protocol includes sociodemographic information, use of pain-related health resources in the past week (i.e., emergency services, family physician, or pain clinic), pain-related physical symptoms experienced in the past week (i.e., side medication effects), the Brief Pain Inventory (pain severity and interference) [39], the Pain Catastrophizing Scale [40], and the Hospital Anxiety and Depression Scale [41]. In addition to this paper-and-pencil evaluation, participants in the TAU+app+web condition also install the Pain Monitor app and complete a pre-intervention assessment in the app after the paper-and-pencil

evaluation. Both baseline assessments include the same content and are duplicated to provide further evidence for the validity of app content. After this pretreatment evaluation, participants in the TAU+app+web group are asked to answer to the app assessments twice a day during one month (study duration). A push-up system notifies the patient about the need to respond to the app evaluation at 10:00 am and 7:00 pm. These times can be adjusted by the patient with a 2-hour flexibility from the preset times.

Daily morning and evening assessments differ in a number of items. Some items are asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g., activity level during the day, interference of pain on daily activities, or physical symptoms experienced during the day).

Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a post-assessment protocol. The measures included in this final evaluation are similar to the ones included in the baseline assessment, with the inclusion of a measure of negative events experienced during the study period and the evaluation of perceived change due to treatment.

In the study, primary outcomes are pain intensity and the number of side effects of the medication reported in the app, while secondary outcomes include mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Note that app reports in the TAU+app+web condition are not used to determine treatment effectiveness compared to the TAU only condition because in the latter condition participants do not use the app. Therefore, app responses are only used for telemonitoring and early detection of treatment problems that result in an alarm to the physicians. The comparison of both conditions will be made using the traditional paper-and-pencil evaluations which will be available for both groups.

Patient and public Involvement

In the current study, patients or the public will not be involved in the design, or conduct, or dissemination of the research.

Data analysis

The aim of the present study is to explore the effect of an integrated technology-based solution for chronic pain monitoring (an app that monitors pain patients daily and sends clinical alarms to physicians and a web for physicians that graphically represents patient evolution as reported in the app) compared to the usual treatment where monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim in mind, and intention-to-treat analyses will be performed following the recommendations of the CONSORT guidelines (http://www.consort-statement.org/). First, the two conditions will be compared at baseline in the different continuous measures with a between-group analysis via a *t*-test to ensure that randomization indeed resulted in comparable groups prior to intervention. Chi-squared tests will be used for all the categorical variables. To evaluate our hypothesis, mixed repeated-measure MANOVAs will be conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition (TAU or TAU+app+web). Distribution normality and homoscedasticity assumptions will be tested by means of Kolmogorov-Smirnov and and Levene tests, respectively, and a Mann-Whitney *U* test and Brown-Forsythe *F*-test will be used where necessary. Effect size will be calculated to complement the MANOVA results with the standardized mean difference (Cohen's *d*) for both between and within group analyses. This is a novel study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e. moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and number of side effects of the medication) when compared to secondary outcomes since medical interventions do not specifically focus on these symptoms (i.e., pain interference, mood, fatigue, rescue meditation use, and quality of life). The analysis will

be performed by CSR, who will be blinded to the treatment allocation. Only the present study authors will have access to the final trial dataset.

Regarding dropouts, we will choose a strict criterion and the analyses will only include participants who complete both the pre and the post assessments. Because of the short duration of the trial (one month per patient) and the minimal risks expected from the use of the app, a data monitoring committee will not be required.

Discussion

Chronic pain is a major public health challenge due to its high prevalence in the population and high direct and indirect costs for the institutions and the individuals [42, 43]. Pain assessment is a complex process characterized by a high variability between and within days, which is usually performed by clinicians using self-report, onsite, single ratings which are based on recall [39,40]. EMA using smartphone apps appears to be an innovative and promising alternative to these traditional assessment methods [46] as smartphone apps have demonstrated to be accurate tools to assess pain intensity and related variables from the patients' home, thus facilitating telemonitoring and contributing to the personalization of medical interventions by rapidly adjusting treatments to every individual as a result of telemonitoring [19].

In the present study protocol, we describe a randomized controlled trial designed to test an integrative technology-based solution for chronic pain monitoring consisting of a web application for the healthcare professional which is linked to the patient's app (i.e., Pain Monitor). Specifically, we want to explore whether the use of this integrative technology improves the effectiveness of the usual treatment for this population thanks to telemonitoring and the rapid detection of unwanted events. We expect that the use of Pain monitor, with the support of therapist's web, will result in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment due to the professional's rapid reaction in the presence of undesired outcomes.

To our knowledge, this is the first study to assess the effectiveness of this type of integrative technology solution (i.e., a therapist web site linked to a patient smartphone app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis is confirmed, our findings will serve to demonstrate the feasibility and utility of smartphones and specialized webs for therapists so that they can be implemented in specialized care contexts (i.e., pain clinics). Likewise, our results will provide important information about the potential benefits of smartphone apps for the personalization of pain treatments (i.e., treatment can be rapidly personalized to a given patient as a function of individual responses reported in the app). Ultimately, this might help change the model of care for this chronic disease (i.e., episodic, onsite assessment and treatment), since the use of this integrative technology system allows for a continuous and remote evaluation and intervention, providing a faster response to the patient needs and improving self-management and empowerment of patients who attend pain clinics as they become important agents of treatment effectiveness by being in charge of daily reporting of pain-related experiences in the app. In sum, the results of the present investigation could serve an important first step towards the implementation of apps and other Information and Communication Technologies in health services.

List of Abbreviations

TAU = Treatment as usual; EMA = Ecological Momentary Assessment; IMEI = International Mobile Equipment Identity; SPIRIT = Standard Protocol Items Recommendations for Interventional Trials; CONSORT = Consolidated Standards of Reporting Trials; MANOVA = Multivariate Analysis of Variance.

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Author Statement: All authors were strongly involved in the study conceptualization and design and have reviewed and discussed the manuscript. IJ and CSR prepared the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG. After changes were incorporated, a final version was approved by all authors. IJ and JLG are currently in charge of recruitment and IJ and CSR will be in charge of data analysis.

Funding: Funded by *Plan de Promoción de la investigación Universitat Jaume I*. Ref UJI-B2016-39 and a Predoctoral Grant (PREDOC/2017/26) by the Universitat Jaume I to IJ. The first grant allowed for the development of the technological systems used in the study (physician website and link to the app). The second grant serves to pay the salary of the lead researcher and predoctoral candidate, IJ.

Competing interests: The intellectual property of the Pain Monitor app is owned by co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any competing interests to declare as they do not receive any financial gain from these technologies.

Ethics approval and consent to participate: Ethical approval from the Hospital General Universitari de Castelló was obtained, in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study. The informed consent form was approved by the ethics committee of the Hospital General Universitari de Castelló.

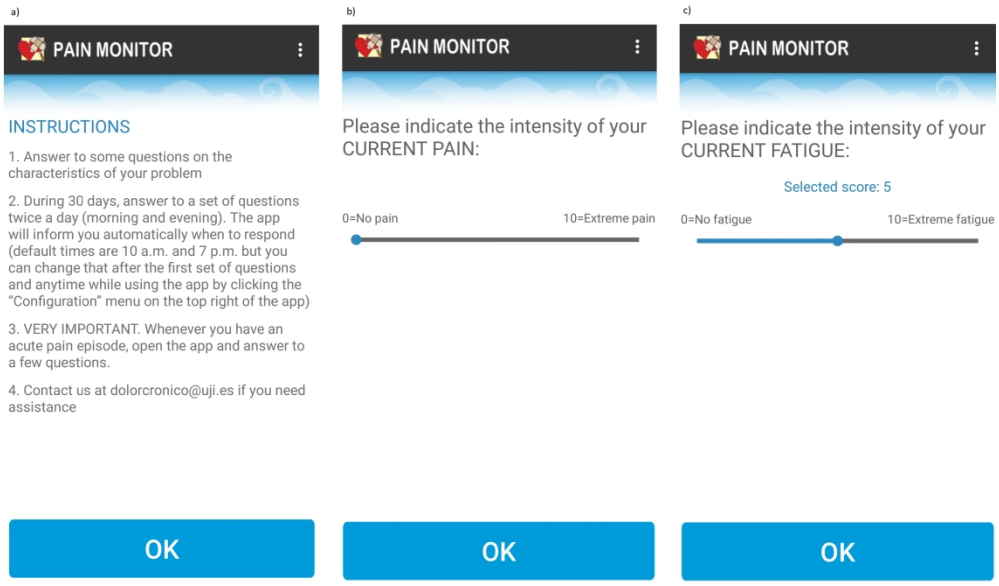
FIGURES

Figure 1. Study schedule of enrolment, interventions, and assessments.

Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

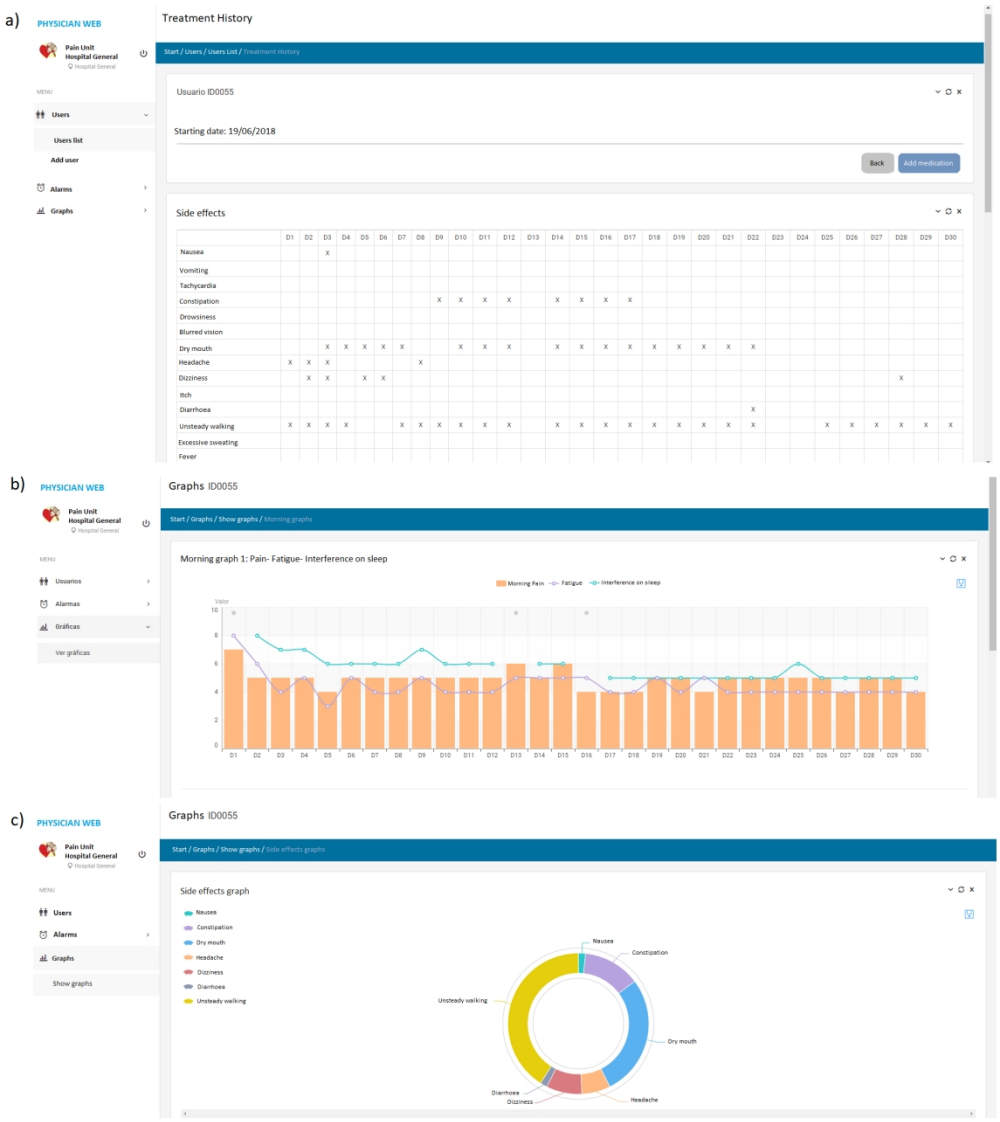
Figure 3. Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

	STUDY PERIOD		
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**0**	**T_1**	**T_2**
	Pre-Intervention	*Between assessments*	*One month follow-up*
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
Allocation	X		
INTERVENTIONS:			
Medical treatment		X	
App use		App condition only	
ASSESSMENTS:			
Demographics	X		X
Primary outcomes			
Pain intensity	X	App condition only	X
Physical symptoms	X	App condition only	X
Secondary outcomes			
Pain interference	X	App condition only	X
Mood	X	App condition only	X
Fatigue	X	App condition only	X
Rescue medication	X	App condition only	X
Quality of life	X	App condition only	X



a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

289x168mm (300 x 300 DPI)



Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

168x189mm (300 x 300 DPI)

Supplement 1. WHO registration dataset

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03606265
Date of registration in primary registry	July 30, 2018
Secondary identifying numbers	UJI-B2016-39,
Source(s) of monetary of material support	Universitat Jaume I
Primary sponsor	Universitat Jaume I
Secondary sponsor(s)	None
Contact for public queries	+34 964387640 azucena@uji.es
Contact for scientific queries	+34 964387649 ijaen@uji.es
Public title	Utility od a Web-based App for Chronic Pain
Scientific title	Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial
Countries of recruitment	Spain
Health condition(s) or problem(s) studied	Chronic pain
Intervention(s)	Device: Treatment as usual+App+Web Device: Treatment as usual
Key inclusion and exclusion criteria	Inclusion Criteria: The patient is over 18 years of age The patient has a mobile phone with Android operating system The patient has the physical ability to use the application The patient does not present psychological and / or cognitive alterations or problems with language that make their participation difficult The patient voluntarily wants to participate and signs the informed consent Exclusion Criteria: The patient is under 18 years The patient does not have a mobile phone or has a mobile phone in which Android is not the operating system (the app is currently only available for Android for economic reasons) The patient does not have the physical capacity to use the application The patient does not have the capacity to participate due to psychological and / or cognitive alterations or problems with language

	The patient does not want to participate
Study type	Interventional
Date of first enrolment	August, 2018
Target sample size	250
Recruitment status	Ongoing
Primary outcome(s)	Changes in pain intensity and side effects
Key secondary outcomes	Changes in pain-related variables as mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Supplement 2: Study information sheet and informed consent

INFORMATION ABOUT THE STUDY

You have shown your interest in participating in a scientific study of Universitat Jaume I and the Hospital General de Castellón. Your participation in the study is completely voluntary. You will then be asked to provide us with your written consent to participate in this study. There will be no inconvenience if you do not wish to participate and your decision will in no way affect the treatment received at the Hospital General de Castellón. In addition, you may discontinue your participation at any time. Please, read the following text carefully and do not hesitate to ask any questions.

Why is this study being carried out?

This study is part of a project called "DOLOR-TIC. Development and validation of an eHealth network for chronic pain" (REF: UJI-B2016-39) funded by the Plan de Promoción de la investigacion Universitat Jaume I. The general objective of this project is to explore the benefits of using a network of technologies for the evaluation and treatment of chronic pain. The treatment by means of new technologies will be compared with the usual treatment provided in the pain unit of the Hospital General de Castellón.

What will be the procedure implemented in the study?

In the first sessions we will examine your state of health and check whether it meets the criteria for inclusion in the study. If you meet the established inclusion criteria, you will then be assigned to one of two study conditions: a) Habitual Treatment (TAU) or b) TAU supported by new technologies (TAU+ICTs). You will receive this treatment for 1 months and your clinical status will be evaluated before starting treatment, at the end of treatment (1 month). If, in fact, the treatments supported by the new technologies prove to be more effective than the usual treatment, you will be offered the possibility of benefiting from the treatment of new technologies at the end of the study, whether you were initially assigned to the TAU condition or to the TAU+TICs condition.

Are there any risks associated with my participation?

According to existing knowledge, the evaluation and treatment protocol used in this study does not pose risks to participants.

What are the possible benefits of my participation?

The treatment protocols included in this study are designed to improve your health. Your participation in this study will contribute to improving the health of a large number of citizens of the Spanish state. In addition, if the objectives of the study are achieved, the results will lead to a significant reduction in treatment costs and a

reduction in the increase in access to health services for a large number of people who do not have access to health services suffer from mental disorders.

How will my data be treated?

All data relevant to the study will be collected and stored in compliance with data protection regulations in force. These data will only be used anonymously for the purpose of scientific analysis. All persons involved in the study have an obligation to comply with data protection laws. We will make sure that all your information - without restrictions - is treated as in a confidential manner. Any data collected will be deleted as soon as it is not necessary for scientific purposes.

Can I decline or suspend my participation?

Yes, you may refuse to participate in this study or terminate your participation at any time. In the event that you decide to discontinue your participation in the study all of your data will be destroyed immediately.

Who is the researcher responsible for the study?

Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail: azucena@uji.es

You may contact the principal investigator if you have any questions, concerns about the study, about the data being collected, or if you wish to make use of your right to suspend your participation.

INFORMED CONSENT

Study DOLOR-TIC. Development and validation of an eHealth network for chronic pain. REF: UJI-B2016-39.

I (first name and last name) _____

- I have read the information sheet given to me.
- I was able to ask questions about the study.
- I have received enough information about the study.

I've been talking to: _____ (name of researcher).

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. When I want to
2. Without having to give explanations
3. Without this affecting my medical care

I freely give my consent to participate in the study.

Date: …/ … /…

Participant's signature:

Date: …/ … /…

Researcher's signature:

Revocation of consent:

I revoke the consent given on ..../..../..... and I do not wish to continue in the study that I give on this date for finished.

Signature of participant:

Signature of investigator:

Supplement 3: Items in the Pain Monitor app

Items assessed once, the first day of app use:

1. Please indicate your date of birth (DD/MM/YYYY)

2. Please indicate your gender:
   a. Male
   b. Female

3. Please indicate your type of pain. You may select more than one option:
   a. Fibromyalgia
   b. Low back pain
   c. Cervical pain
   d. Rheumatoid arthritis
   e. Osteoarthritis; Headache
   f. Neuropathic pain
   g. Cancer pain
   h. None of the above

4. If you selected "None of the above" please indicate your type of pain. Otherwise, leave this question blank. Press OK to continue.

5. Please indicate the location where your pain is more intense:
   a. Head
   b. Shoulder
   c. Neck
   d. High back
   e. Lower back
   f. Arm
   g. Elbow
   h. Wrist
   i. Hand
   j. Abdomen
   k. Chest
   l. Buttock
   m. Hip
   n. Leg
   o. Knee
   p. Foot
   q. Whole body
   r. Somewhere not listed

6. Who is currently treating your pain? You may select more than one option:
   a. General practitioner
   b. Rheumatologist
   c. Orthopedic specialist
   d. Rehabilitation physician
   e. Psychiatrist
   f. Pain Unit

g. Neurosurgeon
h. Neurologist
i. Oncologist
j. Another professional.

7. When did your current pain start?
   a. Less than one year ago
   b. Between 1 and 5 years ago
   c. Between 5 and 10 years ago
   d. More than 10 years ago

8. What is your current treatment for pain? You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. My pain is not being treated

9. Did you start a new treatment for pain in the last month?
   a. Yes
   b. No

10. Please select the treatment/s you started in the last month. You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. I have not started a new treatment

11. What is your marital status?
   a. Single
   b. Married
   c. In a relationship
   d. Divorced
   e. Separated
   f. Widowed

12. What is your job status?
   a. Active worker
   b. Sick leave
   c. Permanent disability
   d. Unemployed
   e. Homemaker
   f. Retired
   g. Student

13. What is the highest level of education you have completed?

a. No studies
b. Less than high school
c. High school graduate
d. Technical training
e. University degree

14. Do you currently have a diagnosis of depression by a physician or a psychologist?
    a. Yes
    b. No

15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
    a. Yes
    b. No

Items assessed twice a day and in the event of acute pain episodes:

16. Please indicate the intensity of your CURRENT PAIN:
    0 No pain ---------10 Extreme pain

17. Please indicate the intensity of your CURRENT FATIGUE:
    0 No fatigue ---------10 Extreme fatigue

18. Please indicate the intensity of your CURRENT HAPPINESS:
    0 No happiness -------10 Extremely happy

19. Please indicate the intensity of your CURRENT SADNESS:
    0 No sadness -------- 10 Extremely sad

20. Please indicate the intensity of your CURRENT ANXIETY:
    0 No anxiety ------- 10 Extremely anxious

21. Please indicate the intensity of your CURRENT ANGER:
    0 No anger ------- 10 Extremely angry

22. Does your pain have any of these characteristics? You may select more than one option:
    a. Burning
    b. Painful cold
    c. Electric shocks
    d. Tingling
    e. Pins and needles
    f. Numbness
    g. Itching
    h. Reduced sensitivity to touch

i. Pain when brushing against the skin
j. None of the above

Items assessed in the morning:

23. In general, your HEALTH is:
    1) Very poor
    2) Poor
    3) Average
    4) Good
    5) Very good

24. Did your PAIN interfere with the quality of your SLEEP LAST NIGHT?
    0 No interference ------- 10 Maximum interference

25. Indicate your degree of agreement with the following sentence: With my current pain, I should not do my usual job (it includes housework and work outside the home).
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

26. Indicate your degree of agreement with the following sentence: Experiencing pain is terrible and I feel that pain is stronger than me.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

27. Indicate your degree of agreement with the following sentence: I need some control over pain before I can make serious plans.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

28. Indicate your degree of agreement with the following sentence: Physical activity aggravates my pain.
    1) Strongly disagree

2) Disagree
3) Neither agree nor disagree
4) Agree
5) Strongly agree

29. Indicate your degree of agreement with the following sentence: I am living a rewarding life despite my pain.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

Items assessed in the evening:

30. Did your PAIN interfere with your ability to perform your USUAL WORK or HOUSEWORK TODAY?
    0 No interference ------- 10 Maximum interference

31. Did your PAIN interfere with your LEISURE ACTIVITIES TODAY?
    0 No interference ------- 10 Maximum interference

32. Did your PAIN interfere with your SOCIAL INTERACTIONS TODAY?
    0 No interference ------- 10 Maximum interference

33. Which STRATEGY did you use to COPE WITH YOUR PAIN TODAY? You may select more than one option:
    a. Inactivity / rest
    b. Relaxation exercise
    c. Speak with someone
    d. Physical Activity / Stretching
    e. Self-statements to persist in a task
    f. Do something to feel positive emotions
    g. Ignore the pain/distract
    h. Pray for the pain to disappear

34. Indicate your degree of agreement with the following sentence: I fear that the pain will get worse.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

35. Indicate your degree of agreement with the following sentence: Today I could not keep my pain out of my mind.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

36. Please rate your degree of activity TODAY:
0%= Completely inactive -100%= Completely active.

37. In which area have you been more active today? You may select more than one option:
    a. Work
    b. Family
    c. Couple
    d. Friends
    e. Leisure
    f. Physical activity
    g. Other.

38. Did you take a rescue medication TODAY (i.e., medication you only use in the event of acute pain)?
    a. Yes
    b. No

39. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Nausea
    b. Vomiting
    c. Tachycardia
    d. Constipation
    e. Drowsiness / sedation
    f. Blurred vision
    g. Dry mouth
    h. Headache
    i. None of the above

40. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Dizziness
    b. Itching
    c. Diarrhea
    d. Gait instability

e. Excessive sweating
f. Fever
g. Urine retention
h. Facial redness
i. A different symptom
j. None of the above

41. Did you take your prescribed medication TODAY?
a. Yes
b. No, but I will do it later
c. No and I do not plan to take it
d. I haven't been prescribed a pain medication

42. How many times did you take a rescue medication TODAY?
a. 0
b. 1
c. 2
d. 3
e. 4
f. 5
g. 6
h. 7
i. 8
j. 9
k. 10
l. More than 10

Items assessed the last day of app use:

43. With respect to the beginning of treatment, how are you feeling NOW?
1) Much worse
2) Somewhat worse
3) The same
4) Somewhat better
5) Much better

44. Have you experienced any negative life event in the PAST MONTH?
a. No
b. Yes, but it did not affect me at all
c. Yes, but it did not affect me much
d. Yes and it had quite an effect on me
e. Yes and it affected me a lot

45. If you experienced a major negative life event in the last month, please indicate its characteristics using the list below. You may select more than one option:
    a. Death of a close person
    b. Job problem
    c. Relationship problem
    d. Economic problem
    e. Health problem
    f. Family problem
    g. An event not listed above
    h. I have not experienced any major negative event this month

46. Please indicate the location where your pain is more intense:
    a. Head
    b. Shoulder
    c. Neck
    d. High back
    e. Lower back
    f. Arm
    g. Elbow
    h. Wrist
    i. Hand
    j. Abdomen
    k. Chest
    l. Buttock
    m. Hip
    n. Leg
    o. Knee
    p. Foot
    q. Whole body
    r. Somewhere not listed

47. What is your current treatment for pain? You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment
    e. Natural / alternative treatments
    f. My pain is not being treated

48. Did you start a new treatment for pain in the last month?
    a. Yes
    b. No

49. Please select the treatment/s you started in the last month. You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment

e. Natural / alternative treatments
f. I have not started a new treatment

50. What is your marital status?
a. Single
b. Married
c. In a relationship
d. Divorced
e. Separated
f. Widowed

51. What is your job status?
a. Active worker
b. Sick leave
c. Permanent disability
d. Unemployed
e. Homemaker
f. Retired
g. Student

52. Do you currently have a diagnosis of depression by a physician or a psychologist?
a. Yes
b. No

53. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
a. Yes
b. No

Supplement 4: Alarms integrated into the Pain Monitor app

- Morning pain severity > 7 during 5 consecutive days
- Evening pain severity > 7 during 5 consecutive days
- Morning sadness >7 during 5 consecutive days
- Evening sadness >7 during 5 consecutive days
- Morning anxiety >7 during 5 consecutive days
- Evening anxiety >7 during 5 consecutive days
- Vomiting during 2 consecutive days
- Tachycardia during 2 consecutive days
- Blurred vision during 2 consecutive days
- Headache during 2 consecutive days
- Dry mouth during 2 consecutive days
- Constipation during 5 consecutive days
- Drowsiness during 5 consecutive days
- Nausea during 3 consecutive days
- Itching during 3 consecutive days
- Diarrhea during 2 consecutive days
- Fever during 2 consecutive days
- Facial redness during 2 consecutive days
- Urine retention during 2 consecutive days
- Gait instability during 3 consecutive days
- Excessive sweating during 7 consecutive days
- Dizziness during 3 consecutive days
- Treatment discontinuation during 3 consecutive days
- Rescue medication > 3 during 3 consecutive days
- Sleep interference > 7 during 5 consecutive days

Additional file 2: SPIRIT Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, page 1
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 1
Protocol version	3	Date and version identifier	Protocol Amendment Number, page 1
Funding	4	Sources and types of financial, material, and other support	Declarations, page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Authors, page 1
	5b	Name and contact information for the trial sponsor	Trial sponsor, page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, page 14

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, Page 12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, page 1-3
	6b	Explanation for choice of comparators	Method, page 6
Objectives	7	Specific objectives or hypotheses	Introduction, page 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction, page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Sample, page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Interventions and Assessment plan, page 8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Sample, page 7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Assessment plan, page 10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample, page 6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Sample, page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Sample, page 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 6 and 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Pages 6 and 13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Assessment plan, page 10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Procedure, page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Sample, page 7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Data analysis, page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Data analysys, page 12-13

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, Page 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Data analysis, page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Sample, page 8

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Sample, page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Sample, page 7-8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data analysis, page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Sample, page 8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Study design, page 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Availability of data and material, page 15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial

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Title: Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial

Running Head: Telemonitoring of pain by Pain Monitor App

Authors: Irene Jaén[1,a], Carlos Suso-Ribera[1], Diana Castilla[2,3], Irene Zaragoza[3], Azucena García-Palacios[1,3] and José Luis Gómez Palonés[4]

[1] Universitat Jaume I, Castelló 12007, Spain

[2] Universidad de Zaragoza, Teruel 44003, Spain

[3] CIBER of Physiopathology of Obesity and Nutrition CIBERobn, CB06/03 Instituto de Salud Carlos III, Spain

[4] Hospital General Universitari de Castelló, 12004, Spain

[a] Corresponding author. Universitat Jaume I. Facultad de Ciencias de la Salud. Departamento de Psicología Básica, Clínica y Psicobiología. Avda. Vicente Sos Baynat s/n. Castellón de la Plana E-12071 Spain

ijaen@uji.es

Trial Sponsor: Universitat Jaume I.: Avda. Vicente Sos Baynat, s/n Castellón de la Plana E-12071 Spain; **Telephone:** +34 964 38 74 80; e-mail: ocit@uji.es

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Abstract

Introduction: Chronic pain has become a matter of public health concern due to its high prevalence and because public costs associated with treatment and disability increase each year. Research suggests that limitations in the traditional assessment of chronic pain patients limit the effectiveness of current medical treatments. The use of technology might serve change patient traditional monitoring into Ecological Momentary Assessments, which might be visualized by physicians live. This study describes a Randomized Control Trial designed 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. The goal of this study will be to explore whether this combination of eHealth and mHealth improves the effectiveness of existing pain treatments.

*Methods and analysis***:** Participants will be 250 patients randomly assigned to one of these two conditions: treatment as usual (TAU) and TAU+app+web. All participants will receive the usual treatment for their pain. Only the TAU+app+web group use Pain Monitor app, which generates alarms that are sent to the physicians in the face of previously-established undesired events. Physicians will be able to monitor app reports using a web application, which might result in an adjustment of treatment. We anticipate that the use of Pain Monitor plus the therapist web will result in a reduction of pain intensity and side effects of the medication. Improvements on secondary outcomes, namely fatigue, mood, pain interference, rescue medication use, and quality of life, are also expected. Mixed repeated-measure MANOVAs will be conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition.

Ethics and dissemination: Ethical approval from the Hospital General Universitari de Castellon was obtained. The findings will be published in peer-reviewed journals.

Trial registration: NCT03606265. The trial is active. Recruitment is ongoing.

Keywords: Chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring.

Strengths and limitations of this study

- To the best of our knowledge, this is the first randomized, controlled clinical trial to test the effectiveness of implementing an integrative e-health and m-health solution for chronic pain that provides support to patients and physicians.
- Contrary to traditional face-to-face monitoring, patient monitoring in this study becomes ecological and momentary, so that patients can report their evolution at home whenever they want.
- Patient responses to the App are used to generate alarms in the presence of unwanted clinical events, such as the onset of side treatment effects or a poor response to treatment.
- Physicians can track patient evolution at any time on a website and receive clinical alarms daily, so that rapid responses can be offered.
- Study limitations include the fact that physicians who participate in the investigation are not blinded to the participants' assigned condition, since they need to respond to alarms generated by the app, and the fact that the assessment protocol in the App includes more variables than those actually used for the study because the protocol in the App could not be flexibly changed when the study began.

Introduction

Pain can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1) and can only be understood as an interplay between "sensory, emotional, cognitive, and social components" (2). Although pain often is acute and disappears as tissues heal, sometimes pain persists for long periods of time and becomes chronic. For instance, it

has been reported that 15% of individuals admitted to trauma hospitals due to a severe injury and 15- 60% of patients after surgery will continue to experience chronic pain months and years later (3). In general, a cut-off of 3 to 6 months is used to define the transition from acute/subacute to chronic pain (4).

The aforementioned chronification of pain is becoming a major public health problem across the globe (5). 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 (6). Specifically, epidemiological studies indicate that the prevalence of this disease in the adult population ranges from 19% to 38% worldwide (7–10). Furthermore, the increase in life expectancy and the ageing of the population is likely to have an important impact on the number of individuals experiencing chronic pain, since the prevalence of this syndrome boosts dramatically with age (11). For instance, it is expected that the population of chronic pain individuals will be doubled in 2050 for people older than 65 years and tripled for people over 80 years of age (12). Thus, chronic pain is a major public health challenge due to its high prevalence in the population and high direct and indirect costs for the institutions and the individuals (13,14).

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 (15,16) Not surprisingly, as a result of the growing concern about this disease, there have been numerous attempts to improve treatments for pain in the past decades. However, recent reviews on the effectiveness of numerous interventions, including medical treatments, psychological therapy, physical rehabilitation, or a combination of these indicate that the effectiveness of existing treatments is, on average, only modest (17–19). While there might be numerous factors explaining the limited effectiveness of current interventions for pain, including unexplored biomechanical mechanisms or genetic factors, patient characteristics, or therapists' training, some authors have

pointed to methodological shortcomings as key elements explaining the modest effectiveness of pain interventions. Specifically, the way assessment is currently performed (i.e., a single measure of pain intensity performed episodically during onsite appointments) has been argued to impact negatively in the ability of existing interventions to achieve more reliable and powerful changes in patient outcomes (20,21). For instance, a single rate of pain intensity has been shown to be an unreliable measure of pain as this experience can vary dramatically within the same day and across days (22–24). In addition, pain is frequently assessed retrospectively, which is known to lead to recall bias and to decrease the accuracy of pain ratings (25) and does not allow for timely responses to undesired events, so these often take place time after the problem occurred (21).

As a consequence of the above, Ecological Momentary Assessment (EMA), which refers to the assessment of pain repeatedly and in real life, has received renewed interest in the past years in the pain literature and is now considered by many as the gold standard method to assess the pain experience (26–29). Traditionally, EMA has been difficult due to the limitations and costs of repeated measurement procedures (i.e., paper diaries or phone calls). However, with the explosion and availability of smartphones, EMA has become easier than ever and immediate communication between the patient and the physician is now a more feasible practice (30).

It has been argued that this change in the assessment paradigm towards ecological daily telemonitoring using apps will improve treatment effectiveness and reduce costs if used to respond to patient reports quickly (21,31). Indeed, there is evidence to suggest that smartphones are useful tools to be used for the assessment of pain core outcome measures in chronic pain settings (21,32,33). However, the extent to which this EMA of pain patients can effectively lead to better practices in pain medicine is still unknown.

For this purpose, we developed a technology-based solution that integrated a pain and symptom tracking app for patients and a web for physicians where app-generated alarms are received daily and patient app responses can be monitored in real time. To

the best of our knowledge, no study has yet investigated the utility of using such an integrative technology-based solution for remote, ecological monitoring of patient evolution and to adjust treatment in response to app alarms in a randomized controlled trial.

With the previous goal in mind, in the present parallel group, superiority trial we will use the *Pain Monitor* app (https://play.google.com/store/apps/details?id=painmonitor.srccode), which was developed by a team of psychologists and an engineer with the collaboration of physicians and nurses and has been recently validated in clinical settings (21), together with a web for the physicians where app responses and alarms can be tracked in real time to facilitate the professional's decision-making process. As we will explain in more detail in the Methods section, Pain Monitor assesses a number of pain-related outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of pain-related health resources) and the most frequent side effects of medical treatments for pain. In the study, patients will be randomly assigned to a treatment as usual condition (TAU) or to a TAU with the support of the patients' app and the physician's web. We anticipate that the use of the web application linked with the smartphone app (TAU+app+web condition) will improve the effectiveness of usual treatments resulting in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment. 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 (34). We also expect that the rapid detection of treatment undesired events will rapidly minimize threats to the patient's quality of life and mood.

Method

Study design

The current investigation is a randomized superiority clinical trial composed of two parallel groups (1:1 allocation ratio): a) TAU and b) TAU+app+web. In the study, participants in the TAU condition receive the usual pain treatment by the physicians working at the pain unit (i.e., pharmacological treatment or infiltration). Participants included in TAU+app+web group receive the usual treatment for their pain plus daily monitoring of their symptoms and pain experience with the Pain Monitor app during one month. In the TAU+app+web condition, alarms are generated in the presence of previously established undesired events, which have been previously determined by the physicians at the pain clinic (e.g., pain intensity is higher than 7 in an 11-point numerical scale during 3 consecutive days). Physicians are able to monitor these patients' app reports using a web application created for this purpose (https://monitordolor.dolortic.com/). Thus, phone calls can be conducted in the presence of alarms in order to change or discontinue the medical treatment when necessary. If the study results indicate that the use of technology leads to better outcomes, participants in the TAU condition will be informed about these findings and will be offered the possibility to use the app after study participation. In the TAU condition only, assessment is performed as usual, that is, using self-report measures administered onsite at the beginning and the end of the study (1 month later). Neither the physicians nor the patients will be blind to the treatment condition assigned. Physicians will not be blind because they will receive alarms from the TAU+app+web participants only. Patients will not be blind because only those in the TAU+app+web condition will be using technology in addition to usual treatment and because patients in the TAU condition must know that there is no telemonitoring in their condition.

The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All items from the World Health Organization Trial Registration Data Set are showed in the Supplementary file 1. The recruitment started at the end of the same month. SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were followed to design the trial. The participant timeline (i.e., schedule of enrolment,

interventions, and assessments) is shown in Figure 1. Recruitment is currently ongoing and is expected to end in November 2019.

Sample

Participants will be 250 consecutive chronic pain patients attending the pain clinic at the Hospital General Universitari de Castello (Spain) for the first time. Required sample size was calculated using *G**Power (35). Although the a priori calculation resulted in 198 participants, the sample size was increased to 250 considering a dropout rate of 27-30% based on previous studies (36,37). Thus, 125 participants were assigned to each condition. Randomization of participants was performed by an independent researcher using a computer-generated sequence with *Randomizer* (38). Inclusion criteria are shown in Table 1. 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.

Table 1. Inclusion criteria

The patient is over 18 years of age
The patient has a mobile phone with Android operating system (the app is currently only available for Android, which is the operating system used by more than 80% of users in Spain) (39).
The patient has the physical ability to use the application
A new treatment plan is started during the first week after study onset
The patient does not present psychological and/or cognitive alterations or problems with language that make his/her participation difficult

The patient voluntarily wants to participate and signs the informed consent form

In the study, all participants are identified using an alphanumeric code. In the case of participants in the TAU+app+web condition, this code is automatically generated by the app. Thus, the database generated by the app is anonymized and the app only collects the international mobile equipment identity (IMEI). The association between app codes and patient identifiable characteristics is stored locally at the pain clinic. All data storage procedures follow the European law and data protection rules (European Union General Data Protection Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016). In addition, ethical approval from the Hospital General Universitari de Castello was obtained, in accordance with the Declaration of Helsinki. Important protocol modifications will be notified and require the approval of the Ethics Committee of the Hospital General Universitari de Castello. Approved changes will be made public at clinicaltrials.gov. All the participants read and sign an informed consent form before randomization (see Supplementary file 2). Patients who do not agree with the assigned condition, are given the opportunity to be allocated to the preferred condition, but are not used in the analyses. Any changes to modify the assigned condition are accepted at any time during the study, again resulting in an exclusion from the study. Changes in the medication or improvement of disease do not result in study discontinuation. Disease worsening is not expected to be associated with the inclusion of the app but, if existent, will result in the discontinuation of app use.

Procedure

The study is conducted at the pain clinic of the Hospital General Universitari de Castelló. The study is advertised by physicians to all consecutive patients attending the pain clinic for the first time. To ensure enrolment, physicians will emphasize the importance of active patient participation in research in general and in self-monitoring

in particular. Patients interested in participating are directed to another office where the lead author, I.J., explains the study procedures in more detail and ensures their eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by explaining the utility of the study and by contacting patients when an alarm informing of low app adherence (i.e., more than three consecutive days without response) is received. All participants are provided with an information sheet and sign the informed consent. After participation acceptance, participants are assigned to one of the experimental conditions (TAU or TAU+app+web), which had been previously randomized by an external researcher. All participants then complete a paper-and-pencil assessment protocol in order to control for differences between the two assessment formats (app vs. pen and pencil) and to compare both conditions using the same assessment approach. In addition to this paper-and-pencil evaluation, patients in the TAU+app+web condition download and install the Pain Monitor app into their phones. Once they install the app, they answer to an initial assessment and then complete two measures daily (10 am and 7 pm) during one month (study duration). Finally, an end of study appointment is set (one month later) to conduct the post-assessment evaluation. Due to difficulties in transportation or availability, the post-assessment intervention can either be completed onsite or via an on-line survey.

Pain monitor

The Pain Monitor app (Figure 2) has been developed by a group of pain psychologists and an engineer, with the collaboration of physicians and nurses specialized in pain care. Pain Monitor is composed of several pain-related items which are to be answered twice a day at preset times (10 am and 7 pm, with a two-hour flexibility) during 30 days. The app content has been previously validated with chronic pain patients at the pain unit of the Vall d'Hebron Hospital (21). This assessment protocol contains sociodemographic items (i.e., age, sex, and education level, among others) which are evaluated on the first day of app use only, as well as a number of pain-related

outcomes that are evaluated daily, which have been selected following recent guidelines on core outcome domains for pain treatments (40,41). Constructs in the app, including pain intensity, pain interference, anxiety, depression, catastrophizing, social support, acceptance, and coping, among others, are measured with a single item to reduce the burden of daily assessment, each of which was adapted and validated against well-established paper-and-pencil measures (21). Additionally, the assessment protocol includes a list of side effects created *ad hoc* based on the literature findings on the most frequent adverse effects of pain treatments (42,43), as well as measures of treatment adherence, use of rescue medication, neuropathic characteristics of pain, and use of medical services in the past month. All app items can be found in Supplementary file 3.

The app generates alarms in the presence of predefined events (see Supplementary file 4 for the alarms set in the present study in collaboration with the participating physicians). These alarms are sent to the physicians early in the morning on working days so that they can decide whether an action from their side is required (e.g., calling the patient and setting an earlier appointment or suggesting a change in the medication). For this study, a website linked to the app was created for the physicians to observe patient alarms and evolution live. Examples of the physician web are presented in Figure 3. Physicians are only asked to check the website when an alarm happens, but they are allowed to check any patient status at any time.

Interventions

Five physicians at the pain clinic of the Hospital General Universitari de Castelló participate in this study. All patients in the study receive the usual treatment for their pain irrespective of their assigned condition. However, a change in treatment might occur in the TAU+app+web condition at the discretion of the physicians in charge of treatment after receiving an alarm and consulting the web page with the graphical

representation of patient app responses. As usual, patients in the TAU condition without the app are not contacted by the physicians between appointments. It is important to note that both patients in the TAU only and patients in the TAU+app+web condition are allowed to attend to the emergency services or the family physician in the event of an emergency at any stage of the study due to ethical reasons. At the end of the study, this practice is investigated for each participant in the final assessment.

Assessment plan

All participants in the study fill in a number of questionnaires in a paper-and-pencil format at the beginning and at the end of the study. This assessment protocol includes sociodemographic information, sickness work absence during the past month, use of pain-related health resources in the past month (i.e., emergency services, family physician, or pain clinic), pain-related physical symptoms experienced in the past week (i.e., side medication effects), the Brief Pain Inventory (pain severity and interference) (44), the Pain Catastrophizing Scale (45), and the Hospital Anxiety and Depression Scale (46). In addition to this paper-and-pencil evaluation, participants in the TAU+app+web condition also install the Pain Monitor app and complete a pre-intervention assessment in the app after the paper-and-pencil evaluation. Both baseline assessments include the same content and are duplicated to provide further evidence for the validity of app content. After this pretreatment evaluation, participants in the TAU+app+web group are asked to answer to the app assessments twice a day during one month (study duration). A push-up system notifies the patient about the need to respond to the app evaluation at 10:00 am and 7:00 pm. These times can be adjusted by the patient with a 2-hour flexibility from the preset times.

Daily morning and evening assessments differ in a number of items. Some items are asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g.,

activity level during the day, interference of pain on daily activities, or physical symptoms experienced during the day).

Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a post-assessment protocol. The measures included in this final evaluation are similar to the ones included in the baseline assessment, with the inclusion of a measure of negative events experienced during the study period and the evaluation of perceived change due to treatment.

In the study, primary outcomes are pain intensity and the number of side effects of the medication reported in the app, while secondary outcomes include mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Note that app reports in the TAU+app+web condition are not used to determine treatment effectiveness compared to the TAU only condition because in the latter condition participants do not use the app. Therefore, app responses are only used for telemonitoring and early detection of treatment problems that result in an alarm to the physicians. The comparison of both conditions will be made using the traditional paper-and-pencil evaluations which will be available for both groups. Additionally, the number of alarms and the physician's responses to such alarms (e.g., change in treatment strategies) will be registered. This information will be used to get better insight into the utility of the integrated technology to improve treatment efficacy.

Patient and public Involvement

In the current study, patients or the public will not be involved in the design, or conduct, or dissemination of the research.

Data analysis

The aim of the present study is to explore the effect of an integrated technology-based solution for chronic pain monitoring (an app that monitors pain patients daily and sends

clinical alarms to physicians and a web for physicians that graphically represents patient evolution as reported in the app) compared to the usual treatment where monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim in mind, and completer analyses will be performed following the recommendations of the CONSORT guidelines (http://www.consort-statement.org/). First, the two conditions will be compared at baseline in the different continuous measures with a between-group analysis via a *t*-test to ensure that randomization indeed resulted in comparable groups prior to intervention. Chi-squared tests will be used for all the categorical variables. To evaluate our hypothesis, mixed repeated-measure MANOVAs will be conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition (TAU or TAU+app+web). Distribution normality and homoscedasticity assumptions will be tested by means of Kolmogorov-Smirnov and and Levene tests, respectively, and a Mann-Whitney *U* test and Brown-Forsythe *F*-test will be used where necessary. Effect size will be calculated to complement the MANOVA results with the standardized mean difference (Cohen's *d*) for both between and within group analyses. This is a novel study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e. moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and number of side effects of the medication) when compared to secondary outcomes since medical interventions do not specifically focus on these symptoms (i.e., pain interference, mood, fatigue, rescue meditation use, and quality of life). The analysis will be performed by CSR, who will be blinded to the treatment allocation. Only the present study authors will have access to the final trial dataset.

Regarding dropouts, we will choose a strict criterion and the analyses will only include participants who complete both the pre and the post assessments. Because of the short duration of the trial (one month per patient) and the minimal risks expected from the use of the app, a data monitoring committee will not be required. Despite the previous, an alarm has been set so that the physicians are warned if a patient fails to

respond to the App during three consecutive days (i.e., an indirect measure of potential dropouts attributable to the App use). If this happens, the physicians will call the patient and explore the reasons for discontinuation and try to obtain a post-treatment assessment to reduce bias.

Discussion

Pain assessment is a complex process characterized by a high variability between and within days, which is usually performed by clinicians using self-report, onsite, single ratings which are based on recall (47,48). EMA using smartphone apps appears to be an innovative and promising alternative to these traditional assessment methods (49) as smartphone apps have demonstrated to be accurate tools to assess pain intensity and related variables from the patients' home, thus facilitating telemonitoring and contributing to the personalization of medical interventions by rapidly adjusting treatments to every individual as a result of telemonitoring (25).

In the present study protocol, we describe a randomized controlled trial designed to test an integrative technology-based solution for chronic pain monitoring consisting of a web application for the healthcare professional which is linked to the patient's app (i.e., Pain Monitor). Specifically, we want to explore whether the use of this integrative technology improves the effectiveness of the usual treatment for this population thanks to telemonitoring and the rapid detection of unwanted events. We expect that the use of Pain monitor, with the support of therapist's web, will result in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment due to the professional's rapid reaction in the presence of undesired outcomes. 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).

To our knowledge, this is the first study to assess the effectiveness of this type of integrative technology solution (i.e., a therapist web site linked to a patient smartphone app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis is confirmed, our findings will serve to demonstrate the feasibility and utility of smartphones and specialized webs for therapists so that they can be implemented in specialized care contexts (i.e., pain clinics). Likewise, our results will provide important information about the potential benefits of smartphone apps for the personalization of pain treatments (i.e., treatment can be rapidly personalized to a given patient as a function of individual responses reported in the app). Ultimately, this might help change the model of care for this chronic disease (i.e., episodic, onsite assessment and treatment), since the use of this integrative technology system allows for a continuous and remote evaluation and intervention, providing a faster response to the patient needs and improving self-management and empowerment of patients who attend pain clinics as they become important agents of treatment effectiveness by being in charge of daily reporting of pain-related experiences in the app. In sum, the results of the present investigation could serve an important first step towards the implementation of apps and other Information and Communication Technologies in health services.

List of Abbreviations

TAU = Treatment as usual; EMA = Ecological Momentary Assessment; IMEI = International Mobile Equipment Identity; SPIRIT = Standard Protocol Items Recommendations for Interventional Trials; CONSORT = Consolidated Standards of Reporting Trials; MANOVA = Multivariate Analysis of Variance.

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Author Statement: All authors were strongly involved in the study conceptualization and design and have reviewed and discussed the manuscript. IJ and CSR prepared the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG. After changes were incorporated, a final version was approved by all authors. IJ and

JLG are currently in charge of recruitment and IJ and CSR will be in charge of data analysis.

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Competing interests: The intellectual property of the Pain Monitor app is owned by co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any competing interests to declare as they do not receive any financial gain from these technologies.

Ethics approval and consent to participate: Ethical approval from the Hospital General Universitari de Castelló was obtained, in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study. The informed consent form was approved by the ethics committee of the Hospital General Universitari de Castelló.

FIGURES

Figure 1. Study schedule of enrolment, interventions, and assessments.

Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

Figure 3. Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

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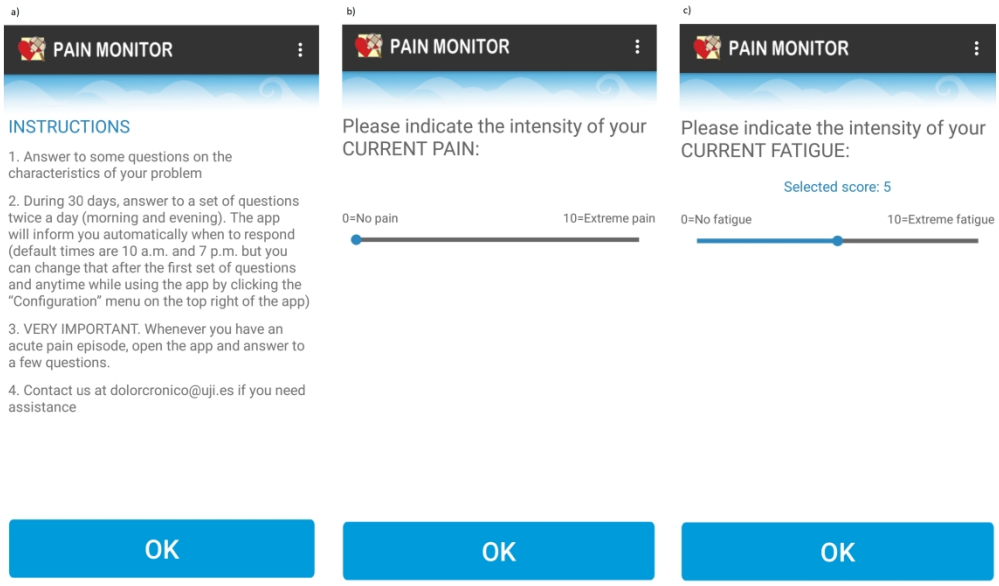
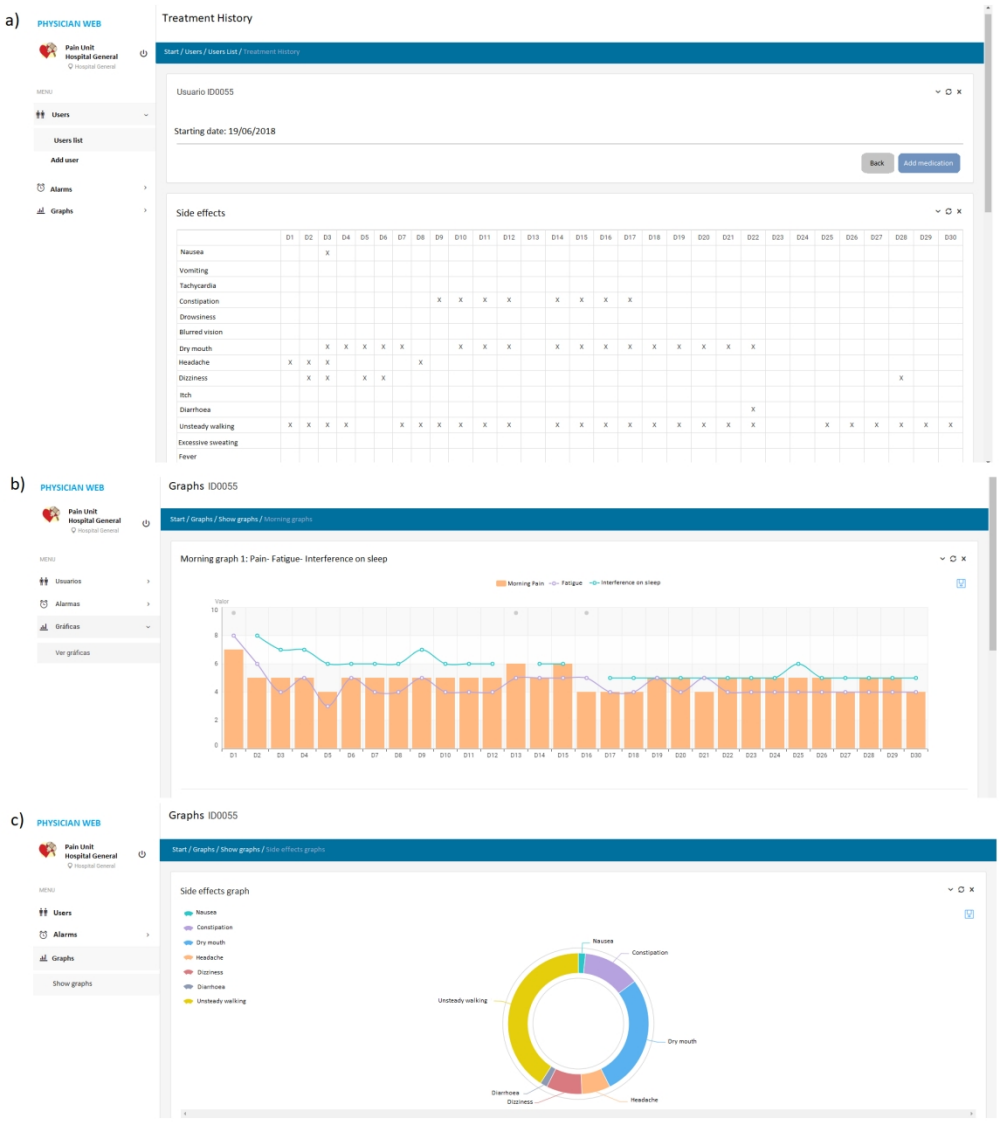
	STUDY PERIOD		
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**0**	***T_1***	***T_2***
	Pre-Intervention	*Between assessments*	*One month follow-up*
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
Allocation	X		
INTERVENTIONS:			
Medical treatment		X	
App use		App condition only	
ASSESSMENTS:			
Demographics	X		X
Primary outcomes			
Pain intensity	X	App condition only	X
Physical symptoms	X	App condition only	X
Secondary outcomes			
Pain interference	X	App condition only	X
Mood	X	App condition only	X
Fatigue	X	App condition only	X
Rescue medication	X	App condition only	X
Quality of life	X	App condition only	X



a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

289x168mm (300 x 300 DPI)



Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

168x189mm (300 x 300 DPI)

Supplement 1. WHO registration dataset

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03606265
Date of registration in primary registry	July 30, 2018
Secondary identifying numbers	UJI-B2016-39,
Source(s) of monetary of material support	Universitat Jaume I
Primary sponsor	Universitat Jaume I
Secondary sponsor(s)	None
Contact for public queries	+34 964387640 azucena@uji.es
Contact for scientific queries	+34 964387649 ijaen@uji.es
Public title	Utility od a Web-based App for Chronic Pain
Scientific title	Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial
Countries of recruitment	Spain
Health condition(s) or problem(s) studied	Chronic pain
Intervention(s)	Device: Treatment as usual+App+Web Device: Treatment as usual
Key inclusion and exclusion criteria	Inclusion Criteria: The patient is over 18 years of age The patient has a mobile phone with Android operating system The patient has the physical ability to use the application The patient does not present psychological and / or cognitive alterations or problems with language that make their participation difficult The patient voluntarily wants to participate and signs the informed consent Exclusion Criteria: The patient is under 18 years The patient does not have a mobile phone or has a mobile phone in which Android is not the operating system (the app is currently only available for Android for economic reasons) The patient does not have the physical capacity to use the application The patient does not have the capacity to participate due to psychological and / or cognitive alterations or problems with language

	The patient does not want to participate
Study type	Interventional
Date of first enrolment	August, 2018
Target sample size	250
Recruitment status	Ongoing
Primary outcome(s)	Changes in pain intensity and side effects
Key secondary outcomes	Changes in pain-related variables as mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Supplement 2: Study information sheet and informed consent

INFORMATION ABOUT THE STUDY

You have shown your interest in participating in a scientific study of Universitat Jaume I and the Hospital General de Castellón. Your participation in the study is completely voluntary. You will then be asked to provide us with your written consent to participate in this study. There will be no inconvenience if you do not wish to participate and your decision will in no way affect the treatment received at the Hospital General de Castellón. In addition, you may discontinue your participation at any time. Please, read the following text carefully and do not hesitate to ask any questions.

Why is this study being carried out?

This study is part of a project called "DOLOR-TIC. Development and validation of an eHealth network for chronic pain" (REF: UJI-B2016-39) funded by the Plan de Promoción de la investigacion Universitat Jaume I. The general objective of this project is to explore the benefits of using a network of technologies for the evaluation and treatment of chronic pain. The treatment by means of new technologies will be compared with the usual treatment provided in the pain unit of the Hospital General de Castellón.

What will be the procedure implemented in the study?

In the first sessions we will examine your state of health and check whether it meets the criteria for inclusion in the study. If you meet the established inclusion criteria, you will then be assigned to one of two study conditions: a) Habitual Treatment (TAU) or b) TAU supported by new technologies (TAU+ICTs). You will receive this treatment for 1 months and your clinical status will be evaluated before starting treatment, at the end of treatment (1 month). If, in fact, the treatments supported by the new technologies prove to be more effective than the usual treatment, you will be offered the possibility of benefiting from the treatment of new technologies at the end of the study, whether you were initially assigned to the TAU condition or to the TAU+TICs condition.

Are there any risks associated with my participation?

According to existing knowledge, the evaluation and treatment protocol used in this study does not pose risks to participants.

What are the possible benefits of my participation?

The treatment protocols included in this study are designed to improve your health. Your participation in this study will contribute to improving the health of a large number of citizens of the Spanish state. In addition, if the objectives of the study are achieved, the results will lead to a significant reduction in treatment costs and a

reduction in the increase in access to health services for a large number of people who do not have access to health services suffer from mental disorders.

How will my data be treated?

All data relevant to the study will be collected and stored in compliance with data protection regulations in force. These data will only be used anonymously for the purpose of scientific analysis. All persons involved in the study have an obligation to comply with data protection laws. We will make sure that all your information - without restrictions - is treated as in a confidential manner. Any data collected will be deleted as soon as it is not necessary for scientific purposes.

Can I decline or suspend my participation?

Yes, you may refuse to participate in this study or terminate your participation at any time. In the event that you decide to discontinue your participation in the study all of your data will be destroyed immediately.

Who is the researcher responsible for the study?

Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail: azucena@uji.es

You may contact the principal investigator if you have any questions, concerns about the study, about the data being collected, or if you wish to make use of your right to suspend your participation.

INFORMED CONSENT

Study DOLOR-TIC. Development and validation of an eHealth network for chronic pain. REF: UJI-B2016-39.

I (first name and last name) _____

- I have read the information sheet given to me.
- I was able to ask questions about the study.
- I have received enough information about the study.

I've been talking to: _____ (name of researcher).

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. When I want to
2. Without having to give explanations
3. Without this affecting my medical care

I freely give my consent to participate in the study.

Date: …/ … /… Date: …/ … /…

Participant's signature: Researcher's signature:

Revocation of consent:

I revoke the consent given on ..../..../..... and I do not wish to continue in the study that I give on this date for finished.

Signature of participant: Signature of investigator:

Supplement 3: Items in the Pain Monitor app

Items assessed once, the first day of app use:

1. Please indicate your date of birth (DD/MM/YYYY)

2. Please indicate your gender:
   a. Male
   b. Female

3. Please indicate your type of pain. You may select more than one option:
   a. Fibromyalgia
   b. Low back pain
   c. Cervical pain
   d. Rheumatoid arthritis
   e. Osteoarthritis; Headache
   f. Neuropathic pain
   g. Cancer pain
   h. None of the above

4. If you selected "None of the above" please indicate your type of pain. Otherwise, leave this question blank. Press OK to continue.

5. Please indicate the location where your pain is more intense:
   a. Head
   b. Shoulder
   c. Neck
   d. High back
   e. Lower back
   f. Arm
   g. Elbow
   h. Wrist
   i. Hand
   j. Abdomen
   k. Chest
   l. Buttock
   m. Hip
   n. Leg
   o. Knee
   p. Foot
   q. Whole body
   r. Somewhere not listed

6. Who is currently treating your pain? You may select more than one option:
   a. General practitioner
   b. Rheumatologist
   c. Orthopedic specialist
   d. Rehabilitation physician
   e. Psychiatrist
   f. Pain Unit

g. Neurosurgeon
h. Neurologist
i. Oncologist
j. Another professional.

7. When did your current pain start?
   a. Less than one year ago
   b. Between 1 and 5 years ago
   c. Between 5 and 10 years ago
   d. More than 10 years ago

8. What is your current treatment for pain? You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. My pain is not being treated

9. Did you start a new treatment for pain in the last month?
   a. Yes
   b. No

10. Please select the treatment/s you started in the last month. You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. I have not started a new treatment

11. What is your marital status?
   a. Single
   b. Married
   c. In a relationship
   d. Divorced
   e. Separated
   f. Widowed

12. What is your job status?
   a. Active worker
   b. Sick leave
   c. Permanent disability
   d. Unemployed
   e. Homemaker
   f. Retired
   g. Student

13. What is the highest level of education you have completed?

a. No studies
b. Less than high school
c. High school graduate
d. Technical training
e. University degree

14. Do you currently have a diagnosis of depression by a physician or a psychologist?
    a. Yes
    b. No

15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
    a. Yes
    b. No

Items assessed twice a day and in the event of acute pain episodes:

16. Please indicate the intensity of your CURRENT PAIN:
    0 No pain ---------10 Extreme pain

17. Please indicate the intensity of your CURRENT FATIGUE:
    0 No fatigue ---------10 Extreme fatigue

18. Please indicate the intensity of your CURRENT HAPPINESS:
    0 No happiness -------10 Extremely happy

19. Please indicate the intensity of your CURRENT SADNESS:
    0 No sadness -------- 10 Extremely sad

20. Please indicate the intensity of your CURRENT ANXIETY:
    0 No anxiety ------- 10 Extremely anxious

21. Please indicate the intensity of your CURRENT ANGER:
    0 No anger ------- 10 Extremely angry

22. Does your pain have any of these characteristics? You may select more than one option:
    a. Burning
    b. Painful cold
    c. Electric shocks
    d. Tingling
    e. Pins and needles
    f. Numbness
    g. Itching
    h. Reduced sensitivity to touch

i. Pain when brushing against the skin
j. None of the above

Items assessed in the morning:

23. In general, your HEALTH is:
    1) Very poor
    2) Poor
    3) Average
    4) Good
    5) Very good

24. Did your PAIN interfere with the quality of your SLEEP LAST NIGHT?
    0 No interference ------- 10 Maximum interference

25. Indicate your degree of agreement with the following sentence: With my current pain, I should not do my usual job (it includes housework and work outside the home).
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

26. Indicate your degree of agreement with the following sentence: Experiencing pain is terrible and I feel that pain is stronger than me.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

27. Indicate your degree of agreement with the following sentence: I need some control over pain before I can make serious plans.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

28. Indicate your degree of agreement with the following sentence: Physical activity aggravates my pain.
    1) Strongly disagree

2) Disagree
3) Neither agree nor disagree
4) Agree
5) Strongly agree

29. Indicate your degree of agreement with the following sentence: I am living a rewarding life despite my pain.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

Items assessed in the evening:

30. Did your PAIN interfere with your ability to perform your USUAL WORK or HOUSEWORK TODAY?
    0 No interference ------- 10 Maximum interference

31. Did your PAIN interfere with your LEISURE ACTIVITIES TODAY?
    0 No interference ------- 10 Maximum interference

32. Did your PAIN interfere with your SOCIAL INTERACTIONS TODAY?
    0 No interference ------- 10 Maximum interference

33. Which STRATEGY did you use to COPE WITH YOUR PAIN TODAY? You may select more than one option:
    a. Inactivity / rest
    b. Relaxation exercise
    c. Speak with someone
    d. Physical Activity / Stretching
    e. Self-statements to persist in a task
    f. Do something to feel positive emotions
    g. Ignore the pain/distract
    h. Pray for the pain to disappear

34. Indicate your degree of agreement with the following sentence: I fear that the pain will get worse.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

35. Indicate your degree of agreement with the following sentence: Today I could not keep my pain out of my mind.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

36. Please rate your degree of activity TODAY:
0%= Completely inactive -100%= Completely active.

37. In which area have you been more active today? You may select more than one option:
    a. Work
    b. Family
    c. Couple
    d. Friends
    e. Leisure
    f. Physical activity
    g. Other.

38. Did you take a rescue medication TODAY (i.e., medication you only use in the event of acute pain)?
    a. Yes
    b. No

39. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Nausea
    b. Vomiting
    c. Tachycardia
    d. Constipation
    e. Drowsiness / sedation
    f. Blurred vision
    g. Dry mouth
    h. Headache
    i. None of the above

40. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Dizziness
    b. Itching
    c. Diarrhea
    d. Gait instability

e. Excessive sweating
f. Fever
g. Urine retention
h. Facial redness
i. A different symptom
j. None of the above

41. Did you take your prescribed medication TODAY?
a. Yes
b. No, but I will do it later
c. No and I do not plan to take it
d. I haven't been prescribed a pain medication

42. How many times did you take a rescue medication TODAY?
a. 0
b. 1
c. 2
d. 3
e. 4
f. 5
g. 6
h. 7
i. 8
j. 9
k. 10
l. More than 10

Items assessed the last day of app use:

43. With respect to the beginning of treatment, how are you feeling NOW?
1) Much worse
2) Somewhat worse
3) The same
4) Somewhat better
5) Much better

44. Have you experienced any negative life event in the PAST MONTH?
a. No
b. Yes, but it did not affect me at all
c. Yes, but it did not affect me much
d. Yes and it had quite an effect on me
e. Yes and it affected me a lot

45. If you experienced a major negative life event in the last month, please indicate its characteristics using the list below. You may select more than one option:
    a. Death of a close person
    b. Job problem
    c. Relationship problem
    d. Economic problem
    e. Health problem
    f. Family problem
    g. An event not listed above
    h. I have not experienced any major negative event this month

46. Please indicate the location where your pain is more intense:
    a. Head
    b. Shoulder
    c. Neck
    d. High back
    e. Lower back
    f. Arm
    g. Elbow
    h. Wrist
    i. Hand
    j. Abdomen
    k. Chest
    l. Buttock
    m. Hip
    n. Leg
    o. Knee
    p. Foot
    q. Whole body
    r. Somewhere not listed

47. What is your current treatment for pain? You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment
    e. Natural / alternative treatments
    f. My pain is not being treated

48. Did you start a new treatment for pain in the last month?
    a. Yes
    b. No

49. Please select the treatment/s you started in the last month. You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment

e. Natural / alternative treatments
f. I have not started a new treatment

50. What is your marital status?
a. Single
b. Married
c. In a relationship
d. Divorced
e. Separated
f. Widowed

51. What is your job status?
a. Active worker
b. Sick leave
c. Permanent disability
d. Unemployed
e. Homemaker
f. Retired
g. Student

52. Do you currently have a diagnosis of depression by a physician or a psychologist?
a. Yes
b. No

53. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
a. Yes
b. No

Supplement 4: Alarms integrated into the Pain Monitor app

- Morning pain severity > 7 during 5 consecutive days
- Evening pain severity > 7 during 5 consecutive days
- Morning sadness >7 during 5 consecutive days
- Evening sadness >7 during 5 consecutive days
- Morning anxiety >7 during 5 consecutive days
- Evening anxiety >7 during 5 consecutive days
- Vomiting during 2 consecutive days
- Tachycardia during 2 consecutive days
- Blurred vision during 2 consecutive days
- Headache during 2 consecutive days
- Dry mouth during 2 consecutive days
- Constipation during 5 consecutive days
- Drowsiness during 5 consecutive days
- Nausea during 3 consecutive days
- Itching during 3 consecutive days
- Diarrhea during 2 consecutive days
- Fever during 2 consecutive days
- Facial redness during 2 consecutive days
- Urine retention during 2 consecutive days
- Gait instability during 3 consecutive days
- Excessive sweating during 7 consecutive days
- Dizziness during 3 consecutive days
- Treatment discontinuation during 3 consecutive days
- Rescue medication > 3 during 3 consecutive days
- Sleep interference > 7 during 5 consecutive days

Additional file 2: SPIRIT Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, page 1
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 1
Protocol version	3	Date and version identifier	Protocol Amendment Number, page 1
Funding	4	Sources and types of financial, material, and other support	Declarations, page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Authors, page 1
	5b	Name and contact information for the trial sponsor	Trial sponsor, page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, page 14

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, Page 12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, page 1-3
	6b	Explanation for choice of comparators	Method, page 6
Objectives	7	Specific objectives or hypotheses	Introduction, page 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction, page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Sample, page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Interventions and Assessment plan, page 8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Sample, page 7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Assessment plan, page 10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample, page 6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Sample, page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Sample, page 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 6 and 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Pages 6 and 13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Assessment plan, page 10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Procedure, page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Sample, page 7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Data analysis, page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Data analysys, page 12-13

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, Page 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Data analysis, page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Sample, page 8

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Sample, page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Sample, page 7-8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data analysis, page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Sample, page 8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Study design, page 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Availability of data and material, page 15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial

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Title: Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial

Running Head: Telemonitoring of pain by Pain Monitor App

Authors: Irene Jaén[1,a], Carlos Suso-Ribera[1], Diana Castilla[2,3], Irene Zaragoza[3], Azucena García-Palacios[1,3] and José Luis Gómez Palonés[4]

[1] Universitat Jaume I, Castelló 12007, Spain

[2] Universidad de Zaragoza, Teruel 44003, Spain

[3] CIBER of Physiopathology of Obesity and Nutrition CIBERobn, CB06/03 Instituto de Salud Carlos III, Spain

[4] Hospital General Universitari de Castelló, 12004, Spain

[a] Corresponding author. Universitat Jaume I. Facultad de Ciencias de la Salud. Departamento de Psicología Básica, Clínica y Psicobiología. Avda. Vicente Sos Baynat s/n. Castellón de la Plana E-12071 Spain

ijaen@uji.es

Trial Sponsor: Universitat Jaume I.: Avda. Vicente Sos Baynat, s/n Castellón de la Plana E-12071 Spain; **Telephone:** +34 964 38 74 80; e-mail: ocit@uji.es

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Abstract

Introduction: Chronic pain has become a matter of public health concern due to its high prevalence and because public costs associated with treatment and disability increase each year. Research suggests that limitations in the traditional assessment of chronic pain patients limit the effectiveness of current medical treatments. The use of technology might serve change patient traditional monitoring into Ecological Momentary Assessments, which might be visualized by physicians live. This study describes a Randomized Control Trial designed 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. The goal of this study will be to explore whether this combination of eHealth and mHealth improves the effectiveness of existing pain treatments.

*Methods and analysis***:** Participants will be 250 patients randomly assigned to one of these two conditions: treatment as usual (TAU) and TAU+app+web. All participants will receive the usual treatment for their pain. Only the TAU+app+web group use Pain Monitor app, which generates alarms that are sent to the physicians in the face of previously-established undesired events. Physicians will be able to monitor app reports using a web application, which might result in an adjustment of treatment. We anticipate that the use of Pain Monitor plus the therapist web will result in a reduction of pain intensity and side effects of the medication. Improvements on secondary outcomes, namely fatigue, mood, pain interference, rescue medication use, and quality of life, are also expected. Mixed repeated-measure MANOVAs will be conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition.

Ethics and dissemination: Ethical approval from the Hospital General Universitari de Castellon was obtained. The findings will be published in peer-reviewed journals.

Trial registration: NCT03606265. The trial is active. Recruitment is ongoing.

Keywords: Chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring.

Strengths and limitations of this study

- In the present randomized, controlled clinical, an integrative e-health and m-health solution for chronic pain management is implemented.
- Patient monitoring is performed remotely in an ecological and momentary manner with a smartphone app.
- Patient responses to the app might generate alarms in the presence of unwanted clinical events.
- Physicians can track patient evolution at any time on a website and receive clinical alarms daily.
- Study limitations include the fact that physicians are not blinded to the patients' condition and the rigidity of the app assessment protocol.

Introduction

Pain can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1) and can only be understood as an interplay between "sensory, emotional, cognitive, and social components" (2). Although pain often is acute and disappears as tissues heal, sometimes pain persists for long periods of time and becomes chronic. For instance, it has been reported that 15% of individuals admitted to trauma hospitals due to a severe injury and 15- 60% of patients after surgery will continue to experience chronic pain months and years later (3). In general, a cut-off of 3 to 6 months is used to define the transition from acute/subacute to chronic pain (4).

The aforementioned chronification of pain is becoming a major public health problem across the globe (5). 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 (6). Specifically, epidemiological studies indicate that the prevalence of this disease in the adult population ranges from 19% to 38% worldwide (7–10). Furthermore, the increase in life expectancy and the ageing of the population is likely to have an important impact on the number of individuals experiencing chronic pain, since the prevalence of this syndrome boosts dramatically with age (11). For instance, it is expected that the population of chronic pain individuals will be doubled in 2050 for people older than 65 years and tripled for people over 80 years of age (12). Thus, chronic pain is a major public health challenge due to its high prevalence in the population and high direct and indirect costs for the institutions and the individuals (13,14).

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 (15,16) Not surprisingly, as a result of the growing concern about this disease, there have been numerous attempts to improve treatments for pain in the past decades. However, recent reviews on the effectiveness of numerous interventions, including medical treatments, psychological therapy, physical rehabilitation, or a combination of these indicate that the effectiveness of existing treatments is, on average, only modest (17–19). While there might be numerous factors explaining the limited effectiveness of current interventions for pain, including unexplored biomechanical mechanisms or genetic factors, patient characteristics, or therapists' training, some authors have pointed to methodological shortcomings as key elements explaining the modest effectiveness of pain interventions. Specifically, the way assessment is currently performed (i.e., a single measure of pain intensity performed episodically during onsite appointments) has been argued to impact negatively in the ability of existing interventions to achieve more reliable and powerful changes in patient outcomes (20,21). For instance, a single rate of pain intensity has been shown to be an unreliable measure of pain as this experience can vary dramatically within the same day and

across days (22–24). In addition, pain is frequently assessed retrospectively, which is known to lead to recall bias and to decrease the accuracy of pain ratings (25) and does not allow for timely responses to undesired events, so these often take place time after the problem occurred (21).

As a consequence of the above, Ecological Momentary Assessment (EMA), which refers to the assessment of pain repeatedly and in real life, has received renewed interest in the past years in the pain literature and is now considered by many as the gold standard method to assess the pain experience (26–29). Traditionally, EMA has been difficult due to the limitations and costs of repeated measurement procedures (i.e., paper diaries or phone calls). However, with the explosion and availability of smartphones, EMA has become easier than ever and immediate communication between the patient and the physician is now a more feasible practice (30).

It has been argued that this change in the assessment paradigm towards ecological daily telemonitoring using apps will improve treatment effectiveness and reduce costs if used to respond to patient reports quickly (21,31). Indeed, there is evidence to suggest that smartphones are useful tools to be used for the assessment of pain core outcome measures in chronic pain settings (21,32,33). However, the extent to which this EMA of pain patients can effectively lead to better practices in pain medicine is still unknown.

For this purpose, we developed a technology-based solution that integrated a pain and symptom tracking app for patients and a web for physicians where app-generated alarms are received daily and patient app responses can be monitored in real time. To the best of our knowledge, no study has yet investigated the utility of using such an integrative technology-based solution for remote, ecological monitoring of patient evolution and to adjust treatment in response to app alarms in a randomized controlled trial.

With the previous goal in mind, in the present parallel group, superiority trial we will use the *Pain Monitor* app (https://play.google.com/store/apps/details?id=painmonitor.srccode), which was

developed by a team of psychologists and an engineer with the collaboration of physicians and nurses and has been recently validated in clinical settings (21), together with a web for the physicians where app responses and alarms can be tracked in real time to facilitate the professional's decision-making process. As we will explain in more detail in the Methods section, Pain Monitor assesses a number of pain-related outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of pain-related health resources) and the most frequent side effects of medical treatments for pain. In the study, patients will be randomly assigned to a treatment as usual condition (TAU) or to a TAU with the support of the patients' app and the physician's web. We anticipate that the use of the web application linked with the smartphone app (TAU+app+web condition) will improve the effectiveness of usual treatments resulting in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment. 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 (34). We also expect that the rapid detection of treatment undesired events will rapidly minimize threats to the patient's quality of life and mood.

Method

Study design

The current investigation is a randomized superiority clinical trial composed of two parallel groups (1:1 allocation ratio): a) TAU and b) TAU+app+web. In the study, participants in the TAU condition receive the usual pain treatment by the physicians working at the pain unit (i.e., pharmacological treatment or infiltration). Participants included in TAU+app+web group receive the usual treatment for their pain plus daily monitoring of their symptoms and pain experience with the Pain Monitor app during one month. In the TAU+app+web condition, alarms are generated in the presence of

previously established undesired events, which have been previously determined by the physicians at the pain clinic (e.g., pain intensity is higher than 7 in an 11-point numerical scale during 3 consecutive days). Physicians are able to monitor these patients' app reports using a web application created for this purpose (https://monitordolor.dolortic.com/). Thus, phone calls can be conducted in the presence of alarms in order to change or discontinue the medical treatment when necessary. If the study results indicate that the use of technology leads to better outcomes, participants in the TAU condition will be informed about these findings and will be offered the possibility to use the app after study participation. In the TAU condition only, assessment is performed as usual, that is, using self-report measures administered onsite at the beginning and the end of the study (1 month later). Neither the physicians nor the patients will be blind to the treatment condition assigned. Physicians will not be blind because they will receive alarms from the TAU+app+web participants only. Patients will not be blind because only those in the TAU+app+web condition will be using technology in addition to usual treatment and because patients in the TAU condition must know that there is no telemonitoring in their condition.

The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All items from the World Health Organization Trial Registration Data Set are showed in the Supplementary file 1. The recruitment started at the end of the same month. SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were followed to design the trial. The participant timeline (i.e., schedule of enrolment, interventions, and assessments) is shown in Figure 1. Recruitment is currently ongoing and is expected to end in November 2019.

Sample

Participants will be 250 consecutive chronic pain patients attending the pain clinic at the Hospital General Universitari de Castello (Spain) for the first time. Required sample size was calculated using *G**Power (35). Although the a priori calculation resulted in

198 participants, the sample size was increased to 250 considering a dropout rate of 27-30% based on previous studies (36,37). Thus, 125 participants were assigned to each condition. Randomization of participants was performed by an independent researcher using a computer-generated sequence with *Randomizer* (38). Inclusion criteria are shown in Table 1. 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.

Table 1. Inclusion criteria

The patient is over 18 years of age
The patient has a mobile phone with Android operating system (the app is currently only available for Android, which is the operating system used by more than 80% of users in Spain) (39).
The patient has the physical ability to use the application
A new treatment plan is started during the first week after study onset
The patient does not present psychological and/or cognitive alterations or problems with language that make his/her participation difficult
The patient voluntarily wants to participate and signs the informed consent form

In the study, all participants are identified using an alphanumeric code. In the case of participants in the TAU+app+web condition, this code is automatically generated by the app. Thus, the database generated by the app is anonymized and the app only collects the international mobile equipment identity (IMEI). The association between app codes and patient identifiable characteristics is stored locally at the pain clinic. All data

storage procedures follow the European law and data protection rules (European Union General Data Protection Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016). In addition, ethical approval from the Hospital General Universitari de Castello was obtained, in accordance with the Declaration of Helsinki. Important protocol modifications will be notified and require the approval of the Ethics Committee of the Hospital General Universitari de Castello. Approved changes will be made public at clinicaltrials.gov. All the participants read and sign an informed consent form before randomization (see Supplementary file 2). Patients who do not agree with the assigned condition, are given the opportunity to be allocated to the preferred condition, but are not used in the analyses. Any changes to modify the assigned condition are accepted at any time during the study, again resulting in an exclusion from the study. Changes in the medication or improvement of disease do not result in study discontinuation. Disease worsening is not expected to be associated with the inclusion of the app but, if existent, will result in the discontinuation of app use.

Procedure

The study is conducted at the pain clinic of the Hospital General Universitari de Castelló. The study is advertised by physicians to all consecutive patients attending the pain clinic for the first time. To ensure enrolment, physicians will emphasize the importance of active patient participation in research in general and in self-monitoring in particular. Patients interested in participating are directed to another office where the lead author, I.J., explains the study procedures in more detail and ensures their eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by explaining the utility of the study and by contacting patients when an alarm informing of low app adherence (i.e., more than three consecutive days without response) is received. All participants are provided with an information sheet and sign the informed consent. After participation acceptance, participants are assigned to one of the experimental conditions (TAU or TAU+app+web), which had been previously

randomized by an external researcher. All participants then complete a paper-and-pencil assessment protocol in order to control for differences between the two assessment formats (app vs. pen and pencil) and to compare both conditions using the same assessment approach. In addition to this paper-and-pencil evaluation, patients in the TAU+app+web condition download and install the Pain Monitor app into their phones. Once they install the app, they answer to an initial assessment and then complete two measures daily (10 am and 7 pm) during one month (study duration). Finally, an end of study appointment is set (one month later) to conduct the post-assessment evaluation. Due to difficulties in transportation or availability, the post-assessment intervention can either be completed onsite or via an on-line survey.

Pain monitor

The Pain Monitor app (Figure 2) has been developed by a group of pain psychologists and an engineer, with the collaboration of physicians and nurses specialized in pain care. Pain Monitor is composed of several pain-related items which are to be answered twice a day at preset times (10 am and 7 pm, with a two-hour flexibility) during 30 days. The app content has been previously validated with chronic pain patients at the pain unit of the Vall d'Hebron Hospital (21). This assessment protocol contains sociodemographic items (i.e., age, sex, and education level, among others) which are evaluated on the first day of app use only, as well as a number of pain-related outcomes that are evaluated daily, which have been selected following recent guidelines on core outcome domains for pain treatments (40,41). Constructs in the app, including pain intensity, pain interference, anxiety, depression, catastrophizing, social support, acceptance, and coping, among others, are measured with a single item to reduce the burden of daily assessment, each of which was adapted and validated against well-established paper-and-pencil measures (21). Additionally, the assessment protocol includes a list of side effects created *ad hoc* based on the literature findings on the most frequent adverse effects of pain treatments (42,43), as well as measures of

treatment adherence, use of rescue medication, neuropathic characteristics of pain, and use of medical services in the past month. All app items can be found in Supplementary file 3.

The app generates alarms in the presence of predefined events (see Supplementary file 4 for the alarms set in the present study in collaboration with the participating physicians). These alarms are sent to the physicians early in the morning on working days so that they can decide whether an action from their side is required (e.g., calling the patient and setting an earlier appointment or suggesting a change in the medication). For this study, a website linked to the app was created for the physicians to observe patient alarms and evolution live. Examples of the physician web are presented in Figure 3. Physicians are only asked to check the website when an alarm happens, but they are allowed to check any patient status at any time.

Interventions

Five physicians at the pain clinic of the Hospital General Universitari de Castelló participate in this study. All patients in the study receive the usual treatment for their pain irrespective of their assigned condition. However, a change in treatment might occur in the TAU+app+web condition at the discretion of the physicians in charge of treatment after receiving an alarm and consulting the web page with the graphical representation of patient app responses. As usual, patients in the TAU condition without the app are not contacted by the physicians between appointments. It is important to note that both patients in the TAU only and patients in the TAU+app+web condition are allowed to attend to the emergency services or the family physician in the event of an emergency at any stage of the study due to ethical reasons. At the end of the study, this practice is investigated for each participant in the final assessment.

Assessment plan

All participants in the study fill in a number of questionnaires in a paper-and-pencil format at the beginning and at the end of the study. This assessment protocol includes sociodemographic information, sickness work absence during the past month, use of pain-related health resources in the past month (i.e., emergency services, family physician, or pain clinic), pain-related physical symptoms experienced in the past week (i.e., side medication effects), the Brief Pain Inventory (pain severity and interference) (44), the Pain Catastrophizing Scale (45), and the Hospital Anxiety and Depression Scale (46). In addition to this paper-and-pencil evaluation, participants in the TAU+app+web condition also install the Pain Monitor app and complete a pre-intervention assessment in the app after the paper-and-pencil evaluation. Both baseline assessments include the same content and are duplicated to provide further evidence for the validity of app content. After this pretreatment evaluation, participants in the TAU+app+web group are asked to answer to the app assessments twice a day during one month (study duration). A push-up system notifies the patient about the need to respond to the app evaluation at 10:00 am and 7:00 pm. These times can be adjusted by the patient with a 2-hour flexibility from the preset times.

Daily morning and evening assessments differ in a number of items. Some items are asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g., activity level during the day, interference of pain on daily activities, or physical symptoms experienced during the day).

Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a post-assessment protocol. The measures included in this final evaluation are similar to the ones included in the baseline assessment, with the inclusion of a measure of negative events experienced during the study period and the evaluation of perceived change due to treatment.

In the study, primary outcomes are pain intensity and the number of side effects of the medication reported in the app, while secondary outcomes include mood (depression

and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Note that app reports in the TAU+app+web condition are not used to determine treatment effectiveness compared to the TAU only condition because in the latter condition participants do not use the app. Therefore, app responses are only used for telemonitoring and early detection of treatment problems that result in an alarm to the physicians. The comparison of both conditions will be made using the traditional paper-and-pencil evaluations which will be available for both groups. Additionally, the number of alarms and the physician's responses to such alarms (e.g., change in treatment strategies) will be registered. This information will be used to get better insight into the utility of the integrated technology to improve treatment efficacy.

Patient and public Involvement

In the current study, patients or the public will not be involved in the design, or conduct, or dissemination of the research.

Data analysis

The aim of the present study is to explore the effect of an integrated technology-based solution for chronic pain monitoring (an app that monitors pain patients daily and sends clinical alarms to physicians and a web for physicians that graphically represents patient evolution as reported in the app) compared to the usual treatment where monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim in mind, and completer analyses will be performed following the recommendations of the CONSORT guidelines (http://www.consort-statement.org/). First, the two conditions will be compared at baseline in the different continuous measures with a between-group analysis via a *t*-test to ensure that randomization indeed resulted in comparable groups prior to intervention. Chi-squared tests will be used for all the categorical variables. To evaluate our hypothesis, mixed repeated-measure MANOVAs will be

conducted to investigate whether there are differences between pre- and post-assessment scores as a function of the experimental condition (TAU or TAU+app+web). Distribution normality and homoscedasticity assumptions will be tested by means of Kolmogorov-Smirnov and and Levene tests, respectively, and a Mann-Whitney *U* test and Brown-Forsythe *F*-test will be used where necessary. Effect size will be calculated to complement the MANOVA results with the standardized mean difference (Cohen's *d*) for both between and within group analyses. This is a novel study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e. moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and number of side effects of the medication) when compared to secondary outcomes since medical interventions do not specifically focus on these symptoms (i.e., pain interference, mood, fatigue, rescue meditation use, and quality of life). The analysis will be performed by CSR, who will be blinded to the treatment allocation. Only the present study authors will have access to the final trial dataset.

Regarding dropouts, we will choose a strict criterion and the analyses will only include participants who complete both the pre and the post assessments. Because of the short duration of the trial (one month per patient) and the minimal risks expected from the use of the app, a data monitoring committee will not be required. Despite the previous, an alarm has been set so that the physicians are warned if a patient fails to respond to the App during three consecutive days (i.e., an indirect measure of potential dropouts attributable to the App use). If this happens, the physicians will call the patient and explore the reasons for discontinuation and try to obtain a post-treatment assessment to reduce bias.

Discussion

Pain assessment is a complex process characterized by a high variability between and within days, which is usually performed by clinicians using self-report, onsite, single

ratings which are based on recall (47,48). EMA using smartphone apps appears to be an innovative and promising alternative to these traditional assessment methods (49) as smartphone apps have demonstrated to be accurate tools to assess pain intensity and related variables from the patients' home, thus facilitating telemonitoring and contributing to the personalization of medical interventions by rapidly adjusting treatments to every individual as a result of telemonitoring (25).

In the present study protocol, we describe a randomized controlled trial designed to test an integrative technology-based solution for chronic pain monitoring consisting of a web application for the healthcare professional which is linked to the patient's app (i.e., Pain Monitor). Specifically, we want to explore whether the use of this integrative technology improves the effectiveness of the usual treatment for this population thanks to telemonitoring and the rapid detection of unwanted events. We expect that the use of Pain monitor, with the support of therapist's web, will result in reduced pain intensity and less frequent side effects of the medication after one month of medical treatment due to the professional's rapid reaction in the presence of undesired outcomes. 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).

To our knowledge, this is the first study to assess the effectiveness of this type of integrative technology solution (i.e., a therapist web site linked to a patient smartphone app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis is confirmed, our findings will serve to demonstrate the feasibility and utility of smartphones and specialized webs for therapists so that they can be implemented in specialized care contexts (i.e., pain clinics). Likewise, our results will provide important information about the potential benefits of smartphone apps for the personalization of pain treatments (i.e., treatment can be rapidly personalized to a given patient as a

function of individual responses reported in the app). Ultimately, this might help change the model of care for this chronic disease (i.e., episodic, onsite assessment and treatment), since the use of this integrative technology system allows for a continuous and remote evaluation and intervention, providing a faster response to the patient needs and improving self-management and empowerment of patients who attend pain clinics as they become important agents of treatment effectiveness by being in charge of daily reporting of pain-related experiences in the app. In sum, the results of the present investigation could serve an important first step towards the implementation of apps and other Information and Communication Technologies in health services.

List of Abbreviations

TAU = Treatment as usual; EMA = Ecological Momentary Assessment; IMEI = International Mobile Equipment Identity; SPIRIT = Standard Protocol Items Recommendations for Interventional Trials; CONSORT = Consolidated Standards of Reporting Trials; MANOVA = Multivariate Analysis of Variance.

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Author Statement: All authors were strongly involved in the study conceptualization and design and have reviewed and discussed the manuscript. IJ and CSR prepared the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG. After changes were incorporated, a final version was approved by all authors. IJ and JLG are currently in charge of recruitment and IJ and CSR will be in charge of data analysis.

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Competing interests: The intellectual property of the Pain Monitor app is owned by co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any

competing interests to declare as they do not receive any financial gain from these technologies.

Ethics and dissemination: Ethical approval from the Hospital General Universitari de Castelló was obtained, in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study. The informed consent form was approved by the ethics committee of the Hospital General Universitari de Castelló. The findings of this study will be published in peer-reviewed journals.

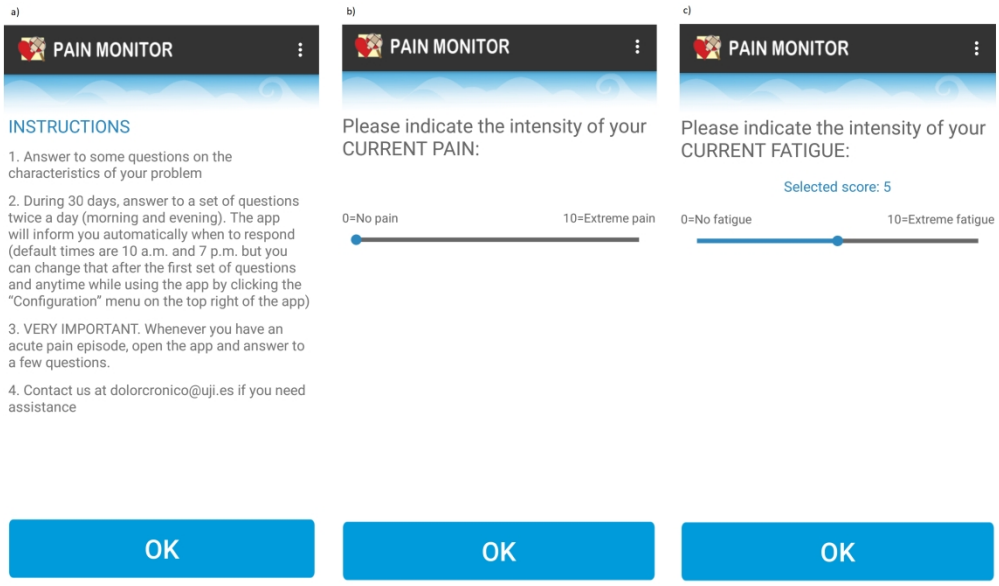
FIGURES

Figure 1. Study schedule of enrolment, interventions, and assessments.

Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

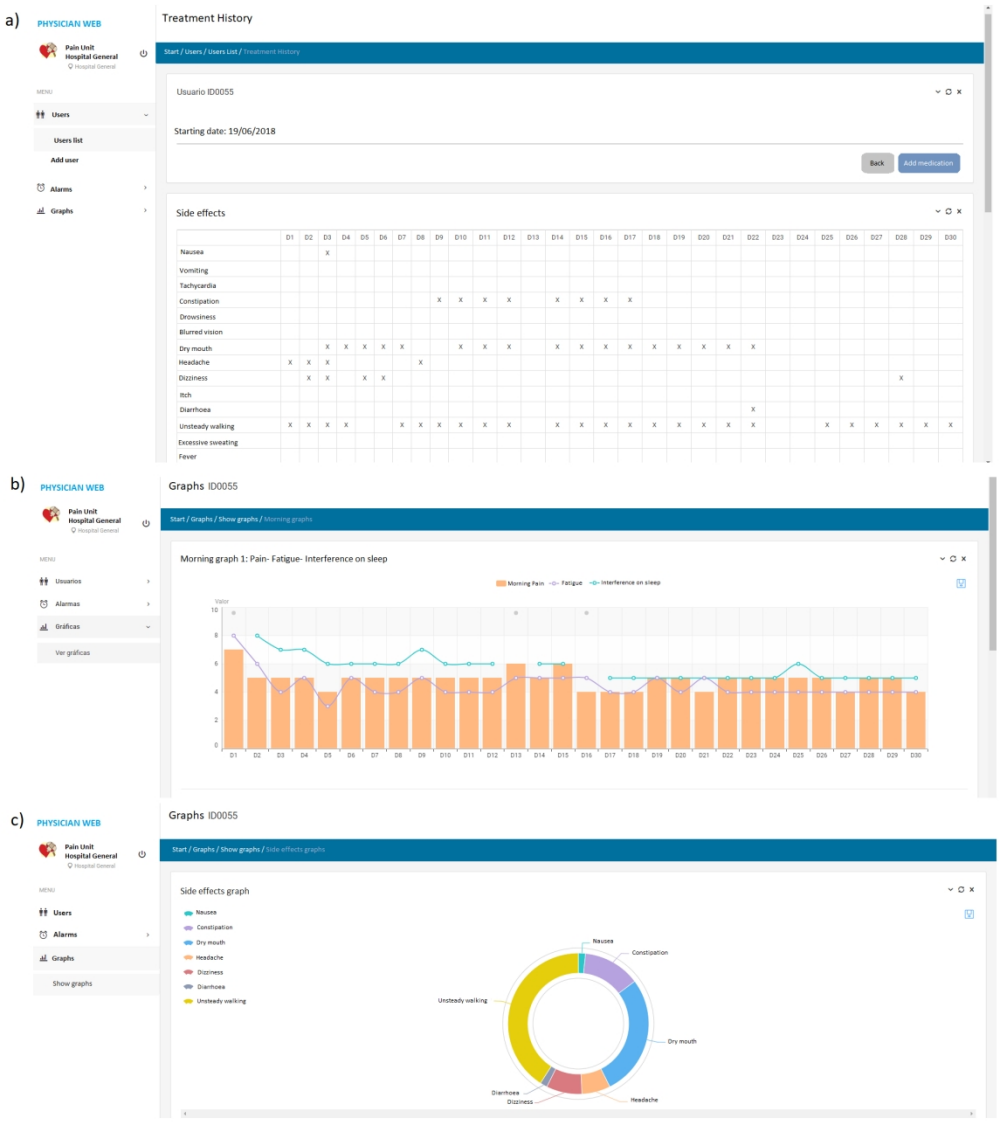
Figure 3. Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

	STUDY PERIOD		
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**0**	***T_1***	***T_2***
	Pre-Intervention	*Between assessments*	*One month follow-up*
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
Allocation	X		
INTERVENTIONS:			
Medical treatment		X	
App use		App condition only	
ASSESSMENTS:			
Demographics	X		X
Primary outcomes			
Pain intensity	X	App condition only	X
Physical symptoms	X	App condition only	X
Secondary outcomes			
Pain interference	X	App condition only	X
Mood	X	App condition only	X
Fatigue	X	App condition only	X
Rescue medication	X	App condition only	X
Quality of life	X	App condition only	X



a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c) Pain Monitor assessment of fatigue.

289x168mm (300 x 300 DPI)



Examples of the web for the physician. a) Patient's side effects during 30 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c) Distribution of patient side effects.

168x189mm (300 x 300 DPI)

Supplement 1. WHO registration dataset

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03606265
Date of registration in primary registry	July 30, 2018
Secondary identifying numbers	UJI-B2016-39,
Source(s) of monetary of material support	Universitat Jaume I
Primary sponsor	Universitat Jaume I
Secondary sponsor(s)	None
Contact for public queries	+34 964387640 azucena@uji.es
Contact for scientific queries	+34 964387649 ijaen@uji.es
Public title	Utility od a Web-based App for Chronic Pain
Scientific title	Improving chronic pain management with eHealth and mHealth: study protocol for a randomized controlled trial
Countries of recruitment	Spain
Health condition(s) or problem(s) studied	Chronic pain
Intervention(s)	Device: Treatment as usual+App+Web Device: Treatment as usual
Key inclusion and exclusion criteria	Inclusion Criteria: The patient is over 18 years of age The patient has a mobile phone with Android operating system The patient has the physical ability to use the application The patient does not present psychological and / or cognitive alterations or problems with language that make their participation difficult The patient voluntarily wants to participate and signs the informed consent Exclusion Criteria: The patient is under 18 years The patient does not have a mobile phone or has a mobile phone in which Android is not the operating system (the app is currently only available for Android for economic reasons) The patient does not have the physical capacity to use the application The patient does not have the capacity to participate due to psychological and / or cognitive alterations or problems with language

	The patient does not want to participate
Study type	Interventional
Date of first enrolment	August, 2018
Target sample size	250
Recruitment status	Ongoing
Primary outcome(s)	Changes in pain intensity and side effects
Key secondary outcomes	Changes in pain-related variables as mood (depression and anxiety), pain interference, pain catastrophizing, and use of pain-related health resources in the past month.

Supplement 2: Study information sheet and informed consent

INFORMATION ABOUT THE STUDY

You have shown your interest in participating in a scientific study of Universitat Jaume I and the Hospital General de Castellón. Your participation in the study is completely voluntary. You will then be asked to provide us with your written consent to participate in this study. There will be no inconvenience if you do not wish to participate and your decision will in no way affect the treatment received at the Hospital General de Castellón. In addition, you may discontinue your participation at any time. Please, read the following text carefully and do not hesitate to ask any questions.

Why is this study being carried out?

This study is part of a project called "DOLOR-TIC. Development and validation of an eHealth network for chronic pain" (REF: UJI-B2016-39) funded by the Plan de Promoción de la investigacion Universitat Jaume I. The general objective of this project is to explore the benefits of using a network of technologies for the evaluation and treatment of chronic pain. The treatment by means of new technologies will be compared with the usual treatment provided in the pain unit of the Hospital General de Castellón.

What will be the procedure implemented in the study?

In the first sessions we will examine your state of health and check whether it meets the criteria for inclusion in the study. If you meet the established inclusion criteria, you will then be assigned to one of two study conditions: a) Habitual Treatment (TAU) or b) TAU supported by new technologies (TAU+ICTs). You will receive this treatment for 1 months and your clinical status will be evaluated before starting treatment, at the end of treatment (1 month). If, in fact, the treatments supported by the new technologies prove to be more effective than the usual treatment, you will be offered the possibility of benefiting from the treatment of new technologies at the end of the study, whether you were initially assigned to the TAU condition or to the TAU+TICs condition.

Are there any risks associated with my participation?

According to existing knowledge, the evaluation and treatment protocol used in this study does not pose risks to participants.

What are the possible benefits of my participation?

The treatment protocols included in this study are designed to improve your health. Your participation in this study will contribute to improving the health of a large number of citizens of the Spanish state. In addition, if the objectives of the study are achieved, the results will lead to a significant reduction in treatment costs and a

reduction in the increase in access to health services for a large number of people who do not have access to health services suffer from mental disorders.

How will my data be treated?

All data relevant to the study will be collected and stored in compliance with data protection regulations in force. These data will only be used anonymously for the purpose of scientific analysis. All persons involved in the study have an obligation to comply with data protection laws. We will make sure that all your information - without restrictions - is treated as in a confidential manner. Any data collected will be deleted as soon as it is not necessary for scientific purposes.

Can I decline or suspend my participation?

Yes, you may refuse to participate in this study or terminate your participation at any time. In the event that you decide to discontinue your participation in the study all of your data will be destroyed immediately.

Who is the researcher responsible for the study?

Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail: azucena@uji.es

You may contact the principal investigator if you have any questions, concerns about the study, about the data being collected, or if you wish to make use of your right to suspend your participation.

INFORMED CONSENT

Study DOLOR-TIC. Development and validation of an eHealth network for chronic pain. REF: UJI-B2016-39.

I (first name and last name) _____

- I have read the information sheet given to me.
- I was able to ask questions about the study.
- I have received enough information about the study.

I've been talking to: _____ (name of researcher).

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. When I want to
2. Without having to give explanations
3. Without this affecting my medical care

I freely give my consent to participate in the study.

Date: …/ … /… Date: …/ … /…

Participant's signature: Researcher's signature:

Revocation of consent:

I revoke the consent given on ..../..../..... and I do not wish to continue in the study that I give on this date for finished.

Signature of participant: Signature of investigator:

Supplement 3: Items in the Pain Monitor app

Items assessed once, the first day of app use:

1. Please indicate your date of birth (DD/MM/YYYY)

2. Please indicate your gender:
   a. Male
   b. Female

3. Please indicate your type of pain. You may select more than one option:
   a. Fibromyalgia
   b. Low back pain
   c. Cervical pain
   d. Rheumatoid arthritis
   e. Osteoarthritis; Headache
   f. Neuropathic pain
   g. Cancer pain
   h. None of the above

4. If you selected "None of the above" please indicate your type of pain. Otherwise, leave this question blank. Press OK to continue.

5. Please indicate the location where your pain is more intense:
   a. Head
   b. Shoulder
   c. Neck
   d. High back
   e. Lower back
   f. Arm
   g. Elbow
   h. Wrist
   i. Hand
   j. Abdomen
   k. Chest
   l. Buttock
   m. Hip
   n. Leg
   o. Knee
   p. Foot
   q. Whole body
   r. Somewhere not listed

6. Who is currently treating your pain? You may select more than one option:
   a. General practitioner
   b. Rheumatologist
   c. Orthopedic specialist
   d. Rehabilitation physician
   e. Psychiatrist
   f. Pain Unit

g. Neurosurgeon
h. Neurologist
i. Oncologist
j. Another professional.

7. When did your current pain start?
   a. Less than one year ago
   b. Between 1 and 5 years ago
   c. Between 5 and 10 years ago
   d. More than 10 years ago

8. What is your current treatment for pain? You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. My pain is not being treated

9. Did you start a new treatment for pain in the last month?
   a. Yes
   b. No

10. Please select the treatment/s you started in the last month. You may select more than one option:
   a. Physiotherapy
   b. Pharmacotherapy
   c. Infiltrations
   d. Psychological treatment
   e. Natural / alternative treatments
   f. I have not started a new treatment

11. What is your marital status?
   a. Single
   b. Married
   c. In a relationship
   d. Divorced
   e. Separated
   f. Widowed

12. What is your job status?
   a. Active worker
   b. Sick leave
   c. Permanent disability
   d. Unemployed
   e. Homemaker
   f. Retired
   g. Student

13. What is the highest level of education you have completed?

a. No studies
b. Less than high school
c. High school graduate
d. Technical training
e. University degree

14. Do you currently have a diagnosis of depression by a physician or a psychologist?
    a. Yes
    b. No

15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
    a. Yes
    b. No

Items assessed twice a day and in the event of acute pain episodes:

16. Please indicate the intensity of your CURRENT PAIN:
    0 No pain ---------10 Extreme pain

17. Please indicate the intensity of your CURRENT FATIGUE:
    0 No fatigue ---------10 Extreme fatigue

18. Please indicate the intensity of your CURRENT HAPPINESS:
    0 No happiness -------10 Extremely happy

19. Please indicate the intensity of your CURRENT SADNESS:
    0 No sadness -------- 10 Extremely sad

20. Please indicate the intensity of your CURRENT ANXIETY:
    0 No anxiety ------- 10 Extremely anxious

21. Please indicate the intensity of your CURRENT ANGER:
    0 No anger ------- 10 Extremely angry

22. Does your pain have any of these characteristics? You may select more than one option:
    a. Burning
    b. Painful cold
    c. Electric shocks
    d. Tingling
    e. Pins and needles
    f. Numbness
    g. Itching
    h. Reduced sensitivity to touch

i. Pain when brushing against the skin
j. None of the above

Items assessed in the morning:

23. In general, your HEALTH is:
    1) Very poor
    2) Poor
    3) Average
    4) Good
    5) Very good

24. Did your PAIN interfere with the quality of your SLEEP LAST NIGHT?
    0 No interference ------- 10 Maximum interference

25. Indicate your degree of agreement with the following sentence: With my current pain, I should not do my usual job (it includes housework and work outside the home).
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

26. Indicate your degree of agreement with the following sentence: Experiencing pain is terrible and I feel that pain is stronger than me.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

27. Indicate your degree of agreement with the following sentence: I need some control over pain before I can make serious plans.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

28. Indicate your degree of agreement with the following sentence: Physical activity aggravates my pain.
    1) Strongly disagree

2) Disagree
3) Neither agree nor disagree
4) Agree
5) Strongly agree

29. Indicate your degree of agreement with the following sentence: I am living a rewarding life despite my pain.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

Items assessed in the evening:

30. Did your PAIN interfere with your ability to perform your USUAL WORK or HOUSEWORK TODAY?
    0 No interference ------- 10 Maximum interference

31. Did your PAIN interfere with your LEISURE ACTIVITIES TODAY?
    0 No interference ------- 10 Maximum interference

32. Did your PAIN interfere with your SOCIAL INTERACTIONS TODAY?
    0 No interference ------- 10 Maximum interference

33. Which STRATEGY did you use to COPE WITH YOUR PAIN TODAY? You may select more than one option:
    a. Inactivity / rest
    b. Relaxation exercise
    c. Speak with someone
    d. Physical Activity / Stretching
    e. Self-statements to persist in a task
    f. Do something to feel positive emotions
    g. Ignore the pain/distract
    h. Pray for the pain to disappear

34. Indicate your degree of agreement with the following sentence: I fear that the pain will get worse.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

35. Indicate your degree of agreement with the following sentence: Today I could not keep my pain out of my mind.
    1) Strongly disagree
    2) Disagree
    3) Neither agree nor disagree
    4) Agree
    5) Strongly agree

36. Please rate your degree of activity TODAY:
0%= Completely inactive -100%= Completely active.

37. In which area have you been more active today? You may select more than one option:
    a. Work
    b. Family
    c. Couple
    d. Friends
    e. Leisure
    f. Physical activity
    g. Other.

38. Did you take a rescue medication TODAY (i.e., medication you only use in the event of acute pain)?
    a. Yes
    b. No

39. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Nausea
    b. Vomiting
    c. Tachycardia
    d. Constipation
    e. Drowsiness / sedation
    f. Blurred vision
    g. Dry mouth
    h. Headache
    i. None of the above

40. Did you experience any of these symptoms TODAY? You may select more than one option:
    a. Dizziness
    b. Itching
    c. Diarrhea
    d. Gait instability

e. Excessive sweating
f. Fever
g. Urine retention
h. Facial redness
i. A different symptom
j. None of the above

41. Did you take your prescribed medication TODAY?
a. Yes
b. No, but I will do it later
c. No and I do not plan to take it
d. I haven't been prescribed a pain medication

42. How many times did you take a rescue medication TODAY?
a. 0
b. 1
c. 2
d. 3
e. 4
f. 5
g. 6
h. 7
i. 8
j. 9
k. 10
l. More than 10

Items assessed the last day of app use:

43. With respect to the beginning of treatment, how are you feeling NOW?
1) Much worse
2) Somewhat worse
3) The same
4) Somewhat better
5) Much better

44. Have you experienced any negative life event in the PAST MONTH?
a. No
b. Yes, but it did not affect me at all
c. Yes, but it did not affect me much
d. Yes and it had quite an effect on me
e. Yes and it affected me a lot

45. If you experienced a major negative life event in the last month, please indicate its characteristics using the list below. You may select more than one option:
    a. Death of a close person
    b. Job problem
    c. Relationship problem
    d. Economic problem
    e. Health problem
    f. Family problem
    g. An event not listed above
    h. I have not experienced any major negative event this month

46. Please indicate the location where your pain is more intense:
    a. Head
    b. Shoulder
    c. Neck
    d. High back
    e. Lower back
    f. Arm
    g. Elbow
    h. Wrist
    i. Hand
    j. Abdomen
    k. Chest
    l. Buttock
    m. Hip
    n. Leg
    o. Knee
    p. Foot
    q. Whole body
    r. Somewhere not listed

47. What is your current treatment for pain? You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment
    e. Natural / alternative treatments
    f. My pain is not being treated

48. Did you start a new treatment for pain in the last month?
    a. Yes
    b. No

49. Please select the treatment/s you started in the last month. You may select more than one option:
    a. Physiotherapy
    b. Pharmacotherapy
    c. Infiltrations
    d. Psychological treatment

e. Natural / alternative treatments
f. I have not started a new treatment

50. What is your marital status?
a. Single
b. Married
c. In a relationship
d. Divorced
e. Separated
f. Widowed

51. What is your job status?
a. Active worker
b. Sick leave
c. Permanent disability
d. Unemployed
e. Homemaker
f. Retired
g. Student

52. Do you currently have a diagnosis of depression by a physician or a psychologist?
a. Yes
b. No

53. Do you currently have a diagnosis of anxiety by a physician or a psychologist?
a. Yes
b. No

Supplement 4: Alarms integrated into the Pain Monitor app

- Morning pain severity > 7 during 5 consecutive days
- Evening pain severity > 7 during 5 consecutive days
- Morning sadness >7 during 5 consecutive days
- Evening sadness >7 during 5 consecutive days
- Morning anxiety >7 during 5 consecutive days
- Evening anxiety >7 during 5 consecutive days
- Vomiting during 2 consecutive days
- Tachycardia during 2 consecutive days
- Blurred vision during 2 consecutive days
- Headache during 2 consecutive days
- Dry mouth during 2 consecutive days
- Constipation during 5 consecutive days
- Drowsiness during 5 consecutive days
- Nausea during 3 consecutive days
- Itching during 3 consecutive days
- Diarrhea during 2 consecutive days
- Fever during 2 consecutive days
- Facial redness during 2 consecutive days
- Urine retention during 2 consecutive days
- Gait instability during 3 consecutive days
- Excessive sweating during 7 consecutive days
- Dizziness during 3 consecutive days
- Treatment discontinuation during 3 consecutive days
- Rescue medication > 3 during 3 consecutive days
- Sleep interference > 7 during 5 consecutive days

Additional file 2: SPIRIT Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, page 1
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 1
Protocol version	3	Date and version identifier	Protocol Amendment Number, page 1
Funding	4	Sources and types of financial, material, and other support	Declarations, page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Authors, page 1
	5b	Name and contact information for the trial sponsor	Trial sponsor, page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, page 14

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, Page 12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, page 1-3
	6b	Explanation for choice of comparators	Method, page 6
Objectives	7	Specific objectives or hypotheses	Introduction, page 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction, page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Sample, page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Interventions and Assessment plan, page 8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Sample, page 7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Assessment plan, page 10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample, page 6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Sample, page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Sample, page 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 6 and 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Pages 6 and 13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Assessment plan, page 10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Procedure, page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Sample, page 7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Data analysis, page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Data analysys, page 12-13

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, Page 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Data analysis, page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Sample, page 8

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Sample, page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Sample, page 7-8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data analysis, page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Sample, page 8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Study design, page 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Availability of data and material, page 15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.