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

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Keywords:	chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring

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

4 **Running Head:** Telemonitoring of pain by Pain Monitor App

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28

29 Abstract

30 *Introduction:* Chronic pain has become a matter of concern for public health due to its
31 high prevalence and because public costs associated with treatment and disability
32 increase each year. Research suggests that limitations in the traditional assessment of
33 chronic pain patients limit the effectiveness of current medical treatments. The use of
34 technology might serve change patient traditional monitoring into Ecological
35 Momentary Assessments, which might be visualized by physicians live. This study
36 describes a Randomized Control Trial designed to test the utility of a technology-based
37 solution for pain telemonitoring consisting of a smartphone app for patients and a web
38 application for physicians. The goal of this study will be to explore whether this
39 combination of eHealth and mHealth improves the effectiveness of existing pain
40 treatments.

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

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

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

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

9 59
10

11 60 **Strengths and limitations of this study**

- 13 61 – To the best of our knowledge, this is the first randomized, controlled clinical trial
14 62 to test the effectiveness of the implementation of an integrative technology-
15 63 based solution for chronic pain that provides support to patients and physicians.
- 16 64 – The results obtained from this study may have important implications for the
17 65 personalization of pain treatments and to enhance the effectiveness and safety
18 66 of pain interventions.
- 19 67 – A study limitation is that physicians who participate in the investigation are not
20 68 blinded to the participants' assigned condition since they need to respond to
21 69 alarms generated by the app.
- 22 70 – An additional shortcoming is that the results will not necessarily be
23 71 generalizable to all pain patients but only to those who met the eligibility criteria
24 72 for the study. This excludes patients not using a smartphone with Internet
25 73 connection (e.g., some older adults).

26 74
27

28 75 **Introduction**

29 76 Pain can be defined as “an unpleasant sensory and emotional experience associated
30 77 with actual or potential tissue damage, or described in terms of such damage” [1] and
31 78 can only be understood as an interplay between “sensory, emotional, cognitive, and
32 79 social components” [2]. Although pain often is acute and disappears as tissues heal,
33 80 sometimes pain persists for long periods of time and becomes chronic. For instance, it
34 81 has been reported that 15% of individuals admitted to trauma hospitals due to a severe
35 82 injury and up to 60% of patients after surgery will continue to experience severe

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3 83 chronic pain months and years later [3]. In general, a cut-off of 3 to 6 months is used to
4
5 84 define the transition from acute/subacute to chronic pain [4].
6

7 85 The aforementioned chronification of pain is becoming a major public health problem
8
9 86 across the globe [5]. Specifically, epidemiological studies indicate that the prevalence
10
11 87 of this disease in the adult population ranges from 19% to 38% worldwide [6–9].
12

13 88 Furthermore, the increase in life expectancy and the ageing of the population is likely to
14
15 89 have an important impact on the number of individuals experiencing chronic pain, since
16
17 90 the prevalence of this syndrome boosts dramatically with age [9]. For instance, it is
18
19 91 expected that the population of chronic pain individuals will be doubled in 2050 for
20
21 92 people older than 65 years and tripled for people over 80 years of age [10].
22
23

24 93 As a result of the growing concern about this disease, there have been numerous
25
26 94 attempts to improve treatments for pain in the past decades. However, recent reviews
27
28 95 on the effectiveness of numerous interventions, including medical treatments,
29
30 96 psychological therapy, physical rehabilitation, or a combination of these indicate that
31
32 97 the effectiveness of existing treatments is, on average, only modest [11–13]. While
33
34 98 there might be numerous factors explaining the limited effectiveness of current
35
36 99 interventions for pain, including unexplored biomechanical mechanisms or genetic
37
38 100 factors, patient characteristics, or therapists' training, some authors have pointed to
39
40 101 methodological shortcomings as key elements explaining the modest effectiveness of
41
42 102 pain interventions. Specifically, the way assessment is currently performed (i.e., a
43
44 103 single measure of pain intensity performed episodically during onsite appointments)
45
46 104 has been argued to impact negatively in the ability of existing interventions to achieve
47
48 105 more reliable and powerful changes in patient outcomes [14,15]. For instance, a single
49
50 106 rate of pain intensity has been shown to be an unreliable measure of pain as this
51
52 107 experience can vary dramatically within the same day and across days [16–18]. In
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54 108 addition, pain is frequently assessed retrospectively, which is known to lead to recall
55
56 109 bias and to decrease the accuracy of pain ratings [19] and does not allow for timely
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3 110 responses to undesired events, so these often take place time after the problem
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5 111 occurred [20].
6
7 112 As a consequence of the above, Ecological Momentary Assessment (EMA), which
8
9 113 refers to the assessment of pain repeatedly and in real life, has received renewed
10
11 114 interest in the past years in the pain literature and is now considered by many as the
12
13 115 gold standard method to assess the pain experience [19,21–24]. Traditionally, EMA
14
15 116 has been difficult due to the limitations and costs of repeated measurement procedures
16
17 117 (i.e., paper diaries or phone calls). However, with the explosion and availability of
18
19 118 smartphones, EMA has become easier than ever and immediate communication
20
21 119 between the patient and the physician is now a more feasible practice [25].
22
23
24 120 It has been argued that this change in the assessment paradigm towards ecological
25
26 121 daily telemonitoring using apps will improve treatment effectiveness and reduce costs if
27
28 122 used to respond to patient reports quickly [14,26]. Indeed, there is evidence to suggest
29
30 123 that smartphones are useful tools to be used for the assessment of pain core outcome
31
32 124 measures in chronic pain settings [14,27,28]. However, the extent to which this EMA of
33
34 125 pain patients can effectively lead to better practices in pain medicine is still unknown.
35
36 126 For this purpose, we developed a technology-based solution that integrated a pain and
37
38 127 symptom tracking app for patients and a web for physicians where app-generated
39
40 128 alarms are received daily and patient app responses can be monitored in real time. To
41
42 129 the best of our knowledge, no study has yet investigated the utility of using such an
43
44 130 integrative technology-based solution for remote, ecological monitoring of patient
45
46 131 evolution and to adjust treatment in response to app alarms in a randomized controlled
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48 132 trial.
49
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51 133 With the previous goal in mind, in the present parallel group, 1:1 superiority trial we will
52
53 134 use the *Pain Monitor* app
54
55 135 (<https://play.google.com/store/apps/details?id=painmonitor.srccode>), which was
56
57 136 developed by a team of psychologists and an engineer with the collaboration of
58
59 137 physicians and nurses and has been recently validated in clinical settings [14], together
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3 138 with a web for the physicians where app responses and alarms can be tracked in real
4
5 139 time to facilitate the professional's decision-making process. As we will explain in more
6
7 140 detail in the Methods section, Pain Monitor assesses a number of pain-related
8
9 141 outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of
10
11 142 pain-related health resources) and the most frequent side effects of medical treatments
12
13 143 for pain. In the study, patients will be randomly assigned to a treatment as usual
14
15 144 condition (TAU) or to a TAU with the support of the patients' app and the physician's
16
17 145 web. We anticipate that the use of the web application linked with the smartphone app
18
19 146 (TAU+app+web condition) will improve the effectiveness of usual treatments resulting
20
21 147 in reduced pain intensity and less frequent side effects of the medication after one
22
23 148 month of medical treatment. Additionally, we expect that this group of patients will
24
25 149 present additional improvements on secondary outcomes, including mood (depression
26
27 150 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
28
29 151 resources in the past month.
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34 153 **Method**

35 154 *Study design*

36
37 155 The current investigation is a randomized superiority clinical trial composed of two
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39 156 parallel groups (1:1 allocation ration): a) TAU and b) TAU+app+web. In the study,
40
41 157 participants in the TAU condition receive the usual pain treatment by the physicians
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43 158 working at the pain unit (i.e., pharmacological treatment or infiltration). Participants
44
45 159 included in TAU+app+web group receive the usual treatment for their pain plus daily
46
47 160 monitoring of their symptoms and pain experience with the Pain Monitor app during
48
49 161 one month. In the TAU+app+web condition, alarms are generated in the presence of
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51 162 previously established undesired events, which have been previously determined by
52
53 163 the physicians at the pain clinic. Physicians are able to monitor these patients' app
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55 164 reports using a web application created for this purpose
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57
58 165 (<https://monitordolor.dolortic.com/>). Thus, phone calls can be conducted in the
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3 166 presence of alarms in order to change or discontinue the medical treatment when
4
5 167 necessary. If the study results indicate that the use of technology leads to better
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7 168 outcomes, participants in the TAU condition will be informed about these findings and
8
9 169 will be offered the possibility to use the app after study participation. In the TAU
10
11 170 condition only, assessment is performed as usual, that is, using self-report measures
12
13 171 administered onsite at the beginning and the end of the study (1 month later).
14
15 172 Neither the physicians nor the patients will be blind to the treatment condition assigned.
16
17 173 Physicians will not be blind because they will receive alarms from the TAU+app+web
18
19 174 participants only. Patients will not be blind because only those in the TAU+app+web
20
21 175 condition will be using technology in addition to usual treatment and because patients
22
23 176 in the TAU condition must know that there is no telemonitoring in their condition.
24
25 177 The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All
26
27 178 items from the World Health Organization Trial Registration Data Set are showed in the
28
29 179 Supplementary file 1. The recruitment started at the end of the same month. SPIRIT
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31 180 guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were
32
33 181 followed to design the trial. The participant timeline (i.e., schedule of enrolment,
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35 182 interventions, and assessments) is shown in Figure 1. Recruitment is currently ongoing
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37 183 and is expected to end in November 2019.
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186 *Sample*

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47 187 Participants will be 250 consecutive chronic pain patients attending the pain clinic at
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49 188 the Hospital General Universitari de Castello (Spain) for the first time. Required sample
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51 189 size was calculated using G*Power [29]. Although the a priori calculation resulted in
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53 190 198 participants, the sample size was increased to 250 considering a dropout rate of
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55 191 27-30% based on previous studies [30,31]. Thus, 125 participants were assigned to
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57 192 each condition. Randomization of participants was performed by an independent
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3 193 researcher using a computer-generated sequence with *Randomizer* [32]. Inclusion
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5 194 criteria are shown in Table 1.
6

7 195

8
9 196 Table 1. Inclusion criteria

12 The patient is over 18 years of age

14 The patient has a mobile phone with Android operating system (the app is
15 currently only available for Android, which is the operating system used by more
16 than 80% of users in Spain) [33].
17
18

19 The patient has the physical ability to use the application

22 The patient does not present psychological and/or cognitive alterations or
23 problems with language that make his/her participation difficult
24

26 The patient voluntarily wants to participate and signs the informed consent form
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29 197

31 198 In the study, all participants are identified using an alphanumeric code. In the case of
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33 199 participants in the TAU+app+web condition, this code is automatically generated by the
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35 200 app. Thus, the database generated by the app is anonymized and the app only collects
36
37 201 the international mobile equipment identity (IMEI). The association between app codes
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39 202 and patient identifiable characteristics is stored locally at the pain clinic. All data
40
41 203 storage procedures follow the European law and data protection rules (European
42
43 204 Union General Data Protection Regulation 2016/679 of the European Parliament and of
44
45 205 the Council of 27 April 2016). In addition, ethical approval from the Hospital General
46
47 206 Universitari de Castello was obtained, in accordance with the Declaration of Helsinki.
48
49 207 Important protocol modifications will be notified and require the approval of the Ethics
50
51 208 Committee of the Hospital General Universitari de Castello. Approved changes will be
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53 209 made public at clinicaltrials.gov. All the participants read and sign an informed consent
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55 210 form before randomization (see Supplementary file 2). Patients who do not agree with
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57 211 the assigned condition, are given the opportunity to be allocated to the preferred
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3 212 condition, but are not used in the analyses. Any changes to modify the assigned
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5 213 condition are accepted at any time during the study, again resulting in an exclusion
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7 214 from the study. Changes in the medication or improvement of disease are do not result
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9 215 in study discontinuation. Disease worsening is not expected to be associated with the
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11 216 inclusion of the app but, if existent, will result in the discontinuation of app use.
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15
16 218 *Procedure*

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18 219 The study is conducted at the pain clinic of the Hospital General Universitari de
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20 220 Castelló. The study is advertised by physicians to all consecutive patients attending the
21
22 221 pain clinic for the first time. To ensure enrolment, physicians will emphasize the
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24 222 importance of active patient participation in research in general and in self-monitoring
25
26 223 in particular. Patients interested in participating are directed to another office where the
27
28 224 lead author, I.J., explains the study procedures in more detail and ensures their
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30 225 eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by
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32 226 explaining the utility of the study and by contacting patients when an alarm informing of
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34 227 low app adherence (i.e., more than three consecutive days without response) is
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36 228 received. All participants are provided with an information sheet and sign the informed
37
38 229 consent. After participation acceptance, participants are assigned to one of the
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40 230 experimental conditions (TAU or TAU+app+web), which had been previously
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42 231 randomized by an external researcher. All participants then complete a paper-and-
43
44 232 pencil assessment protocol in order to control for differences between the two
45
46 233 assessment formats (app vs. pen and pencil) and to compare both conditions using the
47
48 234 same assessment approach. In addition to this paper-and-pencil evaluation, patients in
49
50 235 the TAU+app+web condition download and install the Pain Monitor app into their
51
52 236 phones. Once they install the app, they answer to an initial assessment and then
53
54 237 complete two measures daily (10 am and 7 pm) during one month (study duration).
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56 238 Finally, an end of study appointment is set (one month later) to conduct the post-
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3 239 assessment evaluation. Due to difficulties in transportation or availability, the post-
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5 240 assessment intervention can either be completed onsite or via an on-line survey.
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7 241

8
9 242 *Pain monitor*

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11 243 The Pain Monitor app (Figure 2) has been developed by a group of pain psychologists
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13 244 and an engineer, with the collaboration of physicians and nurses specialized in pain
14
15 245 care. Pain Monitor is composed of several pain-related items which are to be answered
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17 246 twice a day at preset times (10 am and 7 pm, with a two-hour flexibility) during 30 days.
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19 247 The app content has been previously validated with chronic pain patients at the pain
20
21 248 unit of the Vall d'Hebron Hospital [14]. This assessment protocol contains
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23 249 sociodemographic items (i.e., age, sex, and education level, among others) which are
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25 250 evaluated on the first day of app use only, as well as a number of pain-related
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27 251 outcomes that are evaluated daily, which have been selected following recent
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29 252 guidelines on core outcome domains for pain treatments [34,35]. Constructs in the app,
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31 253 including pain intensity, pain interference, anxiety, depression, catastrophizing, social
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33 254 support, acceptance, and coping, among others, are measured with a single item to
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35 255 reduce the burden of daily assessment, each of which was adapted and validated
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37 256 against well-established paper-and-pencil measures [14]. Additionally, the assessment
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39 257 protocol includes a list of side effects created *ad hoc* based on the literature findings on
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41 258 the most frequent adverse effects of pain treatments [36,37], as well as measures of
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43 259 treatment adherence, use of rescue medication, neuropathic characteristics of pain,
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45 260 and use of medical services in the past month. All app items can be found in
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47 261 Supplementary file 3.
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52 262 The app generates alarms in the presence of predefined events (see Supplementary
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54 263 file 4 for the alarms set in the present study in collaboration with the participating
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56 264 physicians). These alarms are sent to the physicians early in the morning on working
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58 265 days so that they can decide whether an action from their side is required (e.g., calling
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3 266 the patient and setting an earlier appointment or suggesting a change in the
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5 267 medication). For this study, a website linked to the app was created for the physicians
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7 268 to observe patient alarms and evolution live. Examples of the physician web are
8
9 269 presented in Figure 3.

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11 270

12 13 271 *Interventions*

14
15 272 Five physicians at the pain clinic of the Hospital General Universitari de Castelló
16
17 273 participate in this study. All patients in the study receive the usual treatment for their
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19 274 pain irrespective of their assigned condition. However, a change in treatment might
20
21 275 occur in the TAU+app+web condition at the discretion of the physicians in charge of
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23 276 treatment after receiving an alarm and consulting the web page with the graphical
24
25 277 representation of patient app responses. As usual, patients in the TAU condition
26
27 278 without the app are not contacted by the physicians between appointments. It is
28
29 279 important to note that both patients in the TAU only and patients in the TAU+app+web
30
31 280 condition are allowed to attend to the emergency services or the family physician in the
32
33 281 event of an emergency at any stage of the study due to ethical reasons. At the end of
34
35 282 the study, this practice is investigated for each participant in the final assessment.

36
37 283

38 39 284 *Assessment plan*

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41 285 All participants in the study fill in a number of questionnaires in a paper-and-pencil
42
43 286 format at the beginning and at the end of the study. This assessment protocol includes
44
45 287 sociodemographic information, use of pain-related health resources in the past week
46
47 288 (i.e., emergency services, family physician, or pain clinic), pain-related physical
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49 289 symptoms experienced in the past week (i.e., side medication effects), the Brief Pain
50
51 290 Inventory (pain severity and interference) [39], the Pain Catastrophizing Scale [40], and
52
53 291 the Hospital Anxiety and Depression Scale [41]. In addition to this paper-and-pencil
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55 292 evaluation, participants in the TAU+app+web condition also install the Pain Monitor app
56
57 293 and complete a pre-intervention assessment in the app after the paper-and-pencil

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3 294 evaluation. Both baseline assessments include the same content and are duplicated to
4
5 295 provide further evidence for the validity of app content. After this pretreatment
6
7 296 evaluation, participants in the TAU+app+web group are asked to answer to the app
8
9 297 assessments twice a day during one month (study duration). A push-up system notifies
10
11 298 the patient about the need to respond to the app evaluation at 10:00 am and 7:00 pm.
12
13 299 These times can be adjusted by the patient with a 2-hour flexibility from the preset
14
15 300 times.

16
17 301 Daily morning and evening assessments differ in a number of items. Some items are
18
19 302 asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only
20
21 303 administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g.,
22
23 304 activity level during the day, interference of pain on daily activities, or physical
24
25 305 symptoms experienced during the day).

26
27 306 Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a
28
29 307 post-assessment protocol. The measures included in this final evaluation are similar to
30
31 308 the ones included in the baseline assessment, with the inclusion of a measure of
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33 309 negative events experienced during the study period and the evaluation of perceived
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35 310 change due to treatment.

36
37 311 In the study, primary outcomes are pain intensity and the number of side effects of the
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39 312 medication reported in the app, while secondary outcomes include mood (depression
40
41 313 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
42
43 314 resources in the past month.

44
45 315 Note that app reports in the TAU+app+web condition are not used to determine
46
47 316 treatment effectiveness compared to the TAU only condition because in the latter
48
49 317 condition participants do not use the app. Therefore, app responses are only used for
50
51 318 telemonitoring and early detection of treatment problems that result in an alarm to the
52
53 319 physicians. The comparison of both conditions will be made using the traditional paper-
54
55 320 and-pencil evaluations which will be available for both groups.
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3 322 *Patient and public Involvement*
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5 323 In the current study, patients or the public will not be involved in the design, or conduct,
6
7 324 or dissemination of the research.
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11 326 *Data analysis*
12

13 327 The aim of the present study is to explore the effect of an integrated technology-based
14
15 328 solution for chronic pain monitoring (an app that monitors pain patients daily and sends
16
17 329 clinical alarms to physicians and a web for physicians that graphically represents
18
19 330 patient evolution as reported in the app) compared to the usual treatment where
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21 331 monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim
22
23 332 in mind, and intention-to-treat analyses will be performed following the
24
25 333 recommendations of the CONSORT guidelines (<http://www.consort-statement.org/>).
26
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28 334 First, the two conditions will be compared at baseline in the different continuous
29
30 335 measures with a between-group analysis via a *t*-test to ensure that randomization
31
32 336 indeed resulted in comparable groups prior to intervention. Chi-squared tests will be
33
34 337 used for all the categorical variables. To evaluate our hypothesis, mixed repeated-
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36 338 measure MANOVAs will be conducted to investigate whether there are differences
37
38 339 between pre- and post-assessment scores as a function of the experimental condition
39
40 340 (TAU or TAU+app+web). Distribution normality and homoscedasticity assumptions will
41
42 341 be tested by means of Kolmogorov-Smirnov and Levene tests, respectively, and a
43
44 342 Mann-Whitney *U* test and Brown-Forsythe *F*-test will be used where necessary. Effect
45
46 343 size will be calculated to complement the MANOVA results with the standardized mean
47
48 344 difference (Cohen's *d*) for both between and within group analyses. This is a novel
49
50 345 study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e.
51
52 346 moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and
53
54 347 number of side effects of the medication) when compared to secondary outcomes
55
56 348 since medical interventions do not specifically focus on these symptoms (i.e., pain
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58 349 interference, mood, fatigue, rescue medication use, and quality of life). The analysis will
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3 350 be performed by CSR, who will be blinded to the treatment allocation. Only the present
4
5 351 study authors will have access to the final trial dataset.

6
7 352 Regarding dropouts, we will choose a strict criterion and the analyses will only include
8
9 353 participants who complete both the pre and the post assessments. Because of the
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11 354 short duration of the trial (one month per patient) and the minimal risks expected from
12
13 355 the use of the app, a data monitoring committee will not be required.
14
15

16 356

17 357 **Discussion**

18
19 358 Chronic pain is a major public health challenge due to its high prevalence in the
20
21 359 population and high direct and indirect costs for the institutions and the individuals [42,
22
23 360 43]. Pain assessment is a complex process characterized by a high variability between
24
25 361 and within days, which is usually performed by clinicians using self-report, onsite,
26
27 362 single ratings which are based on recall [39,40]. EMA using smartphone apps appears
28
29 363 to be an innovative and promising alternative to these traditional assessment methods
30
31 364 [46] as smartphone apps have demonstrated to be accurate tools to assess pain
32
33 365 intensity and related variables from the patients' home, thus facilitating telemonitoring
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35 366 and contributing to the personalization of medical interventions by rapidly adjusting
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37 367 treatments to every individual as a result of telemonitoring [19].

38
39 368 In the present study protocol, we describe a randomized controlled trial designed to
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41 369 test an integrative technology-based solution for chronic pain monitoring consisting of a
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43 370 web application for the healthcare professional which is linked to the patient's app (i.e.,
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45 371 Pain Monitor). Specifically, we want to explore whether the use of this integrative
46
47 372 technology improves the effectiveness of the usual treatment for this population thanks
48
49 373 to telemonitoring and the rapid detection of unwanted events. We expect that the use
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51 374 of Pain monitor, with the support of therapist's web, will result in reduced pain intensity
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53 375 and less frequent side effects of the medication after one month of medical treatment
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55 376 due to the professional's rapid reaction in the presence of undesired outcomes.
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3 377 To our knowledge, this is the first study to assess the effectiveness of this type of
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5 378 integrative technology solution (i.e., a therapist web site linked to a patient smartphone
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7 379 app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis
8
9 380 is confirmed, our findings will serve to demonstrate the feasibility and utility of
10
11 381 smartphones and specialized webs for therapists so that they can be implemented in
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13 382 specialized care contexts (i.e., pain clinics). Likewise, our results will provide important
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15 383 information about the potential benefits of smartphone apps for the personalization of
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17 384 pain treatments (i.e., treatment can be rapidly personalized to a given patient as a
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19 385 function of individual responses reported in the app). Ultimately, this might help change
20
21 386 the model of care for this chronic disease (i.e., episodic, onsite assessment and
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23 387 treatment), since the use of this integrative technology system allows for a continuous
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25 388 and remote evaluation and intervention, providing a faster response to the patient
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27 389 needs and improving self-management and empowerment of patients who attend pain
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29 390 clinics as they become important agents of treatment effectiveness by being in charge
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31 391 of daily reporting of pain-related experiences in the app. In sum, the results of the
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33 392 present investigation could serve an important first step towards the implementation of
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35 393 apps and other Information and Communication Technologies in health services.
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41 395 **List of Abbreviations**

42
43 396 TAU = Treatment as usual; EMA = Ecological Momentary Assessment; IMEI =
44
45 397 International Mobile Equipment Identity; SPIRIT = Standard Protocol Items
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47 398 Recommendations for Interventional Trials; CONSORT = Consolidated Standards of
48
49 399 Reporting Trials; MANOVA = Multivariate Analysis of Variance.
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53 402 **References**

54
55
56
57
58
59 403 1. Merskey H. Classification of chronic pain: Descriptions of chronic pain syndromes
60

- 1
2
3 404 and definitions of pain terms. *Pain*. 1986;3:226.
4
5
6 405 2. Williams AC de C, Craig KD. Updating the definition of pain. *Pain*. 2016;157:2420–3.
7
8 406 doi:10.1097/j.pain.0000000000000613.
9
10
11 407 3. Lavand'homme P. The progression from acute to chronic pain. *Curr Opin*
12
13 408 *Anaesthesiol*. 2011;24:545–50. doi:10.1097/ACO.0b013e32834a4f74.
14
15
16 409 4. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification
17
18 410 of chronic pain for ICD-11. *Pain*. 2015;156:1. doi:10.1097/j.pain.0000000000000160.
19
20
21 411 5. Bevan S, Quadrello T, Mcgee R, Mahdon M, Vavrovsky A, Barham L. Fit for Work
22
23 412 pain-European report. 2009.
24
25
26 413 6. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in
27
28 414 Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–287.
29
30 415 doi:10.1016/j.ejpain.2005.06.009.
31
32
33 416 7. Larsson C, Hansson EE, Sundquist K, Jakobsson U. Chronic pain in older adults:
34
35 417 prevalence, incidence, and risk factors. *Scand J Rheumatol*. 2017;46:317–25.
36
37
38 418 8. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012.
39
40 419 *J Pain*. 2015;16:769–80.
41
42
43 420 9. Häuser W, Wolfe F, Henningsen P, Schmutzer G, Brähler E, Hinz A. Untying chronic
44
45 421 pain: Prevalence and societal burden of chronic pain stages in the general population -
46
47 422 A cross-sectional survey. *BMC Public Health*. 2014;14:1–8.
48
49
50 51
52 423 10. Miró J, Paredes S, Rull M, Queral R, Miralles R, Nieto R, et al. Pain in older adults:
53
54 424 a prevalence study in the Mediterranean region of Catalonia. *Eur J Pain*. 2007;11:83–
55
56 425 92. doi:10.1016/j.ejpain.2006.01.001.
57
58
59 426 11. Vincent GE, Velkoff VA. The next four decades the older population in the United
60

- 1
2
3 427 States : 2010 to 2050. 2010.
4
5
6 428 12. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity
7
8 429 and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane
9
10 430 database Syst Rev. 2017;1:CD011279.
11
12
13 431 13. Gatchel RJR, McGeary DD, McGeary CAC, Lippe B. Interdisciplinary chronic pain
14
15 432 management: past, present, and future. *Am Psychol*. 2014;69:119–30.
16
17 433 doi:10.1037/a0035514.
18
19
20 434 14. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and
21
22 435 Commitment Therapy (ACT) for Chronic Pain: A Systematic Review and Meta-
23
24 436 Analyses. *Clin J Pain*. 2017;33:552–68.
25
26
27 437 15. Suso-Ribera C, Castilla D, Zaragoza I, Ribera-Canudas MV, Botella C, Garcia-
28
29 438 Palacios A. Validity, Reliability, Feasibility, and Usefulness of Pain Monitor: A
30
31 439 Multidimensional Smartphone App for Daily Monitoring of Adults With Heterogenous
32
33 440 Chronic Pain. *Clin J Pain*. 2018;34:900–8.
34
35
36
37 441 16. Dansie EJ, Turk DC. Assessment of patients with chronic pain. *Br J Anaesth*.
38
39 442 2013;111:19–25.
40
41
42 443 17. Kikuchi H, Yoshiuchi K, Miyasaka N, Ohashi K, Yamamoto Y, Kumano H, et al.
43
44 444 Reliability of recalled self-report on headache intensity: Investigation using ecological
45
46 445 momentary assessment technique. *Cephalalgia*. 2006;26:1335–43.
47
48
49 446 18. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity
50
51 447 measurement in chronic pain patients. *Pain*. 1993;55:195–203.
52
53
54 448 19. Kratz AL, Murphy SL, Braley TJ. Ecological Momentary Assessment of Pain,
55
56 449 Fatigue, Depressive, and Cognitive Symptoms Reveals Significant Daily Variability in
57
58 450 Multiple Sclerosis. *Arch Phys Med Rehabil*. 2017. doi:10.1016/j.apmr.2017.07.002.
59
60

- 1
2
3 451 20. García-Palacios A, Herrero R, Belmonte MA, Castilla D, Guixeres J, Molinari G, et
4
5 452 al. Ecological momentary assessment for chronic pain in fibromyalgia using a
6
7 453 smartphone: A randomized crossover study. *Eur J Pain*. 2014;18:862–72.
8
9 454 doi:10.1002/j.1532-2149.2013.00425.x.
10
11
12 455 21. Suso-Ribera C, Mesas Á, Medel J, Server A, Márquez E, Castilla D, et al.
13
14 456 Improving pain treatment with a smartphone app: study protocol for a randomized
15
16 457 controlled trial. *Trials*. 2018;19:145. doi:10.1186/s13063-018-2539-1.
17
18
19 458 22. Lin W-C, Burke L, Schlenk EA, Yeh CH. Use of an Ecological Momentary
20
21 459 Assessment Application to Assess the Effects of Auricular Point Acupressure for
22
23 460 Chronic Low Back Pain. *Comput Inform Nurs*. 2018.
24
25
26 461 23. Shiffman S, Stone AA, Hufford MR. Ecological Momentary Assessment. *Annu Rev*
27
28 462 *Clin Psychol*. 2008;4:1–32. doi:10.1146/annurev.clinpsy.3.022806.091415.
29
30
31 463 24. Stone AA, Shiffman S. Ecological momentary assessment (EMA) in behavioral
32
33 464 medicine. *Ann Behav Med*. 1994;16:199–202.
34
35
36 465 25. Smyth JM, Stone AA. Ecological Momentary Assessment Research in Behavioral
37
38 466 medicine. *J Happiness Stud*. 2003;4:35–52. doi:10.1023/A:1023657221954.
39
40
41 467 26. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological Momentary
42
43 468 Assessment Methodology in Chronic Pain Research: A Systematic Review. *J Pain*.
44
45 469 2018;19:699–716. doi:10.1016/j.jpain.2018.01.006.
46
47
48 470 27. Moore J. The benefits of mobile apps for patients and providers. *Br J Healthc*
49
50 471 *Manag*. 2012;18:465–7.
51
52
53 472 28. Reynoldson C, Stones C, Allsop M, Gardner P, Bennett MI, Closs SJ, et al.
54
55 473 Assessing the Quality and Usability of Smartphone Apps for Pain Self-Management.
56
57 474 *Pain Med*. 2014;15:898–909.

- 1
2
3 475 29. Rosser BA, Eccleston C. Smartphone applications for pain management. J
4
5 476 Telemed Telecare. 2011;17:308–12.
6
7
8 477 30. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power
9
10 478 analysis program for the social, behavioral, and biomedical sciences. Behav Res
11
12 479 Methods. 2007;39:175–91. doi:10.3758/BF03193146.
13
14
15 480 31. Kristjansdottir OB, Fors EA, Eide E, Finset A, Stensrud TL, van Dulmen S, et al. A
16
17 481 smartphone-based intervention with diaries and therapist-feedback to reduce
18
19 482 catastrophizing and increase functioning in women with chronic widespread pain:
20
21 483 randomized controlled trial. J Med Internet Res. 2013;15:e5.
22
23
24 484 32. Macea DD, Gajos K, Daglia Calil YA, Fregni F. The Efficacy of Web-Based
25
26 485 Cognitive Behavioral Interventions for Chronic Pain: A Systematic Review and Meta-
27
28 486 Analysis. J Pain. 2010;11:917–29. doi:10.1016/j.jpain.2010.06.005.
29
30
31 487 33. Urbaniak, GC and Plous S. Research randomizer (version 4.0)[computer software].
32
33 488 Social Psychology Network. 2013.
34
35
36
37 489 34. Share. KWPSO sales market. No Title.
38
39
40 490 35. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al.
41
42 491 Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.
43
44 492 Pain. 2005;113:9–19. doi:10.1016/j.pain.2004.09.012.
45
46
47
48 493 36. Kaiser U, Kopkow C, Deckert S, Neustadt K, Jacobi L, Cameron P, et al.
49
50 494 Developing a core outcome domain set to assessing effectiveness of interdisciplinary
51
52 495 multimodal pain therapy: the VAPAIN consensus statement on core outcome domains.
53
54 496 Pain. 2018;159:673–83.
55
56
57 497 37. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS
58
59 498 guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J
60

- 1
2
3 499 Neurol. 2010;17:1113-e88. doi:10.1111/j.1468-1331.2010.02999.x.
4
5
6 500 38. Varrassi G, Müller-Schwefe G, Pergolizzi J, Orónska a, Morlion B, Mavrocordatos
7
8 501 P, et al. Pharmacological treatment of chronic pain - the need for CHANGE. Curr Med
9
10 502 Res Opin. 2010;26:1231–45. doi:10.1185/03007991003689175.
11
12
13 503 39. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory.
14
15 504 Ann Acad Med Singapore. 1994;23:129–38.
16
17 505 <http://europepmc.org/abstract/MED/8080219>.
18
19
20
21 506 40. Sullivan MJLMJL, Bishop SRS, Pivik J. The pain catastrophizing scale:
22
23 507 development and validation. Psychol Assess. 1995;7:524–32. doi:10.1037/1040-
24
25 508 3590.7.4.524.
26
27
28 509 41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr
29
30 510 Scand. 1983;67:361–70. <http://www.ncbi.nlm.nih.gov/pubmed/6880820>. Accessed 11
31
32 511 Jul 2014.
33
34
35 512 42. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic
36
37 513 pain in Europe: The case for strategic prioritisation and action to improve knowledge
38
39 514 and availability of appropriate care. BMC Public Health. 2013;13.
40
41
42
43 515 43. Frieem CH, Willweber-Strumpf A, Zenz MW. Chronic pain in primary care. German
44
45 516 figures from 1991 and 2006. BMC Public Health. 2009;9:1–9.
46
47
48 517 44. Gorin, A. A., & Stone AA. Recall biases and cognitive errors in retrospective self-
49
50 518 reports: A call for momentary assessments. In: Baum A, Revenson T, J. Singer,
51
52 519 editors. Handbook of health psycholog. Mahwah, NJ: Lawrence Erlbaum; 2001. p.
53
54 520 405–13.
55
56
57 521 45. Schwarz N. Retrospective and Concurrent Self-Reports: The Rationale for Real-
58
59 522 Time Data Capture. In: A. Stone, S. S. Shiffman, A. Atienza & LN, editor. The science

1
2
3 523 of real-time data capture: Self-reports in health research. New York: Oxford University
4
5 524 Pres; 2007. p. 11–26.
6
7

8 525 46. Alexander J, Joshi G. Smartphone applications for chronic pain management: a
9
10 526 critical appraisal. *J Pain Res.* 2016;9:731–4. doi:10.2147/JPR.S119966.
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17 528 **Author Statement:** All authors were strongly involved in the study conceptualization
18
19 529 and design and have reviewed and discussed the manuscript. IJ and CSR prepared
20
21 530 the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG.
22
23 531 After changes were incorporated, a final version was approved by all authors. IJ and
24
25 532 JLG are currently in charge of recruitment and IJ and CSR will be in charge of data
26
27 533 analysis.
28
29

30
31 534 **Funding:** Funded by *Plan de Promoción de la investigación Universitat Jaume I*. Ref
32
33 535 UJI-B2016-39 and a Predoctoral Grant (PREDOC/2017/26) by the Universitat Jaume I
34
35 536 to IJ. The first grant allowed for the development of the technological systems used in
36
37 537 the study (physician website and link to the app). The second grant serves to pay the
38
39 538 salary of the lead researcher and predoctoral candidate, IJ.
40
41

42 539 **Competing interests:** The intellectual property of the Pain Monitor app is owned by
43
44 540 co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any
45
46 541 competing interests to declare as they do not receive any financial gain from these
47
48 542 technologies.
49
50

51
52 543 **Ethics approval and consent to participate:** Ethical approval from the Hospital
53
54 544 General Universitari de Castelló was obtained, in accordance with the Declaration of
55
56 545 Helsinki. All participants provided written informed consent to participate in the study.
57
58 546 The informed consent form was approved by the ethics committee of the Hospital
59
60 547 General Universitari de Castelló.

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6 549 **FIGURES**
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9 550 Figure 1. Study schedule of enrolment, interventions, and assessments.
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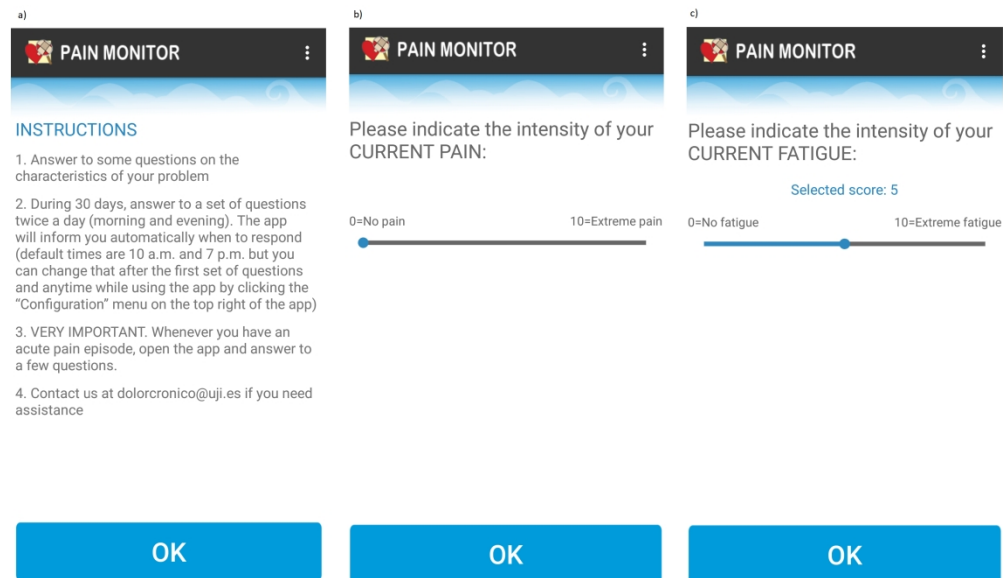
12 551 Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c)
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14 552 Pain Monitor assessment of fatigue.
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17 553 Figure 3. Examples of the web for the physician. a) Patient's side effects during 30
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19 554 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c)
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21 555 Distribution of patient side effects.
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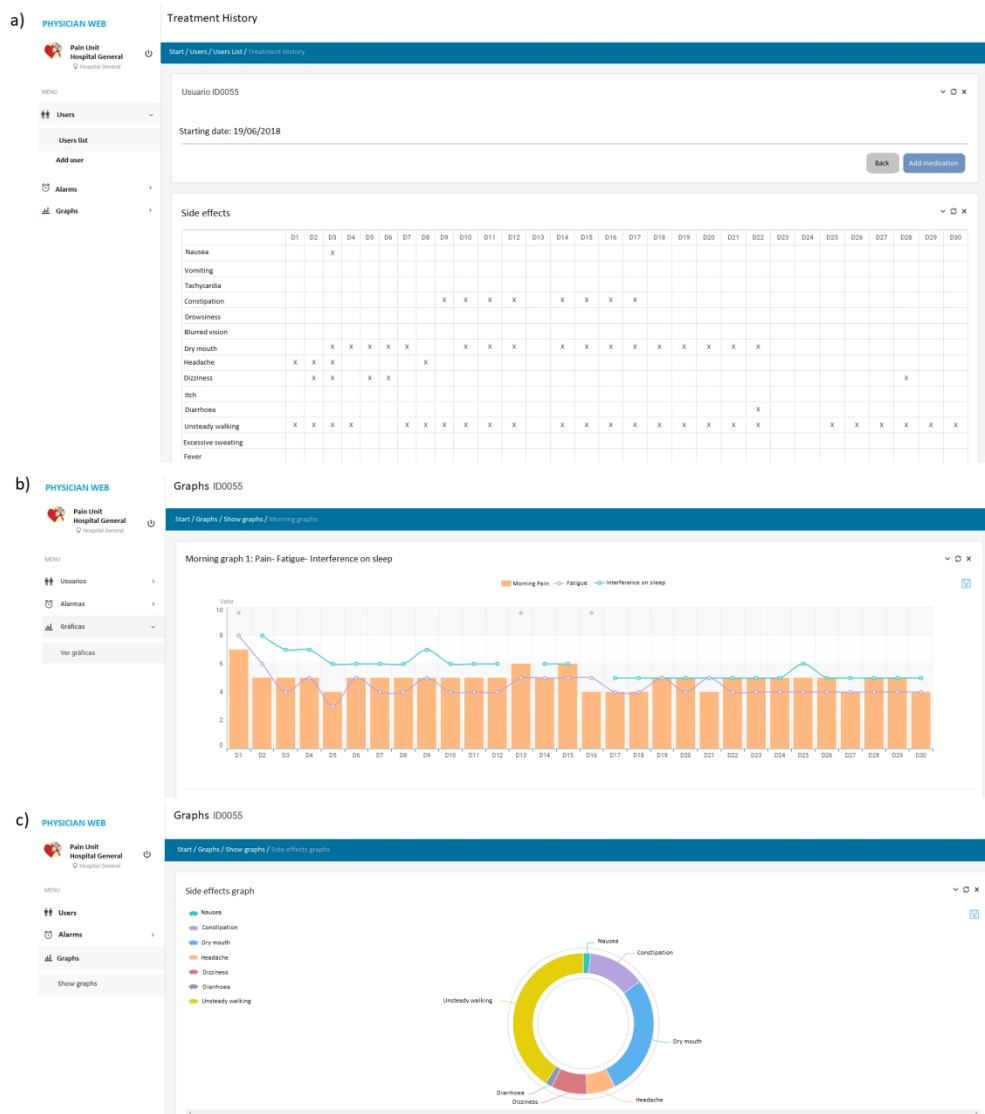
STUDY PERIOD

	Pre-intervention	Intervention period	Close-out
TIMEPOINT	0	T₁	T₂
	<i>Pre-Intervention</i>	<i>Between assessments</i>	<i>One month follow-up</i>
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	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> 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 <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> 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.

For peer review only

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 investigación 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 month 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

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3 reduction in the increase in access to health services for a large number of people who
4 do not have access to health services suffer from mental disorders.
5

6 **How will my data be treated?**

7
8 All data relevant to the study will be collected and stored in compliance with data
9 protection regulations in force. These data will only be used anonymously for the
10 purpose of scientific analysis. All persons involved in the study have an obligation to
11 comply with data protection laws. We will make sure that all your information - without
12 restrictions - is treated as in a confidential manner. Any data collected will be deleted as
13 soon as it is not necessary for scientific purposes.
14
15
16

17 **Can I decline or suspend my participation?**

18
19 Yes, you may refuse to participate in this study or terminate your participation at any
20 time. In the event that you decide to discontinue your participation in the study all of
21 your data will be destroyed immediately.
22
23

24 **Who is the researcher responsible for the study?**

25
26 Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and
27 Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail:
28 azucena@uji.es
29

30
31 You may contact the principal investigator if you have any questions, concerns about
32 the study, about the data being collected, or if you wish to make use of your right to
33 suspend your participation.
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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

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3 g. Neurosurgeon
4 h. Neurologist
5 i. Oncologist
6 j. Another professional.
7
8
9 7. When did your current pain start?
10 a. Less than one year ago
11 b. Between 1 and 5 years ago
12 c. Between 5 and 10 years ago
13 d. More than 10 years ago
14
15
16 8. What is your current treatment for pain? You may select more than one option:
17 a. Physiotherapy
18 b. Pharmacotherapy
19 c. Infiltrations
20 d. Psychological treatment
21 e. Natural / alternative treatments
22 f. My pain is not being treated
23
24
25 9. Did you start a new treatment for pain in the last month?
26 a. Yes
27 b. No
28
29
30 10. Please select the treatment/s you started in the last month. You may select more
31 than one option:
32 a. Physiotherapy
33 b. Pharmacotherapy
34 c. Infiltrations
35 d. Psychological treatment
36 e. Natural / alternative treatments
37 f. I have not started a new treatment
38
39
40 11. What is your marital status?
41 a. Single
42 b. Married
43 c. In a relationship
44 d. Divorced
45 e. Separated
46 f. Widowed
47
48
49 12. What is your job status?
50 a. Active worker
51 b. Sick leave
52 c. Permanent disability
53 d. Unemployed
54 e. Homemaker
55 f. Retired
56 g. Student
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58
59 13. What is the highest level of education you have completed?
60

- 1
- 2
- 3 a. No studies
- 4 b. Less than high school
- 5 c. High school graduate
- 6 d. Technical training
- 7 e. University degree
- 8
- 9

10 14. Do you currently have a diagnosis of depression by a physician or a
11 psychologist?

- 12 a. Yes
- 13 b. No
- 14
- 15

16 15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?

- 17 a. Yes
- 18 b. No
- 19
- 20
- 21

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

23 16. Please indicate the intensity of your CURRENT PAIN:

24 0 No pain -----10 Extreme pain

25 17. Please indicate the intensity of your CURRENT FATIGUE:

26 0 No fatigue -----10 Extreme fatigue

27 18. Please indicate the intensity of your CURRENT HAPPINESS:

28 0 No happiness -----10 Extremely happy

29 19. Please indicate the intensity of your CURRENT SADNESS:

30 0 No sadness ----- 10 Extremely sad

31 20. Please indicate the intensity of your CURRENT ANXIETY:

32 0 No anxiety ----- 10 Extremely anxious

33 21. Please indicate the intensity of your CURRENT ANGER:

34 0 No anger ----- 10 Extremely angry

35 22. Does your pain have any of these characteristics? You may select more than one
36 option:

- 37 a. Burning
- 38 b. Painful cold
- 39 c. Electric shocks
- 40 d. Tingling
- 41 e. Pins and needles
- 42 f. Numbness
- 43 g. Itching
- 44 h. Reduced sensitivity to touch
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- 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

- 1
2
3 35. Indicate your degree of agreement with the following sentence: Today I could
4 not keep my pain out of my mind.
5
6 1) Strongly disagree
7 2) Disagree
8 3) Neither agree nor disagree
9 4) Agree
10 5) Strongly agree
11
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14 36. Please rate your degree of activity TODAY:
15 0%= Completely inactive -100%= Completely active.
16
17
18 37. In which area have you been more active today? You may select more than one
19 option:
20 a. Work
21 b. Family
22 c. Couple
23 d. Friends
24 e. Leisure
25 f. Physical activity
26 g. Other.
27
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30
31 38. Did you take a rescue medication TODAY (i.e., medication you only use in the
32 event of acute pain)?
33 a. Yes
34 b. No
35
36
37
38 39. Did you experience any of these symptoms TODAY? You may select more than
39 one option:
40 a. Nausea
41 b. Vomiting
42 c. Tachycardia
43 d. Constipation
44 e. Drowsiness / sedation
45 f. Blurred vision
46 g. Dry mouth
47 h. Headache
48 i. None of the above
49
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53 40. Did you experience any of these symptoms TODAY? You may select more than
54 one option:
55 a. Dizziness
56 b. Itching
57 c. Diarrhea
58 d. Gait instability
59
60

- 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

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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:
- Death of a close person
 - Job problem
 - Relationship problem
 - Economic problem
 - Health problem
 - Family problem
 - An event not listed above
 - I have not experienced any major negative event this month
46. Please indicate the location where your pain is more intense:
- Head
 - Shoulder
 - Neck
 - High back
 - Lower back
 - Arm
 - Elbow
 - Wrist
 - Hand
 - Abdomen
 - Chest
 - Buttock
 - Hip
 - Leg
 - Knee
 - Foot
 - Whole body
 - Somewhere not listed
47. What is your current treatment for pain? You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - Psychological treatment
 - Natural / alternative treatments
 - My pain is not being treated
48. Did you start a new treatment for pain in the last month?
- Yes
 - No
49. Please select the treatment/s you started in the last month. You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - 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

1		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
2				
3				
4				
5				
6				
7	Introduction			
8				
9	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
10				
11				
12		6b	Explanation for choice of comparators	Method, page 6
13				
14	Objectives	7	Specific objectives or hypotheses	Introduction, page 3
15				
16				
17	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
18				
19				
20				
21				
22	Methods: Participants, interventions, and outcomes			
23				
24	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
25				
26				
27	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
28				
29				
30	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
31				
32				
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35		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
36				
37				
38		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8
39				
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1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
2	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
3				
4				
5	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
6				
7	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
8				
9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
10				

Methods: Assignment of interventions (for controlled trials)

Allocation:

11	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
12				
13				
14	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
15				
16	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
17				
18	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
19				
20		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

1 **Methods: Data collection, management, and analysis**

2

3

4 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

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9 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

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12 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

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17 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

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20 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable

21

22 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 analysis, page 12-13

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27 **Methods: Monitoring**

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29 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

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35 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

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38 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

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1	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
2				
3				
4	Ethics and dissemination			
5				
6	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
7				
8				
9	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
10				
11				
12				
13				
14	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
15				
16				
17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
18				
19				
20	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
21				
22				
23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
24				
25				
26				
27	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
28				
29				
30	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
31				
32				
33	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
34				
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38		31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16
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1	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
2			
3			
4			
5			
6	Appendices		
7			
8	Informed consent materials	32 Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
9			
10			
11	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
12			
13			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033586.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Oct-2019
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
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Public health
Keywords:	chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring

SCHOLARONE™
Manuscripts

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

4 **Running Head:** Telemonitoring of pain by Pain Monitor App

6 **Authors:** Irene Jaén^{1,a}, Carlos Suso-Ribera¹, Diana Castilla^{2,3}, Irene Zaragoza³,
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23 Word count: 3757

24 **Protocol Amendment Number:** 01

2019-July-8	Original
2019-October-13	1 st review

1
2
3 **27 Abstract**
4

5 *28 Introduction:* Chronic pain has become a matter of public health concern due to its high
6
7 *29 prevalence and because public costs associated with treatment and disability increase*
8
9 *30 each year. Research suggests that limitations in the traditional assessment of chronic*
10
11 *31 pain patients limit the effectiveness of current medical treatments. The use of*
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13 *32 technology might serve change patient traditional monitoring into Ecological*
14
15 *33 Momentary Assessments, which might be visualized by physicians live. This study*
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17 *34 describes a Randomized Control Trial designed to test the utility of a technology-based*
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19 *35 solution for pain telemonitoring consisting of a smartphone app for patients and a web*
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21 *36 application for physicians. The goal of this study will be to explore whether this*
22
23 *37 combination of eHealth and mHealth improves the effectiveness of existing pain*
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25 *38 treatments.*

26
27
28 *39 Methods and analysis:* Participants will be 250 patients randomly assigned to one of
29
30 *40 these two conditions: treatment as usual (TAU) and TAU+app+web. All participants will*
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32 *41 receive the usual treatment for their pain. Only the TAU+app+web group use Pain*
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34 *42 Monitor app, which generates alarms that are sent to the physicians in the face of*
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36 *43 previously-established undesired events. Physicians will be able to monitor app reports*
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38 *44 using a web application, which might result in an adjustment of treatment. We*
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40 *45 anticipate that the use of Pain Monitor plus the therapist web will result in a reduction of*
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42 *46 pain intensity and side effects of the medication. Improvements on secondary*
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44 *47 outcomes, namely fatigue, mood, pain interference, rescue medication use, and quality*
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46 *48 of life, are also expected. Mixed repeated-measure MANOVAs will be conducted to*
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48 *49 investigate whether there are differences between pre- and post-assessment scores as*
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50 *50 a function of the experimental condition.*

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52 *51 Ethics and dissemination:* Ethical approval from the Hospital General Universitari de
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54 *52 Castellon was obtained. The findings will be published in peer-reviewed journals.*

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56 *53 Trial registration:* NCT03606265. The trial is active. Recruitment is ongoing.
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1
2
3 55 **Keywords:** Chronic pain, ecological momentary assessment, ehealth, mhealth,
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5 56 telemonitoring.
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9 58 **Strengths and limitations of this study**

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11 59 – To the best of our knowledge, this is the first randomized, controlled clinical trial
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13 60 to test the effectiveness of implementing an integrative e-health and m-health
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15 61 solution for chronic pain that provides support to patients and physicians.
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17 62 – Contrary to traditional face-to-face monitoring, patient monitoring in this study
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19 63 becomes ecological and momentary, so that patients can report their evolution
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21 64 at home whenever they want.
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23 65 – Patient responses to the App are used to generate alarms in the presence of
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25 66 unwanted clinical events, such as the onset of side treatment effects or a poor
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27 67 response to treatment.
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29 68 – Physicians can track patient evolution at any time on a website and receive
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31 69 clinical alarms daily, so that rapid responses can be offered.
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33 70 – Study limitations include the fact that physicians who participate in the
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35 71 investigation are not blinded to the participants' assigned condition, since they
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37 72 need to respond to alarms generated by the app, and the fact that the
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39 73 assessment protocol in the App includes more variables than those actually
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41 74 used for the study because the protocol in the App could not be flexibly
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43 75 changed when the study began.
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49 76
50 77 **Introduction**

51 78 Pain can be defined as “an unpleasant sensory and emotional experience associated
52
53 79 with actual or potential tissue damage, or described in terms of such damage” (1) and
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55 80 can only be understood as an interplay between “sensory, emotional, cognitive, and
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57 81 social components” (2). Although pain often is acute and disappears as tissues heal,
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59 82 sometimes pain persists for long periods of time and becomes chronic. For instance, it
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3 83 has been reported that 15% of individuals admitted to trauma hospitals due to a severe
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5 84 injury and 15- 60% of patients after surgery will continue to experience chronic pain
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7 85 months and years later (3). In general, a cut-off of 3 to 6 months is used to define the
8
9 86 transition from acute/subacute to chronic pain (4).

10
11 87 The aforementioned chronification of pain is becoming a major public health problem
12
13 88 across the globe (5). We refer here to primary chronic pain, a pain associated with
14
15 89 important interference on functioning and/or emotional distress which cannot be better
16
17 90 accounted for by any other condition (6). Specifically, epidemiological studies indicate
18
19 91 that the prevalence of this disease in the adult population ranges from 19% to 38%
20
21 92 worldwide (7–10). Furthermore, the increase in life expectancy and the ageing of the
22
23 93 population is likely to have an important impact on the number of individuals
24
25 94 experiencing chronic pain, since the prevalence of this syndrome boosts dramatically
26
27 95 with age (11). For instance, it is expected that the population of chronic pain individuals
28
29 96 will be doubled in 2050 for people older than 65 years and tripled for people over 80
30
31 97 years of age (12). Thus, chronic pain is a major public health challenge due to its high
32
33 98 prevalence in the population and high direct and indirect costs for the institutions and
34
35 99 the individuals (13,14).

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38
39 100 Indeed, chronic primary pain (e.g., fibromyalgia or nonspecific low back or neck pain, to
40
41 101 name some examples) is imposing a huge burden in our societies as this disease has
42
43 102 become one of the leading causes of years lived with disability globally (15,16) Not
44
45 103 surprisingly, as a result of the growing concern about this disease, there have been
46
47 104 numerous attempts to improve treatments for pain in the past decades. However,
48
49 105 recent reviews on the effectiveness of numerous interventions, including medical
50
51 106 treatments, psychological therapy, physical rehabilitation, or a combination of these
52
53 107 indicate that the effectiveness of existing treatments is, on average, only modest (17–
54
55 108 19). While there might be numerous factors explaining the limited effectiveness of
56
57 109 current interventions for pain, including unexplored biomechanical mechanisms or
58
59 110 genetic factors, patient characteristics, or therapists' training, some authors have

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3 111 pointed to methodological shortcomings as key elements explaining the modest
4
5 112 effectiveness of pain interventions. Specifically, the way assessment is currently
6
7 113 performed (i.e., a single measure of pain intensity performed episodically during onsite
8
9 114 appointments) has been argued to impact negatively in the ability of existing
10
11 115 interventions to achieve more reliable and powerful changes in patient outcomes
12
13 116 (20,21). For instance, a single rate of pain intensity has been shown to be an unreliable
14
15 117 measure of pain as this experience can vary dramatically within the same day and
16
17 118 across days (22–24). In addition, pain is frequently assessed retrospectively, which is
18
19 119 known to lead to recall bias and to decrease the accuracy of pain ratings (25) and does
20
21 120 not allow for timely responses to undesired events, so these often take place time after
22
23 121 the problem occurred (21).
24
25
26 122 As a consequence of the above, Ecological Momentary Assessment (EMA), which
27
28 123 refers to the assessment of pain repeatedly and in real life, has received renewed
29
30 124 interest in the past years in the pain literature and is now considered by many as the
31
32 125 gold standard method to assess the pain experience (26–29). Traditionally, EMA has
33
34 126 been difficult due to the limitations and costs of repeated measurement procedures
35
36 127 (i.e., paper diaries or phone calls). However, with the explosion and availability of
37
38 128 smartphones, EMA has become easier than ever and immediate communication
39
40 129 between the patient and the physician is now a more feasible practice (30).
41
42
43 130 It has been argued that this change in the assessment paradigm towards ecological
44
45 131 daily telemonitoring using apps will improve treatment effectiveness and reduce costs if
46
47 132 used to respond to patient reports quickly (21,31). Indeed, there is evidence to suggest
48
49 133 that smartphones are useful tools to be used for the assessment of pain core outcome
50
51 134 measures in chronic pain settings (21,32,33). However, the extent to which this EMA of
52
53 135 pain patients can effectively lead to better practices in pain medicine is still unknown.
54
55 136 For this purpose, we developed a technology-based solution that integrated a pain and
56
57 137 symptom tracking app for patients and a web for physicians where app-generated
58
59 138 alarms are received daily and patient app responses can be monitored in real time. To
60

1
2
3 139 the best of our knowledge, no study has yet investigated the utility of using such an
4
5 140 integrative technology-based solution for remote, ecological monitoring of patient
6
7 141 evolution and to adjust treatment in response to app alarms in a randomized controlled
8
9 142 trial.

10
11 143 With the previous goal in mind, in the present parallel group, superiority trial we will use
12
13 144 the *Pain Monitor* app
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15 145 (<https://play.google.com/store/apps/details?id=painmonitor.srccode>), which was
16
17 146 developed by a team of psychologists and an engineer with the collaboration of
18
19 147 physicians and nurses and has been recently validated in clinical settings (21), together
20
21 148 with a web for the physicians where app responses and alarms can be tracked in real
22
23 149 time to facilitate the professional's decision-making process. As we will explain in more
24
25 150 detail in the Methods section, Pain Monitor assesses a number of pain-related
26
27 151 outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of
28
29 152 pain-related health resources) and the most frequent side effects of medical treatments
30
31 153 for pain. In the study, patients will be randomly assigned to a treatment as usual
32
33 154 condition (TAU) or to a TAU with the support of the patients' app and the physician's
34
35 155 web. We anticipate that the use of the web application linked with the smartphone app
36
37 156 (TAU+app+web condition) will improve the effectiveness of usual treatments resulting
38
39 157 in reduced pain intensity and less frequent side effects of the medication after one
40
41 158 month of medical treatment. Additionally, we expect that this group of patients will
42
43 159 present additional improvements on secondary outcomes, including mood (depression
44
45 160 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
46
47 161 resources in the past month as secondary gains of reducing pain levels, as suggested
48
49 162 in the literature (34). We also expect that the rapid detection of treatment undesired
50
51 163 events will rapidly minimize threats to the patient's quality of life and mood.
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56 164

57 165 **Method**

58 166 *Study design*

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3 167 The current investigation is a randomized superiority clinical trial composed of two
4
5 168 parallel groups (1:1 allocation ratio): a) TAU and b) TAU+app+web. In the study,
6
7 169 participants in the TAU condition receive the usual pain treatment by the physicians
8
9 170 working at the pain unit (i.e., pharmacological treatment or infiltration). Participants
10
11 171 included in TAU+app+web group receive the usual treatment for their pain plus daily
12
13 172 monitoring of their symptoms and pain experience with the Pain Monitor app during
14
15 173 one month. In the TAU+app+web condition, alarms are generated in the presence of
16
17 174 previously established undesired events, which have been previously determined by
18
19 175 the physicians at the pain clinic (e.g., pain intensity is higher than 7 in an 11-point
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21 176 numerical scale during 3 consecutive days). Physicians are able to monitor these
22
23 177 patients' app reports using a web application created for this purpose
24
25 178 (<https://monitordolor.dolortic.com/>). Thus, phone calls can be conducted in the
26
27 179 presence of alarms in order to change or discontinue the medical treatment when
28
29 180 necessary. If the study results indicate that the use of technology leads to better
30
31 181 outcomes, participants in the TAU condition will be informed about these findings and
32
33 182 will be offered the possibility to use the app after study participation. In the TAU
34
35 183 condition only, assessment is performed as usual, that is, using self-report measures
36
37 184 administered onsite at the beginning and the end of the study (1 month later).
38
39 185 Neither the physicians nor the patients will be blind to the treatment condition assigned.
40
41 186 Physicians will not be blind because they will receive alarms from the TAU+app+web
42
43 187 participants only. Patients will not be blind because only those in the TAU+app+web
44
45 188 condition will be using technology in addition to usual treatment and because patients
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47 189 in the TAU condition must know that there is no telemonitoring in their condition.
48
49 190 The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All
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51 191 items from the World Health Organization Trial Registration Data Set are showed in the
52
53 192 Supplementary file 1. The recruitment started at the end of the same month. SPIRIT
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55 193 guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were
56
57 194 followed to design the trial. The participant timeline (i.e., schedule of enrolment,
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59
60

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

197

198 *Sample*

199 Participants will be 250 consecutive chronic pain patients attending the pain clinic at
 200 the Hospital General Universitari de Castello (Spain) for the first time. Required sample
 201 size was calculated using G*Power (35). Although the a priori calculation resulted in
 202 198 participants, the sample size was increased to 250 considering a dropout rate of
 203 27-30% based on previous studies (36,37). Thus, 125 participants were assigned to
 204 each condition. Randomization of participants was performed by an independent
 205 researcher using a computer-generated sequence with *Randomizer* (38). Inclusion
 206 criteria are shown in Table 1. Only patients for whom a change in the treatment is
 207 planned (e.g., an epidural infiltration or a change in the prescribed medication) will be
 208 included in the study (this includes both new and consecutive patients). The reason for
 209 doing this is that the utility of the technology is expected to be maximized during the
 210 onset of new treatments, as opposed to those cases in which the treatment plan is
 211 already well-established.

212

213 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

214

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

234

235 *Procedure*

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

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2
3 240 in particular. Patients interested in participating are directed to another office where the
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5 241 lead author, I.J., explains the study procedures in more detail and ensures their
6
7 242 eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by
8
9 243 explaining the utility of the study and by contacting patients when an alarm informing of
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11 244 low app adherence (i.e., more than three consecutive days without response) is
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13 245 received. All participants are provided with an information sheet and sign the informed
14
15 246 consent. After participation acceptance, participants are assigned to one of the
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17 247 experimental conditions (TAU or TAU+app+web), which had been previously
18
19 248 randomized by an external researcher. All participants then complete a paper-and-
20
21 249 pencil assessment protocol in order to control for differences between the two
22
23 250 assessment formats (app vs. pen and pencil) and to compare both conditions using the
24
25 251 same assessment approach. In addition to this paper-and-pencil evaluation, patients in
26
27 252 the TAU+app+web condition download and install the Pain Monitor app into their
28
29 253 phones. Once they install the app, they answer to an initial assessment and then
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31 254 complete two measures daily (10 am and 7 pm) during one month (study duration).
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33 255 Finally, an end of study appointment is set (one month later) to conduct the post-
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35 256 assessment evaluation. Due to difficulties in transportation or availability, the post-
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37 257 assessment intervention can either be completed onsite or via an on-line survey.
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43 259 *Pain monitor*

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45 260 The Pain Monitor app (Figure 2) has been developed by a group of pain psychologists
46
47 261 and an engineer, with the collaboration of physicians and nurses specialized in pain
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49 262 care. Pain Monitor is composed of several pain-related items which are to be answered
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51 263 twice a day at preset times (10 am and 7 pm, with a two-hour flexibility) during 30 days.
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53 264 The app content has been previously validated with chronic pain patients at the pain
54
55 265 unit of the Vall d'Hebron Hospital (21). This assessment protocol contains
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57 266 sociodemographic items (i.e., age, sex, and education level, among others) which are
58
59 267 evaluated on the first day of app use only, as well as a number of pain-related
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3 268 outcomes that are evaluated daily, which have been selected following recent
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5 269 guidelines on core outcome domains for pain treatments (40,41). Constructs in the app,
6
7 270 including pain intensity, pain interference, anxiety, depression, catastrophizing, social
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9 271 support, acceptance, and coping, among others, are measured with a single item to
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11 272 reduce the burden of daily assessment, each of which was adapted and validated
12
13 273 against well-established paper-and-pencil measures (21). Additionally, the assessment
14
15 274 protocol includes a list of side effects created *ad hoc* based on the literature findings on
16
17 275 the most frequent adverse effects of pain treatments (42,43), as well as measures of
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19 276 treatment adherence, use of rescue medication, neuropathic characteristics of pain,
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21 277 and use of medical services in the past month. All app items can be found in
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23
24 278 Supplementary file 3.

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26
27 279 The app generates alarms in the presence of predefined events (see Supplementary
28
29 280 file 4 for the alarms set in the present study in collaboration with the participating
30
31 281 physicians). These alarms are sent to the physicians early in the morning on working
32
33 282 days so that they can decide whether an action from their side is required (e.g., calling
34
35 283 the patient and setting an earlier appointment or suggesting a change in the
36
37 284 medication). For this study, a website linked to the app was created for the physicians
38
39 285 to observe patient alarms and evolution live. Examples of the physician web are
40
41 286 presented in Figure 3. Physicians are only asked to check the website when an alarm
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43 287 happens, but they are allowed to check any patient status at any time.
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46 288

47 289 *Interventions*

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50 290 Five physicians at the pain clinic of the Hospital General Universitari de Castelló
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52 291 participate in this study. All patients in the study receive the usual treatment for their
53
54 292 pain irrespective of their assigned condition. However, a change in treatment might
55
56 293 occur in the TAU+app+web condition at the discretion of the physicians in charge of
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58 294 treatment after receiving an alarm and consulting the web page with the graphical
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3 295 representation of patient app responses. As usual, patients in the TAU condition
4
5 296 without the app are not contacted by the physicians between appointments. It is
6
7 297 important to note that both patients in the TAU only and patients in the TAU+app+web
8
9 298 condition are allowed to attend to the emergency services or the family physician in the
10
11 299 event of an emergency at any stage of the study due to ethical reasons. At the end of
12
13 300 the study, this practice is investigated for each participant in the final assessment.
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17 302 *Assessment plan*

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20 303 All participants in the study fill in a number of questionnaires in a paper-and-pencil
21
22 304 format at the beginning and at the end of the study. This assessment protocol includes
23
24 305 sociodemographic information, sickness work absence during the past month, use of
25
26 306 pain-related health resources in the past month (i.e., emergency services, family
27
28 307 physician, or pain clinic), pain-related physical symptoms experienced in the past week
29
30 308 (i.e., side medication effects), the Brief Pain Inventory (pain severity and interference)
31
32 309 (44), the Pain Catastrophizing Scale (45), and the Hospital Anxiety and Depression
33
34 310 Scale (46). In addition to this paper-and-pencil evaluation, participants in the
35
36 311 TAU+app+web condition also install the Pain Monitor app and complete a pre-
37
38 312 intervention assessment in the app after the paper-and-pencil evaluation. Both baseline
39
40 313 assessments include the same content and are duplicated to provide further evidence
41
42 314 for the validity of app content. After this pretreatment evaluation, participants in the
43
44 315 TAU+app+web group are asked to answer to the app assessments twice a day during
45
46 316 one month (study duration). A push-up system notifies the patient about the need to
47
48 317 respond to the app evaluation at 10:00 am and 7:00 pm. These times can be adjusted
49
50 318 by the patient with a 2-hour flexibility from the preset times.
51
52
53 319 Daily morning and evening assessments differ in a number of items. Some items are
54
55 320 asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only
56
57 321 administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g.,
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3 322 activity level during the day, interference of pain on daily activities, or physical
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5 323 symptoms experienced during the day).

6
7 324 Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a
8
9 325 post-assessment protocol. The measures included in this final evaluation are similar to
10
11 326 the ones included in the baseline assessment, with the inclusion of a measure of
12
13 327 negative events experienced during the study period and the evaluation of perceived
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15 328 change due to treatment.

16
17 329 In the study, primary outcomes are pain intensity and the number of side effects of the
18
19 330 medication reported in the app, while secondary outcomes include mood (depression
20
21 331 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
22
23 332 resources in the past month.

24
25 333 Note that app reports in the TAU+app+web condition are not used to determine
26
27 334 treatment effectiveness compared to the TAU only condition because in the latter
28
29 335 condition participants do not use the app. Therefore, app responses are only used for
30
31 336 telemonitoring and early detection of treatment problems that result in an alarm to the
32
33 337 physicians. The comparison of both conditions will be made using the traditional paper-
34
35 338 and-pencil evaluations which will be available for both groups. Additionally, the number
36
37 339 of alarms and the physician's responses to such alarms (e.g., change in treatment
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39 340 strategies) will be registered. This information will be used to get better insight into the
40
41 341 utility of the integrated technology to improve treatment efficacy.
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45 342

46 343 *Patient and public Involvement*

47
48 344 In the current study, patients or the public will not be involved in the design, or conduct,
49
50 345 or dissemination of the research.

51 346

52 347 *Data analysis*

53
54 348 The aim of the present study is to explore the effect of an integrated technology-based
55
56 349 solution for chronic pain monitoring (an app that monitors pain patients daily and sends
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3 350 clinical alarms to physicians and a web for physicians that graphically represents
4
5 351 patient evolution as reported in the app) compared to the usual treatment where
6
7 352 monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim
8
9 353 in mind, and completer analyses will be performed following the recommendations of
10
11 354 the CONSORT guidelines (<http://www.consort-statement.org/>). First, the two conditions
12
13 355 will be compared at baseline in the different continuous measures with a between-
14
15 356 group analysis via a *t*-test to ensure that randomization indeed resulted in comparable
16
17 357 groups prior to intervention. Chi-squared tests will be used for all the categorical
18
19 358 variables. To evaluate our hypothesis, mixed repeated-measure MANOVAs will be
20
21 359 conducted to investigate whether there are differences between pre- and post-
22
23 360 assessment scores as a function of the experimental condition (TAU or
24
25 361 TAU+app+web). Distribution normality and homoscedasticity assumptions will be
26
27 362 tested by means of Kolmogorov-Smirnov and Levene tests, respectively, and a
28
29 363 Mann-Whitney *U* test and Brown-Forsythe *F*-test will be used where necessary. Effect
30
31 364 size will be calculated to complement the MANOVA results with the standardized mean
32
33 365 difference (Cohen's *d*) for both between and within group analyses. This is a novel
34
35 366 study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e.
36
37 367 moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and
38
39 368 number of side effects of the medication) when compared to secondary outcomes
40
41 369 since medical interventions do not specifically focus on these symptoms (i.e., pain
42
43 370 interference, mood, fatigue, rescue medication use, and quality of life). The analysis will
44
45 371 be performed by CSR, who will be blinded to the treatment allocation. Only the present
46
47 372 study authors will have access to the final trial dataset.
48
49 373 Regarding dropouts, we will choose a strict criterion and the analyses will only include
50
51 374 participants who complete both the pre and the post assessments. Because of the
52
53 375 short duration of the trial (one month per patient) and the minimal risks expected from
54
55 376 the use of the app, a data monitoring committee will not be required. Despite the
56
57 377 previous, an alarm has been set so that the physicians are warned if a patient fails to

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3 378 respond to the App during three consecutive days (i.e., an indirect measure of potential
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5 379 dropouts attributable to the App use). If this happens, the physicians will call the patient
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7 380 and explore the reasons for discontinuation and try to obtain a post-treatment
8
9 381 assessment to reduce bias.
10

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13 383

14 384 **Discussion**

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17 385 Pain assessment is a complex process characterized by a high variability between and
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19 386 within days, which is usually performed by clinicians using self-report, onsite, single
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21 387 ratings which are based on recall (47,48). EMA using smartphone apps appears to be
22
23 388 an innovative and promising alternative to these traditional assessment methods (49)
24
25 389 as smartphone apps have demonstrated to be accurate tools to assess pain intensity
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27 390 and related variables from the patients' home, thus facilitating telemonitoring and
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29 391 contributing to the personalization of medical interventions by rapidly adjusting
30
31 392 treatments to every individual as a result of telemonitoring (25).
32
33

34 393 In the present study protocol, we describe a randomized controlled trial designed to
35
36 394 test an integrative technology-based solution for chronic pain monitoring consisting of a
37
38 395 web application for the healthcare professional which is linked to the patient's app (i.e.,
39
40 396 Pain Monitor). Specifically, we want to explore whether the use of this integrative
41
42 397 technology improves the effectiveness of the usual treatment for this population thanks
43
44 398 to telemonitoring and the rapid detection of unwanted events. We expect that the use
45
46 399 of Pain monitor, with the support of therapist's web, will result in reduced pain intensity
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48 400 and less frequent side effects of the medication after one month of medical treatment
49
50 401 due to the professional's rapid reaction in the presence of undesired outcomes. Note
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52 402 that the study goal is not the explore the feasibility of implementing the use of the
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54 403 integrative technology for patient long-term use, but to explore its utility and
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56 404 acceptability when used in the short-term (e.g., during a month) in a critical treatment
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3 405 stage (i.e., after the onset of a new treatment plan, when pain is not well controlled and
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5 406 treatment tolerance is unclear).

6
7 407 To our knowledge, this is the first study to assess the effectiveness of this type of
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9 408 integrative technology solution (i.e., a therapist web site linked to a patient smartphone
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11 409 app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis
12
13 410 is confirmed, our findings will serve to demonstrate the feasibility and utility of
14
15 411 smartphones and specialized webs for therapists so that they can be implemented in
16
17 412 specialized care contexts (i.e., pain clinics). Likewise, our results will provide important
18
19 413 information about the potential benefits of smartphone apps for the personalization of
20
21 414 pain treatments (i.e., treatment can be rapidly personalized to a given patient as a
22
23 415 function of individual responses reported in the app). Ultimately, this might help change
24
25 416 the model of care for this chronic disease (i.e., episodic, onsite assessment and
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27 417 treatment), since the use of this integrative technology system allows for a continuous
28
29 418 and remote evaluation and intervention, providing a faster response to the patient
30
31 419 needs and improving self-management and empowerment of patients who attend pain
32
33 420 clinics as they become important agents of treatment effectiveness by being in charge
34
35 421 of daily reporting of pain-related experiences in the app. In sum, the results of the
36
37 422 present investigation could serve an important first step towards the implementation of
38
39 423 apps and other Information and Communication Technologies in health services.
40
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44

425 **List of Abbreviations**

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

430 431 432 **References**

- 1
2
3 433 1. Merskey H, editor. Classification of chronic pain: Descriptions of chronic pain
4
5 434 syndromes and definitions of pain terms. *Pain*. 1986;Suppl 3:226.
6
7
- 8 435 2. Williams AC de C, Craig KD. Updating the definition of pain. *Pain*.
9
10 436 2016;157(11):2420–3.
11
12
- 13 437 3. Lavand'homme P. The progression from acute to chronic pain. *Curr Opin*
14
15 438 *Anaesthesiol*. 2011;24(5):545–50.
16
17
- 18 439 4. Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification
19
20 440 of chronic pain for ICD-11. *Pain*. 2015;156(6):1003–7.
21
22
- 23 441 5. Bevan S, Quadrello T, Mcgee R, Mahdon M, Vavrovsky A, Barham L. Fit for
24
25 442 Work pain-European report. 2009.
26
27
- 28 443 6. Barke A, Schiller J, Rief W, Treede R-D, Falter S, Schäfer P, et al. The IASP
29
30 444 classification of chronic pain for ICD-11. *Pain*. 2018;160(1):88–94.
31
32
- 33 445 7. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain
34
35 446 in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006
36
37 447 May;10(4):287–333.
38
39
- 40 448 8. Larsson C, Hansson EE, Sundquist K, Jakobsson U. Chronic pain in older
41
42 449 adults: prevalence, incidence, and risk factors. *Scand J Rheumatol*. 2017
43
44 450 Jul;46(4):317–25.
45
46
- 47 451 9. Nahin RL. Estimates of pain prevalence and severity in adults: United States,
48
49 452 2012. *J Pain*. 2015 Aug;16(8):769–80.
50
51
- 52 453 10. Häuser W, Wolfe F, Henningsen P, Schmutzer G, Brähler E, Hinz A. Untying
53
54 454 chronic pain: Prevalence and societal burden of chronic pain stages in the
55
56 455 general population - A cross-sectional survey. *BMC Public Health*. 2014;14(1):1–
57
58
59
60

- 1
2
3 456 8.
4
5
6 457 11. Miró J, Paredes S, Rull M, Queral R, Miralles R, Nieto R, et al. Pain in older
7
8 458 adults: A prevalence study in the Mediterranean region of Catalonia. *Eur J Pain*.
9
10 459 2007;11(1):83.
11
12
13 460 12. Vincent GE, Velkoff VA. The next four decades the older population in the United
14
15 461 States : 2010 to 2050. Vol. 2011, U.S. Department of Commerce. Economics
16
17 462 and Statistics Administration. U.S. Census Bureau. 2010.
18
19
20
21 463 13. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic
22
23 464 pain in Europe: The case for strategic prioritisation and action to improve
24
25 465 knowledge and availability of appropriate care. *BMC Public Health*. 2013;13(1).
26
27
28 466 14. Frießem CH, Willweber-Strumpf A, Zenz MW. Chronic pain in primary care.
29
30 467 German figures from 1991 and 2006. *BMC Public Health*. 2009;9(1):299.
31
32
33 468 15. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global,
34
35 469 regional, and national incidence, prevalence, and years lived with disability for
36
37 470 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a
38
39 471 systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015
40
41 472 Aug;386(9995):743–800.
42
43
44
45 473 16. Blyth FM, Van Der Windt DA, Croft PR. Chronic Disabling Pain. *Am J Prev Med*.
46
47 474 2015 Jul;49(1):98–101.
48
49
50 475 17. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain
51
52 476 management: past, present, and future. *Am Psychol*. 2014;69(2):119–30.
53
54
55 477 18. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical
56
57 478 activity and exercise for chronic pain in adults: an overview of Cochrane
58
59 479 Reviews. *Cochrane database Syst Rev*. 2017 Jan;1:CD011279.
60

- 1
2
3 480 19. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and
4
5 481 Commitment Therapy (ACT) for Chronic Pain: A Systematic Review and Meta-
6
7 482 Analyses. *Clin J Pain*. 2017 Jun;33(6):552–68.
8
9
10 483 20. Dansie EJ, Turk DC. Assessment of patients with chronic pain. *Br J Anaesth*.
11
12 484 2013 Jul;111(1):19–25.
13
14
15 485 21. Suso-Ribera C, Castilla D, Zaragoza I, Ribera-Canudas MV, Botella C, Garcia-
16
17 486 Palacios A. Validity, Reliability, Feasibility, and Usefulness of Pain Monitor: A
18
19 487 Multidimensional Smartphone App for Daily Monitoring of Adults With
20
21 488 Heterogenous Chronic Pain. *Clin J Pain*. 2018 Oct;34(10):900–8.
22
23
24
25 489 22. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity
26
27 490 measurement in chronic pain patients. *Pain*. 1993 Nov;55(2):195–203.
28
29
30 491 23. Kikuchi H, Yoshiuchi K, Miyasaka N, Ohashi K, Yamamoto Y, Kumano H, et al.
31
32 492 Reliability of recalled self-report on headache intensity: investigation using
33
34 493 ecological momentary assessment technique. *Cephalalgia*. 2006
35
36 494 Nov;26(11):1335–43.
37
38
39 495 24. Kratz AL, Murphy SL, Braley TJ. Ecological Momentary Assessment of Pain,
40
41 496 Fatigue, Depressive, and Cognitive Symptoms Reveals Significant Daily
42
43 497 Variability in Multiple Sclerosis. *Arch Phys Med Rehabil*. 2017 Nov;98(11):2142–
44
45 498 50.
46
47
48
49 499 25. García-Palacios A, Herrero R, Belmonte MA, Castilla D, Guixeres J, Molinari G,
50
51 500 et al. Ecological momentary assessment for chronic pain in fibromyalgia using a
52
53 501 smartphone: A randomized crossover study. *Eur J Pain*. 2014;18(6):862–72.
54
55
56 502 26. Smyth JM, Stone AA. Ecological Momentary Assessment Research in
57
58 503 Behavioral medicine. *J Happiness Stud*. 2003 Mar;4(1):35–52.
59
60

- 1
2
3 504 27. Shiffman S, Stone AA, Hufford MR. Ecological Momentary Assessment. *Annu*
4
5 505 *Rev Clin Psychol.* 2008;4(1):1–32.
6
7
8 506 28. Lin W-C, Burke L, Schlenk EA, Yeh CH. Use of an Ecological Momentary
9
10 507 Assessment Application to Assess the Effects of Auricular Point Acupressure for
11
12 508 Chronic Low Back Pain. *Comput Inform Nurs.* 2018 Oct; 37(5), 276-82.
13
14
15 509 29. Suso-Ribera C, Mesas Á, Medel J, Server A, Márquez E, Castilla D, et al.
16
17 510 Improving pain treatment with a smartphone app: study protocol for a
18
19 511 randomized controlled trial. *Trials.* 2018 Dec;19(1):145.
20
21
22
23 512 30. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological Momentary
24
25 513 Assessment Methodology in Chronic Pain Research: A Systematic Review. *J*
26
27 514 *Pain.* 2018;19(7):699–716.
28
29
30 515 31. Moore J. The benefits of mobile apps for patients and providers. *Br J Healthc*
31
32 516 *Manag.* 2012 Sep 1;18(9):465–7.
33
34
35 517 32. Reynoldson C, Stones C, Allsop M, Gardner P, Bennett MI, Closs SJ, et al.
36
37 518 Assessing the Quality and Usability of Smartphone Apps for Pain Self-
38
39 519 Management. *Pain Med.* 2014;15(6):898–909.
40
41
42
43 520 33. Rosser BA, Eccleston C. Smartphone applications for pain management. *J*
44
45 521 *Telemed Telecare.* 2011;17(6):308–12.
46
47
48 522 34. Nieto R, Raichle K a, Jensen MP, Miró J. Changes in pain-related beliefs,
49
50 523 coping, and catastrophizing predict changes in pain intensity, pain interference,
51
52 524 and psychological functioning in individuals with myotonic muscular dystrophy
53
54 525 and facioscapulohumeral dystrophy. *Clin J Pain.* 2012 Jan;28(1):47–54.
55
56
57 526 35. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power
58
59 527 analysis program for the social, behavioral, and biomedical sciences. *Behav Res*

- 1
2
3 528 Methods. 2007 May;39(2):175–91.
4
5
6 529 36. Kristjansdottir OB, Fors EA, Eide E, Finset A, Stensrud TL, van Dulmen S, et al.
7
8 530 A smartphone-based intervention with diaries and therapist-feedback to reduce
9
10 531 catastrophizing and increase functioning in women with chronic widespread
11
12 532 pain: randomized controlled trial. J Med Internet Res. 2013 Jan;15(1):e5.
13
14
15 533 37. Macea DD, Gajos K, Daglia Calil YA, Fregni F. The efficacy of Web-based
16
17 534 cognitive behavioral interventions for chronic pain: a systematic review and
18
19 535 meta-analysis. J Pain. 2010 Oct;11(10):917–29.
20
21
22
23 536 38. Urbaniak, GC and Plous S. Research randomizer (version 4.0)[computer
24
25 537 software]. Social Psychology Network. 2013.
26
27
28 538 39. Kantar World Panel. Smartphone OS sales market share. 2015. Available from:
29
30 539 <http://www.kantarworldpanel.com/global/smartphone-os-market-share>.
31
32 540 Retrieved May 05, 2019.
33
34
35 541 40. Kaiser U, Kopkow C, Deckert S, Neustadt K, Jacobi L, Cameron P, et al.
36
37 542 Developing a core outcome domain set to assessing effectiveness of
38
39 543 interdisciplinary multimodal pain therapy: the VAPAIN consensus statement on
40
41 544 core outcome domains. Pain. 2018 Apr;159(4):673–83.
42
43
44
45 545 41. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et
46
47 546 al. Core outcome measures for chronic pain clinical trials: IMMPACT
48
49 547 recommendations. Pain. 2005 Jan;113(1–2):9–19.
50
51
52 548 42. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS
53
54 549 guidelines on the pharmacological treatment of neuropathic pain: 2010 revision.
55
56 550 Eur J Neurol. 2010 Sep;17(9):1113-e88.
57
58
59 551 43. Varrassi G, Müller-Schwefe G, Pergolizzi J, Orónska A, Morlion B,

- 1
2
3 552 Mavrocordatos P, et al. Pharmacological treatment of chronic pain – the need for
4
5 553 CHANGE. *Curr Med Res Opin.* 2010;26(5):1231–45.
6
7
8 554 44. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory.
9
10 555 *Ann Acad Med Singapore.* 1994 Mar;23(2):129–38.
11
12
13 556 45. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development
14
15 557 and validation. *Psychol Assess.* 1995 Dec;7(4):524–32.
16
17
18 558 46. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta*
19
20 559 *Psychiatr Scand.* 1983 Jun;67(6):361–70.
21
22
23
24 560 47. Gorin, A. A., & Stone AA. Recall biases and cognitive errors in retrospective self-
25
26 561 reports: A call for momentary assessments. In: Baum A, Revenson T, J. Singer,
27
28 562 editors. *Handbook of health psycholog.* Mahwah, NJ: Lawrence Erlbaum; 2001.
29
30 563 p. 405–13.
31
32
33 564 48. Schwarz N. Retrospective and Concurrent Self-Reports: The Rationale for Real-
34
35 565 Time Data Capture. In: A. Stone, S. S. Shiffman, A. Atienza & LN, editor. *The*
36
37 566 *science of real-time data capture: Self-reports in health research.* New York:
38
39 567 Oxford University Pres; 2007. p. 11–26.
40
41
42
43 568 49. Alexander JC, Joshi GP. Smartphone applications for chronic pain
44
45 569 management : a critical appraisal. *J Pain Res.* 2016;9:731–4.
46
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51 **Author Statement:** All authors were strongly involved in the study conceptualization
52
53 572 and design and have reviewed and discussed the manuscript. IJ and CSR prepared
54
55 573 the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG.
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58 574 After changes were incorporated, a final version was approved by all authors. IJ and
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1
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3 575 JLG are currently in charge of recruitment and IJ and CSR will be in charge of data
4
5 576 analysis.

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9
10 578 UJI-B2016-39 and a Predoctoral Grant (PREDOC/2017/26) by the Universitat Jaume I
11
12 579 to IJ. The first grant allowed for the development of the technological systems used in
13
14 580 the study (physician website and link to the app). The second grant serves to pay the
15
16 581 salary of the lead researcher and predoctoral candidate, IJ.

17
18
19
20 582 **Competing interests:** The intellectual property of the Pain Monitor app is owned by
21
22 583 co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any
23
24 584 competing interests to declare as they do not receive any financial gain from these
25
26 585 technologies.

27
28
29
30 586 **Ethics approval and consent to participate:** Ethical approval from the Hospital
31
32 587 General Universitari de Castelló was obtained, in accordance with the Declaration of
33
34 588 Helsinki. All participants provided written informed consent to participate in the study.
35
36 589 The informed consent form was approved by the ethics committee of the Hospital
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38 590 General Universitari de Castelló.

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42 43 44 592 **FIGURES**

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47 593 Figure 1. Study schedule of enrolment, interventions, and assessments.

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49
50 594 Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c)
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52 595 Pain Monitor assessment of fatigue.

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55 596 Figure 3. Examples of the web for the physician. a) Patient's side effects during 30
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57 597 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c)
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59 598 Distribution of patient side effects.

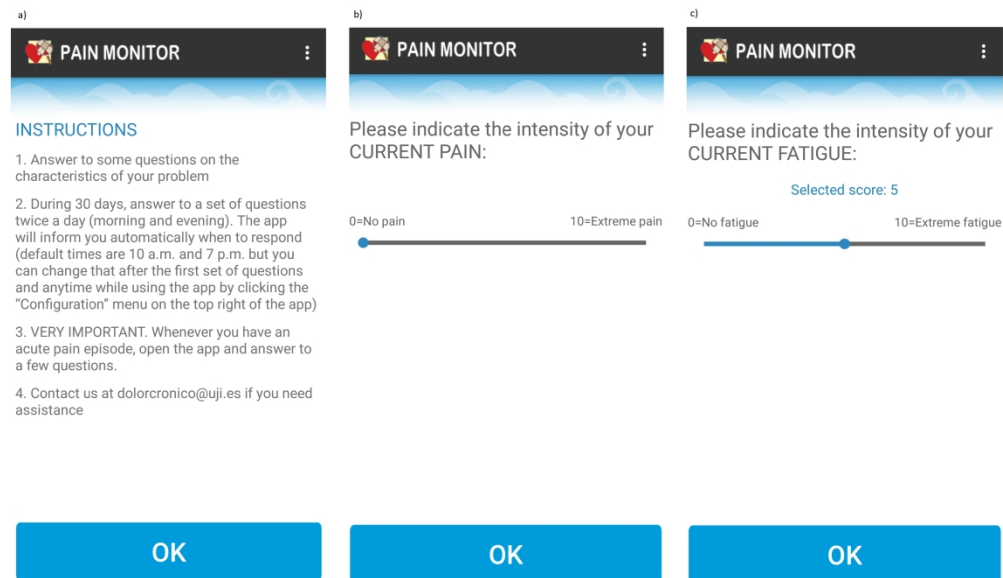
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For peer review only

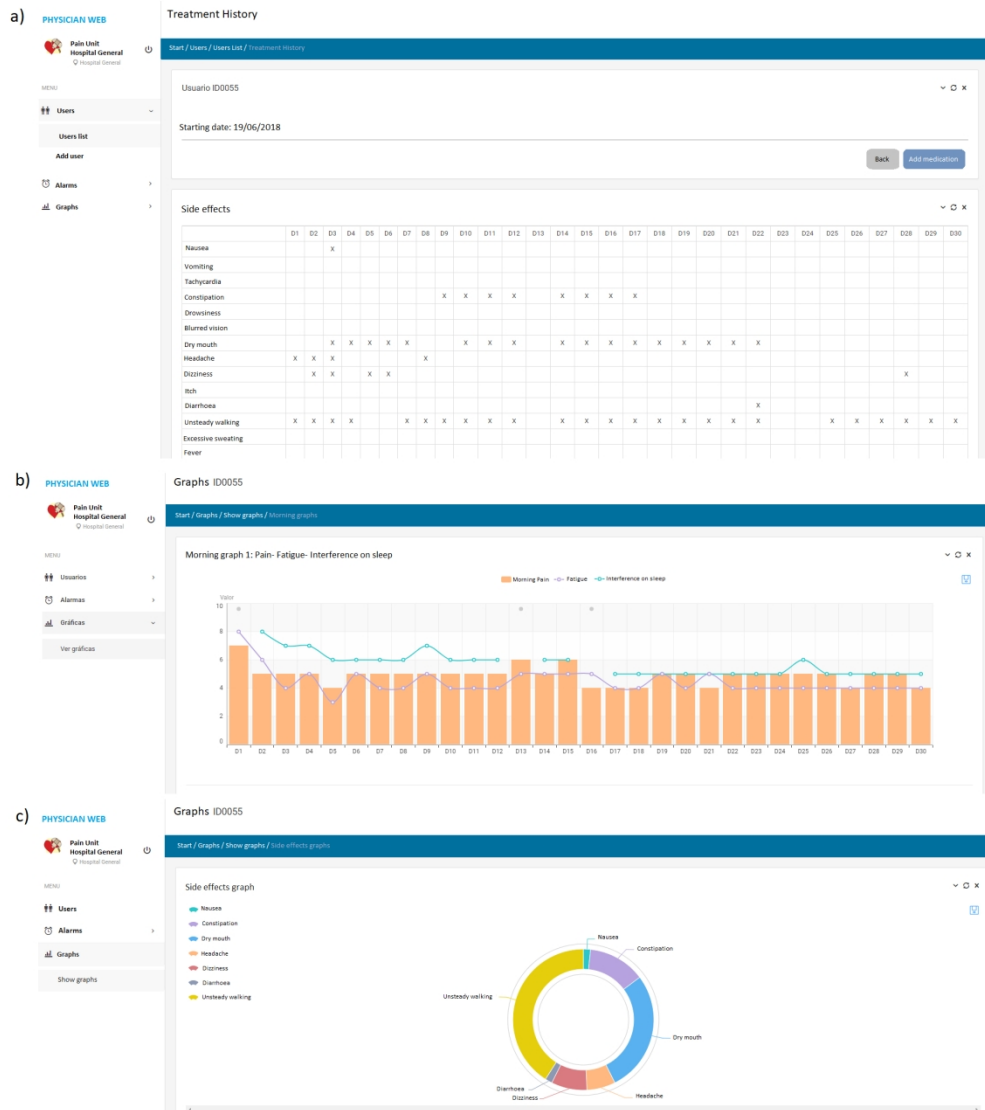
STUDY PERIOD

	Pre-intervention	Intervention period	Close-out
TIMEPOINT	0	T₁	T₂
	<i>Pre-Intervention</i>	<i>Between assessments</i>	<i>One month follow-up</i>
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	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> 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 <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> 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.

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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 investigación 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 month 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

1
2
3 reduction in the increase in access to health services for a large number of people who
4 do not have access to health services suffer from mental disorders.
5

6 **How will my data be treated?**

7
8 All data relevant to the study will be collected and stored in compliance with data
9 protection regulations in force. These data will only be used anonymously for the
10 purpose of scientific analysis. All persons involved in the study have an obligation to
11 comply with data protection laws. We will make sure that all your information - without
12 restrictions - is treated as in a confidential manner. Any data collected will be deleted as
13 soon as it is not necessary for scientific purposes.
14
15
16

17 **Can I decline or suspend my participation?**

18
19 Yes, you may refuse to participate in this study or terminate your participation at any
20 time. In the event that you decide to discontinue your participation in the study all of
21 your data will be destroyed immediately.
22
23

24 **Who is the researcher responsible for the study?**

25
26 Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and
27 Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail:
28 azucena@uji.es
29
30

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

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3 g. Neurosurgeon
4 h. Neurologist
5 i. Oncologist
6 j. Another professional.
7
8
9 7. When did your current pain start?
10 a. Less than one year ago
11 b. Between 1 and 5 years ago
12 c. Between 5 and 10 years ago
13 d. More than 10 years ago
14
15
16 8. What is your current treatment for pain? You may select more than one option:
17 a. Physiotherapy
18 b. Pharmacotherapy
19 c. Infiltrations
20 d. Psychological treatment
21 e. Natural / alternative treatments
22 f. My pain is not being treated
23
24
25 9. Did you start a new treatment for pain in the last month?
26 a. Yes
27 b. No
28
29
30 10. Please select the treatment/s you started in the last month. You may select more
31 than one option:
32 a. Physiotherapy
33 b. Pharmacotherapy
34 c. Infiltrations
35 d. Psychological treatment
36 e. Natural / alternative treatments
37 f. I have not started a new treatment
38
39
40 11. What is your marital status?
41 a. Single
42 b. Married
43 c. In a relationship
44 d. Divorced
45 e. Separated
46 f. Widowed
47
48
49 12. What is your job status?
50 a. Active worker
51 b. Sick leave
52 c. Permanent disability
53 d. Unemployed
54 e. Homemaker
55 f. Retired
56 g. Student
57
58
59 13. What is the highest level of education you have completed?
60

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- 3 a. No studies
- 4 b. Less than high school
- 5 c. High school graduate
- 6 d. Technical training
- 7 e. University degree
- 8
- 9

10 14. Do you currently have a diagnosis of depression by a physician or a
11 psychologist?

- 12 a. Yes
- 13 b. No
- 14
- 15

16 15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?

- 17 a. Yes
- 18 b. No
- 19
- 20

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

22 16. Please indicate the intensity of your CURRENT PAIN:

23 0 No pain -----10 Extreme pain

24 17. Please indicate the intensity of your CURRENT FATIGUE:

25 0 No fatigue -----10 Extreme fatigue

26 18. Please indicate the intensity of your CURRENT HAPPINESS:

27 0 No happiness -----10 Extremely happy

28 19. Please indicate the intensity of your CURRENT SADNESS:

29 0 No sadness ----- 10 Extremely sad

30 20. Please indicate the intensity of your CURRENT ANXIETY:

31 0 No anxiety ----- 10 Extremely anxious

32 21. Please indicate the intensity of your CURRENT ANGER:

33 0 No anger ----- 10 Extremely angry

34 22. Does your pain have any of these characteristics? You may select more than one
35 option:

- 36 a. Burning
- 37 b. Painful cold
- 38 c. Electric shocks
- 39 d. Tingling
- 40 e. Pins and needles
- 41 f. Numbness
- 42 g. Itching
- 43 h. Reduced sensitivity to touch
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- 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

1
2
3 35. Indicate your degree of agreement with the following sentence: Today I could
4 not keep my pain out of my mind.

- 5 1) Strongly disagree
6 2) Disagree
7 3) Neither agree nor disagree
8 4) Agree
9 5) Strongly agree
10
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13
14 36. Please rate your degree of activity TODAY:
15 0%= Completely inactive -100%= Completely active.
16

17
18 37. In which area have you been more active today? You may select more than one
19 option:

- 20 a. Work
21 b. Family
22 c. Couple
23 d. Friends
24 e. Leisure
25 f. Physical activity
26 g. Other.
27
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31 38. Did you take a rescue medication TODAY (i.e., medication you only use in the
32 event of acute pain)?

- 33 a. Yes
34 b. No
35
36

37
38 39. Did you experience any of these symptoms TODAY? You may select more than
39 one option:

- 40 a. Nausea
41 b. Vomiting
42 c. Tachycardia
43 d. Constipation
44 e. Drowsiness / sedation
45 f. Blurred vision
46 g. Dry mouth
47 h. Headache
48 i. None of the above
49
50
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52

53
54 40. Did you experience any of these symptoms TODAY? You may select more than
55 one option:

- 56 a. Dizziness
57 b. Itching
58 c. Diarrhea
59 d. Gait instability
60

- 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

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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:
- Death of a close person
 - Job problem
 - Relationship problem
 - Economic problem
 - Health problem
 - Family problem
 - An event not listed above
 - I have not experienced any major negative event this month
46. Please indicate the location where your pain is more intense:
- Head
 - Shoulder
 - Neck
 - High back
 - Lower back
 - Arm
 - Elbow
 - Wrist
 - Hand
 - Abdomen
 - Chest
 - Buttock
 - Hip
 - Leg
 - Knee
 - Foot
 - Whole body
 - Somewhere not listed
47. What is your current treatment for pain? You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - Psychological treatment
 - Natural / alternative treatments
 - My pain is not being treated
48. Did you start a new treatment for pain in the last month?
- Yes
 - No
49. Please select the treatment/s you started in the last month. You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - Psychological treatment

- 1
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3 e. Natural / alternative treatments
4 f. I have not started a new treatment
5
6

7 50. What is your marital status?

- 8 a. Single
9 b. Married
10 c. In a relationship
11 d. Divorced
12 e. Separated
13 f. Widowed
14

15
16 51. What is your job status?

- 17 a. Active worker
18 b. Sick leave
19 c. Permanent disability
20 d. Unemployed
21 e. Homemaker
22 f. Retired
23 g. Student
24
25

26 52. Do you currently have a diagnosis of depression by a physician or a
27 psychologist?

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

- 33 a. Yes
34 b. No
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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



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

1		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
2				
3				
4				
5				
6				
7	Introduction			
8				
9	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
10				
11				
12		6b	Explanation for choice of comparators	Method, page 6
13				
14	Objectives	7	Specific objectives or hypotheses	Introduction, page 3
15				
16				
17	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
18				
19				
20				
21				
22	Methods: Participants, interventions, and outcomes			
23				
24	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
25				
26				
27	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
28				
29				
30	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
31				
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35		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
36				
37				
38		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8
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1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
2	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
3				
4				
5	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
6				
7	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
8				
9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
10				

Methods: Assignment of interventions (for controlled trials)

Allocation:

11	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
12				
13				
14	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
15				
16	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
17				
18	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
19				
20		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

1 **Methods: Data collection, management, and analysis**

2			
3			
4	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related
5	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
6			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
7			Reference to where data collection forms can be found, if not in the protocol
8			
9		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be
10			collected for participants who discontinue or deviate from intervention protocols
11			
12	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality
13			(eg, double data entry; range checks for data values). Reference to where details of data management
14			procedures can be found, if not in the protocol
15			
16			
17	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the
18			statistical analysis plan can be found, if not in the protocol
19			
20		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
21			
22		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
23			statistical methods to handle missing data (eg, multiple imputation)
24			
25			
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27			
28			
29			
30	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of
31			whether it is independent from the sponsor and competing interests; and reference to where further details
32			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not
33			needed
34			
35		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim
36			results and make the final decision to terminate the trial
37			
38	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse
39			events and other unintended effects of trial interventions or trial conduct
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1	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
2				
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4	Ethics and dissemination			
5				
6	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
7				
8				
9	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
10				
11				
12				
13				
14	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
15				
16				
17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
18				
19				
20	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
21				
22				
23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
24				
25				
26	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
27				
28				
29				
30	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
31				
32				
33	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
34				
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38		31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16
39				
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1	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
2			
3			
4			
5			
6	Appendices		
7			
8	Informed consent materials	32 Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
9			
10			
11	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
12			
13			

14 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 15 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033586.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Nov-2019
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
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Public health
Keywords:	chronic pain, ecological momentary assessment, ehealth, mhealth, telemonitoring

SCHOLARONE™
Manuscripts

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4 **Title:** Improving chronic pain management with eHealth and mHealth: study protocol
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6 for a randomized controlled trial
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10 **Running Head:** Telemonitoring of pain by Pain Monitor App
11
12

13
14 **Authors:** Irene Jaén^{1,a}, Carlos Suso-Ribera¹, Diana Castilla^{2,3}, Irene Zaragoza³,
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51 Word count: 3757
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53 **Protocol Amendment Number:** 01
54

2019-July-8	Original
2019-October-13	1 st review
2019-November-12	2 nd review

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26

1
2
3 **27 Abstract**
4

5 *28 Introduction:* Chronic pain has become a matter of public health concern due to its high
6
7 *29 prevalence* and because public costs associated with treatment and disability increase
8
9 *30 each year.* Research suggests that limitations in the traditional assessment of chronic
10
11 *31 pain patients* limit the effectiveness of current medical treatments. The use of
12
13 *32 technology* might serve change patient traditional monitoring into Ecological
14
15 *33 Momentary Assessments*, which might be visualized by physicians live. This study
16
17 *34 describes* a Randomized Control Trial designed to test the utility of a technology-based
18
19 *35 solution* for pain telemonitoring consisting of a smartphone app for patients and a web
20
21 *36 application* for physicians. The goal of this study will be to explore whether this
22
23 *37 combination* of eHealth and mHealth improves the effectiveness of existing pain
24
25 *38 treatments.*

26
27
28 *39 Methods and analysis:* Participants will be 250 patients randomly assigned to one of
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30 *40 these two conditions:* treatment as usual (TAU) and TAU+app+web. All participants will
31
32 *41 receive* the usual treatment for their pain. Only the TAU+app+web group use Pain
33
34 *42 Monitor* app, which generates alarms that are sent to the physicians in the face of
35
36 *43 previously-established* undesired events. Physicians will be able to monitor app reports
37
38 *44 using* a web application, which might result in an adjustment of treatment. We
39
40 *45 anticipate* that the use of Pain Monitor plus the therapist web will result in a reduction of
41
42 *46 pain intensity* and side effects of the medication. Improvements on secondary
43
44 *47 outcomes*, namely fatigue, mood, pain interference, rescue medication use, and quality
45
46 *48 of life*, are also expected. Mixed repeated-measure MANOVAs will be conducted to
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48 *49 investigate* whether there are differences between pre- and post-assessment scores as
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50 *50 a function* of the experimental condition.

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52 *51 Ethics and dissemination:* Ethical approval from the Hospital General Universitari de
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54 *52 Castellon* was obtained. The findings will be published in peer-reviewed journals.

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56 *53 Trial registration:* NCT03606265. The trial is active. Recruitment is ongoing.
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3 55 **Keywords:** Chronic pain, ecological momentary assessment, ehealth, mhealth,
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5 56 telemonitoring.
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8
9 58 **Strengths and limitations of this study**

- 10
11 59 – In the present randomized, controlled clinical, an integrative e-health and m-
12 health solution for chronic pain management is implemented.
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14 60
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16 61 – Patient monitoring is performed remotely in an ecological and momentary
17 manner with a smartphone app.
18 62
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20 63 – Patient responses to the app might generate alarms in the presence of
21 unwanted clinical events.
22 64
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24 65 – Physicians can track patient evolution at any time on a website and receive
25 clinical alarms daily.
26 66
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28 67 – Study limitations include the fact that physicians are not blinded to the patients'
29 condition and the rigidity of the app assessment protocol.
30 68
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34
35 70 **Introduction**

36
37 71 Pain can be defined as “an unpleasant sensory and emotional experience associated
38 with actual or potential tissue damage, or described in terms of such damage” (1) and
39 72 can only be understood as an interplay between “sensory, emotional, cognitive, and
40 social components” (2). Although pain often is acute and disappears as tissues heal,
41 73 sometimes pain persists for long periods of time and becomes chronic. For instance, it
42 has been reported that 15% of individuals admitted to trauma hospitals due to a severe
43 74 injury and 15- 60% of patients after surgery will continue to experience chronic pain
44 months and years later (3). In general, a cut-off of 3 to 6 months is used to define the
45 75 transition from acute/subacute to chronic pain (4).
46
47 76 The aforementioned chronification of pain is becoming a major public health problem
48 across the globe (5). We refer here to primary chronic pain, a pain associated with
49 77 important interference on functioning and/or emotional distress which cannot be better
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3 83 accounted for by any other condition (6). Specifically, epidemiological studies indicate
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5 84 that the prevalence of this disease in the adult population ranges from 19% to 38%
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7 85 worldwide (7–10). Furthermore, the increase in life expectancy and the ageing of the
8
9 86 population is likely to have an important impact on the number of individuals
10
11 87 experiencing chronic pain, since the prevalence of this syndrome boosts dramatically
12
13 88 with age (11). For instance, it is expected that the population of chronic pain individuals
14
15 89 will be doubled in 2050 for people older than 65 years and tripled for people over 80
16
17 90 years of age (12). Thus, chronic pain is a major public health challenge due to its high
18
19 91 prevalence in the population and high direct and indirect costs for the institutions and
20
21 92 the individuals (13,14).
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24 93 Indeed, chronic primary pain (e.g., fibromyalgia or nonspecific low back or neck pain, to
25
26 94 name some examples) is imposing a huge burden in our societies as this disease has
27
28 95 become one of the leading causes of years lived with disability globally (15,16) Not
29
30 96 surprisingly, as a result of the growing concern about this disease, there have been
31
32 97 numerous attempts to improve treatments for pain in the past decades. However,
33
34 98 recent reviews on the effectiveness of numerous interventions, including medical
35
36 99 treatments, psychological therapy, physical rehabilitation, or a combination of these
37
38 100 indicate that the effectiveness of existing treatments is, on average, only modest (17–
39
40 101 19). While there might be numerous factors explaining the limited effectiveness of
41
42 102 current interventions for pain, including unexplored biomechanical mechanisms or
43
44 103 genetic factors, patient characteristics, or therapists' training, some authors have
45
46 104 pointed to methodological shortcomings as key elements explaining the modest
47
48 105 effectiveness of pain interventions. Specifically, the way assessment is currently
49
50 106 performed (i.e., a single measure of pain intensity performed episodically during onsite
51
52 107 appointments) has been argued to impact negatively in the ability of existing
53
54 108 interventions to achieve more reliable and powerful changes in patient outcomes
55
56 109 (20,21). For instance, a single rate of pain intensity has been shown to be an unreliable
57
58 110 measure of pain as this experience can vary dramatically within the same day and
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3 111 across days (22–24). In addition, pain is frequently assessed retrospectively, which is
4
5 112 known to lead to recall bias and to decrease the accuracy of pain ratings (25) and does
6
7 113 not allow for timely responses to undesired events, so these often take place time after
8
9 114 the problem occurred (21).

11 115 As a consequence of the above, Ecological Momentary Assessment (EMA), which
12
13 116 refers to the assessment of pain repeatedly and in real life, has received renewed
14
15 117 interest in the past years in the pain literature and is now considered by many as the
16
17 118 gold standard method to assess the pain experience (26–29). Traditionally, EMA has
18
19 119 been difficult due to the limitations and costs of repeated measurement procedures
20
21 120 (i.e., paper diaries or phone calls). However, with the explosion and availability of
22
23 121 smartphones, EMA has become easier than ever and immediate communication
24
25 122 between the patient and the physician is now a more feasible practice (30).

26
27 123 It has been argued that this change in the assessment paradigm towards ecological
28
29 124 daily telemonitoring using apps will improve treatment effectiveness and reduce costs if
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31 125 used to respond to patient reports quickly (21,31). Indeed, there is evidence to suggest
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33 126 that smartphones are useful tools to be used for the assessment of pain core outcome
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35 127 measures in chronic pain settings (21,32,33). However, the extent to which this EMA of
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37 128 pain patients can effectively lead to better practices in pain medicine is still unknown.

38
39 129 For this purpose, we developed a technology-based solution that integrated a pain and
40
41 130 symptom tracking app for patients and a web for physicians where app-generated
42
43 131 alarms are received daily and patient app responses can be monitored in real time. To
44
45 132 the best of our knowledge, no study has yet investigated the utility of using such an
46
47 133 integrative technology-based solution for remote, ecological monitoring of patient
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49 134 evolution and to adjust treatment in response to app alarms in a randomized controlled
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51 135 trial.

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53 136 With the previous goal in mind, in the present parallel group, superiority trial we will use
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55 137 the *Pain Monitor* app
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57 138 (<https://play.google.com/store/apps/details?id=painmonitor.srccode>), which was

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3 139 developed by a team of psychologists and an engineer with the collaboration of
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5 140 physicians and nurses and has been recently validated in clinical settings (21), together
6
7 141 with a web for the physicians where app responses and alarms can be tracked in real
8
9 142 time to facilitate the professional's decision-making process. As we will explain in more
10
11 143 detail in the Methods section, Pain Monitor assesses a number of pain-related
12
13 144 outcomes (i.e., pain intensity, pain interference, anxiety and depression and use of
14
15 145 pain-related health resources) and the most frequent side effects of medical treatments
16
17 146 for pain. In the study, patients will be randomly assigned to a treatment as usual
18
19 147 condition (TAU) or to a TAU with the support of the patients' app and the physician's
20
21 148 web. We anticipate that the use of the web application linked with the smartphone app
22
23 149 (TAU+app+web condition) will improve the effectiveness of usual treatments resulting
24
25 150 in reduced pain intensity and less frequent side effects of the medication after one
26
27 151 month of medical treatment. Additionally, we expect that this group of patients will
28
29 152 present additional improvements on secondary outcomes, including mood (depression
30
31 153 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
32
33 154 resources in the past month as secondary gains of reducing pain levels, as suggested
34
35 155 in the literature (34). We also expect that the rapid detection of treatment undesired
36
37 156 events will rapidly minimize threats to the patient's quality of life and mood.
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43 **Method**

45 *Study design*

47 160 The current investigation is a randomized superiority clinical trial composed of two
48
49 161 parallel groups (1:1 allocation ratio): a) TAU and b) TAU+app+web. In the study,
50
51 162 participants in the TAU condition receive the usual pain treatment by the physicians
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53 163 working at the pain unit (i.e., pharmacological treatment or infiltration). Participants
54
55 164 included in TAU+app+web group receive the usual treatment for their pain plus daily
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57 165 monitoring of their symptoms and pain experience with the Pain Monitor app during
58
59 166 one month. In the TAU+app+web condition, alarms are generated in the presence of
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3 167 previously established undesired events, which have been previously determined by
4
5 168 the physicians at the pain clinic (e.g., pain intensity is higher than 7 in an 11-point
6
7 169 numerical scale during 3 consecutive days). Physicians are able to monitor these
8
9 170 patients' app reports using a web application created for this purpose
10
11 171 (<https://monitordolor.dolortic.com/>). Thus, phone calls can be conducted in the
12
13 172 presence of alarms in order to change or discontinue the medical treatment when
14
15 173 necessary. If the study results indicate that the use of technology leads to better
16
17 174 outcomes, participants in the TAU condition will be informed about these findings and
18
19 175 will be offered the possibility to use the app after study participation. In the TAU
20
21 176 condition only, assessment is performed as usual, that is, using self-report measures
22
23 177 administered onsite at the beginning and the end of the study (1 month later).
24
25 178 Neither the physicians nor the patients will be blind to the treatment condition assigned.
26
27 179 Physicians will not be blind because they will receive alarms from the TAU+app+web
28
29 180 participants only. Patients will not be blind because only those in the TAU+app+web
30
31 181 condition will be using technology in addition to usual treatment and because patients
32
33 182 in the TAU condition must know that there is no telemonitoring in their condition.
34
35 183 The trial was registered at clinicaltrials.gov in September 2018 (NCT03606265). All
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37 184 items from the World Health Organization Trial Registration Data Set are showed in the
38
39 185 Supplementary file 1. The recruitment started at the end of the same month. SPIRIT
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41 186 guidelines (Standard Protocol Items: Recommendations for Interventional Trials) were
42
43 187 followed to design the trial. The participant timeline (i.e., schedule of enrolment,
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45 188 interventions, and assessments) is shown in Figure 1. Recruitment is currently ongoing
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47 189 and is expected to end in November 2019.
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51 190

52 191 *Sample*

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54 192 Participants will be 250 consecutive chronic pain patients attending the pain clinic at
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56 193 the Hospital General Universitari de Castello (Spain) for the first time. Required sample
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58 194 size was calculated using G*Power (35). Although the a priori calculation resulted in
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60

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3 195 198 participants, the sample size was increased to 250 considering a dropout rate of
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5 196 27-30% based on previous studies (36,37). Thus, 125 participants were assigned to
6
7 197 each condition. Randomization of participants was performed by an independent
8
9 198 researcher using a computer-generated sequence with *Randomizer* (38). Inclusion
10
11 199 criteria are shown in Table 1. Only patients for whom a change in the treatment is
12
13 200 planned (e.g., an epidural infiltration or a change in the prescribed medication) will be
14
15 201 included in the study (this includes both new and consecutive patients). The reason for
16
17 202 doing this is that the utility of the technology is expected to be maximized during the
18
19 203 onset of new treatments, as opposed to those cases in which the treatment plan is
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21 204 already well-established.
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26 206 Table 1. Inclusion criteria

28 The patient is over 18 years of age

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31 The patient has a mobile phone with Android operating system (the app is
32 currently only available for Android, which is the operating system used by more
33 than 80% of users in Spain) (39).
34
35

36 The patient has the physical ability to use the application

37
38 A new treatment plan is started during the first week after study onset

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40 The patient does not present psychological and/or cognitive alterations or
41 problems with language that make his/her participation difficult
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45 The patient voluntarily wants to participate and signs the informed consent form
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50
51 208 In the study, all participants are identified using an alphanumeric code. In the case of
52 participants in the TAU+app+web condition, this code is automatically generated by the
53 app. Thus, the database generated by the app is anonymized and the app only collects
54
55 210 app. Thus, the database generated by the app is anonymized and the app only collects
56
57 211 the international mobile equipment identity (IMEI). The association between app codes
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59 212 and patient identifiable characteristics is stored locally at the pain clinic. All data
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3 213 storage procedures follow the European law and data protection rules (European
4
5 214 Union General Data Protection Regulation 2016/679 of the European Parliament and of
6
7 215 the Council of 27 April 2016). In addition, ethical approval from the Hospital General
8
9 216 Universitari de Castello was obtained, in accordance with the Declaration of Helsinki.
10
11 217 Important protocol modifications will be notified and require the approval of the Ethics
12
13 218 Committee of the Hospital General Universitari de Castello. Approved changes will be
14
15 219 made public at clinicaltrials.gov. All the participants read and sign an informed consent
16
17 220 form before randomization (see Supplementary file 2). Patients who do not agree with
18
19 221 the assigned condition, are given the opportunity to be allocated to the preferred
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21 222 condition, but are not used in the analyses. Any changes to modify the assigned
22
23 223 condition are accepted at any time during the study, again resulting in an exclusion
24
25 224 from the study. Changes in the medication or improvement of disease do not result in
26
27 225 study discontinuation. Disease worsening is not expected to be associated with the
28
29 226 inclusion of the app but, if existent, will result in the discontinuation of app use.
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227

228 *Procedure*

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36 229 The study is conducted at the pain clinic of the Hospital General Universitari de
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38 230 Castelló. The study is advertised by physicians to all consecutive patients attending the
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40 231 pain clinic for the first time. To ensure enrolment, physicians will emphasize the
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42 232 importance of active patient participation in research in general and in self-monitoring
43
44 233 in particular. Patients interested in participating are directed to another office where the
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46 234 lead author, I.J., explains the study procedures in more detail and ensures their
47
48 235 eligibility. I.J. is in charge of increasing adherence to the treatment (i.e., app) by
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50 236 explaining the utility of the study and by contacting patients when an alarm informing of
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52 237 low app adherence (i.e., more than three consecutive days without response) is
53
54 238 received. All participants are provided with an information sheet and sign the informed
55
56 239 consent. After participation acceptance, participants are assigned to one of the
57
58 240 experimental conditions (TAU or TAU+app+web), which had been previously
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1
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3 241 randomized by an external researcher. All participants then complete a paper-and-
4
5 242 pencil assessment protocol in order to control for differences between the two
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7 243 assessment formats (app vs. pen and pencil) and to compare both conditions using the
8
9 244 same assessment approach. In addition to this paper-and-pencil evaluation, patients in
10
11 245 the TAU+app+web condition download and install the Pain Monitor app into their
12
13 246 phones. Once they install the app, they answer to an initial assessment and then
14
15 247 complete two measures daily (10 am and 7 pm) during one month (study duration).
16
17 248 Finally, an end of study appointment is set (one month later) to conduct the post-
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19 249 assessment evaluation. Due to difficulties in transportation or availability, the post-
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21 250 assessment intervention can either be completed onsite or via an on-line survey.
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252 *Pain monitor*

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

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3 269 treatment adherence, use of rescue medication, neuropathic characteristics of pain,
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5 270 and use of medical services in the past month. All app items can be found in
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7 271 Supplementary file 3.
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10 272 The app generates alarms in the presence of predefined events (see Supplementary
11
12 273 file 4 for the alarms set in the present study in collaboration with the participating
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14 274 physicians). These alarms are sent to the physicians early in the morning on working
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16 275 days so that they can decide whether an action from their side is required (e.g., calling
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18 276 the patient and setting an earlier appointment or suggesting a change in the
19
20 277 medication). For this study, a website linked to the app was created for the physicians
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22 278 to observe patient alarms and evolution live. Examples of the physician web are
23
24 279 presented in Figure 3. Physicians are only asked to check the website when an alarm
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26 280 happens, but they are allowed to check any patient status at any time.
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31 282 *Interventions*

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33 283 Five physicians at the pain clinic of the Hospital General Universitari de Castelló
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35 284 participate in this study. All patients in the study receive the usual treatment for their
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37 285 pain irrespective of their assigned condition. However, a change in treatment might
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39 286 occur in the TAU+app+web condition at the discretion of the physicians in charge of
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41 287 treatment after receiving an alarm and consulting the web page with the graphical
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43 288 representation of patient app responses. As usual, patients in the TAU condition
44
45 289 without the app are not contacted by the physicians between appointments. It is
46
47 290 important to note that both patients in the TAU only and patients in the TAU+app+web
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49 291 condition are allowed to attend to the emergency services or the family physician in the
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51 292 event of an emergency at any stage of the study due to ethical reasons. At the end of
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53 293 the study, this practice is investigated for each participant in the final assessment.
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58 295 *Assessment plan*

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3 296 All participants in the study fill in a number of questionnaires in a paper-and-pencil
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5 297 format at the beginning and at the end of the study. This assessment protocol includes
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7 298 sociodemographic information, sickness work absence during the past month, use of
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9 299 pain-related health resources in the past month (i.e., emergency services, family
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11 300 physician, or pain clinic), pain-related physical symptoms experienced in the past week
12
13 301 (i.e., side medication effects), the Brief Pain Inventory (pain severity and interference)
14
15 302 (44), the Pain Catastrophizing Scale (45), and the Hospital Anxiety and Depression
16
17 303 Scale (46). In addition to this paper-and-pencil evaluation, participants in the
18
19 304 TAU+app+web condition also install the Pain Monitor app and complete a pre-
20
21 305 intervention assessment in the app after the paper-and-pencil evaluation. Both baseline
22
23 306 assessments include the same content and are duplicated to provide further evidence
24
25 307 for the validity of app content. After this pretreatment evaluation, participants in the
26
27 308 TAU+app+web group are asked to answer to the app assessments twice a day during
28
29 309 one month (study duration). A push-up system notifies the patient about the need to
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31 310 respond to the app evaluation at 10:00 am and 7:00 pm. These times can be adjusted
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33 311 by the patient with a 2-hour flexibility from the preset times.
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35 312 Daily morning and evening assessments differ in a number of items. Some items are
36
37 313 asked twice a day (i.e., pain intensity, sadness, anxiety), while others are only
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39 314 administered in the morning (e.g., interference of pain on sleep) or in the evening (e.g.,
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41 315 activity level during the day, interference of pain on daily activities, or physical
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43 316 symptoms experienced during the day).
44
45 317 Finally, 30 days after the treatment onset (i.e., first evaluation), both groups complete a
46
47 318 post-assessment protocol. The measures included in this final evaluation are similar to
48
49 319 the ones included in the baseline assessment, with the inclusion of a measure of
50
51 320 negative events experienced during the study period and the evaluation of perceived
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53 321 change due to treatment.
54
55 322 In the study, primary outcomes are pain intensity and the number of side effects of the
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57 323 medication reported in the app, while secondary outcomes include mood (depression

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3 324 and anxiety), pain interference, pain catastrophizing, and use of pain-related health
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5 325 resources in the past month.
6
7 326 Note that app reports in the TAU+app+web condition are not used to determine
8
9 327 treatment effectiveness compared to the TAU only condition because in the latter
10
11 328 condition participants do not use the app. Therefore, app responses are only used for
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13 329 telemonitoring and early detection of treatment problems that result in an alarm to the
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15 330 physicians. The comparison of both conditions will be made using the traditional paper-
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17 331 and-pencil evaluations which will be available for both groups. Additionally, the number
18
19 332 of alarms and the physician's responses to such alarms (e.g., change in treatment
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21 333 strategies) will be registered. This information will be used to get better insight into the
22
23 334 utility of the integrated technology to improve treatment efficacy.
24
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27 28 336 *Patient and public Involvement*

29
30 337 In the current study, patients or the public will not be involved in the design, or conduct,
31
32 338 or dissemination of the research.
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34

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36 37 340 *Data analysis*

38
39 341 The aim of the present study is to explore the effect of an integrated technology-based
40
41 342 solution for chronic pain monitoring (an app that monitors pain patients daily and sends
42
43 343 clinical alarms to physicians and a web for physicians that graphically represents
44
45 344 patient evolution as reported in the app) compared to the usual treatment where
46
47 345 monitoring is made using a paper-and-pencil, episodic, onsite evaluation. With this aim
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49 346 in mind, and completer analyses will be performed following the recommendations of
50
51 347 the CONSORT guidelines (<http://www.consort-statement.org/>). First, the two conditions
52
53 348 will be compared at baseline in the different continuous measures with a between-
54
55 349 group analysis via a *t*-test to ensure that randomization indeed resulted in comparable
56
57 350 groups prior to intervention. Chi-squared tests will be used for all the categorical
58
59 351 variables. To evaluate our hypothesis, mixed repeated-measure MANOVAs will be
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1
2
3 352 conducted to investigate whether there are differences between pre- and post-
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5 353 assessment scores as a function of the experimental condition (TAU or
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7 354 TAU+app+web). Distribution normality and homoscedasticity assumptions will be
8
9 355 tested by means of Kolmogorov-Smirnov and Levene tests, respectively, and a
10
11 356 Mann-Whitney U test and Brown-Forsythe F -test will be used where necessary. Effect
12
13 357 size will be calculated to complement the MANOVA results with the standardized mean
14
15 358 difference (Cohen's d) for both between and within group analyses. This is a novel
16
17 359 study and effect sizes are difficult to anticipate. However, we expect to find larger (i.e.
18
19 360 moderate) between-groups effect sizes for primary outcomes (i.e., pain intensity and
20
21 361 number of side effects of the medication) when compared to secondary outcomes
22
23 362 since medical interventions do not specifically focus on these symptoms (i.e., pain
24
25 363 interference, mood, fatigue, rescue medication use, and quality of life). The analysis will
26
27 364 be performed by CSR, who will be blinded to the treatment allocation. Only the present
28
29 365 study authors will have access to the final trial dataset.
30
31
32 366 Regarding dropouts, we will choose a strict criterion and the analyses will only include
33
34 367 participants who complete both the pre and the post assessments. Because of the
35
36 368 short duration of the trial (one month per patient) and the minimal risks expected from
37
38 369 the use of the app, a data monitoring committee will not be required. Despite the
39
40 370 previous, an alarm has been set so that the physicians are warned if a patient fails to
41
42 371 respond to the App during three consecutive days (i.e., an indirect measure of potential
43
44 372 dropouts attributable to the App use). If this happens, the physicians will call the patient
45
46 373 and explore the reasons for discontinuation and try to obtain a post-treatment
47
48 374 assessment to reduce bias.
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54 55 377 **Discussion**

56
57 378 Pain assessment is a complex process characterized by a high variability between and
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59 379 within days, which is usually performed by clinicians using self-report, onsite, single

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3 380 ratings which are based on recall (47,48). EMA using smartphone apps appears to be
4
5 381 an innovative and promising alternative to these traditional assessment methods (49)
6
7 382 as smartphone apps have demonstrated to be accurate tools to assess pain intensity
8
9 383 and related variables from the patients' home, thus facilitating telemonitoring and
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11 384 contributing to the personalization of medical interventions by rapidly adjusting
12
13 385 treatments to every individual as a result of telemonitoring (25).
14
15 386 In the present study protocol, we describe a randomized controlled trial designed to
16
17 387 test an integrative technology-based solution for chronic pain monitoring consisting of a
18
19 388 web application for the healthcare professional which is linked to the patient's app (i.e.,
20
21 389 Pain Monitor). Specifically, we want to explore whether the use of this integrative
22
23 390 technology improves the effectiveness of the usual treatment for this population thanks
24
25 391 to telemonitoring and the rapid detection of unwanted events. We expect that the use
26
27 392 of Pain monitor, with the support of therapist's web, will result in reduced pain intensity
28
29 393 and less frequent side effects of the medication after one month of medical treatment
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31 394 due to the professional's rapid reaction in the presence of undesired outcomes. Note
32
33 395 that the study goal is not the explore the feasibility of implementing the use of the
34
35 396 integrative technology for patient long-term use, but to explore its utility and
36
37 397 acceptability when used in the short-term (e.g., during a month) in a critical treatment
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39 398 stage (i.e., after the onset of a new treatment plan, when pain is not well controlled and
40
41 399 treatment tolerance is unclear).
42
43 400 To our knowledge, this is the first study to assess the effectiveness of this type of
44
45 401 integrative technology solution (i.e., a therapist web site linked to a patient smartphone
46
47 402 app) for the telemonitoring of patient symptomatology in chronic pain. If our hypothesis
48
49 403 is confirmed, our findings will serve to demonstrate the feasibility and utility of
50
51 404 smartphones and specialized webs for therapists so that they can be implemented in
52
53 405 specialized care contexts (i.e., pain clinics). Likewise, our results will provide important
54
55 406 information about the potential benefits of smartphone apps for the personalization of
56
57 407 pain treatments (i.e., treatment can be rapidly personalized to a given patient as a
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2
3 408 function of individual responses reported in the app). Ultimately, this might help change
4
5 409 the model of care for this chronic disease (i.e., episodic, onsite assessment and
6
7 410 treatment), since the use of this integrative technology system allows for a continuous
8
9 411 and remote evaluation and intervention, providing a faster response to the patient
10
11 412 needs and improving self-management and empowerment of patients who attend pain
12
13 413 clinics as they become important agents of treatment effectiveness by being in charge
14
15 414 of daily reporting of pain-related experiences in the app. In sum, the results of the
16
17 415 present investigation could serve an important first step towards the implementation of
18
19 416 apps and other Information and Communication Technologies in health services.
20
21
22 417

23 24 418 **List of Abbreviations**

25
26 419 TAU = Treatment as usual; EMA = Ecological Momentary Assessment; IMEI =
27
28 420 International Mobile Equipment Identity; SPIRIT = Standard Protocol Items
29
30 421 Recommendations for Interventional Trials; CONSORT = Consolidated Standards of
31
32 422 Reporting Trials; MANOVA = Multivariate Analysis of Variance.
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38 39 425 **References**

- 40
41
42 426 1. Merskey H, editor. Classification of chronic pain: Descriptions of chronic pain
43
44 427 syndromes and definitions of pain terms. *Pain*. 1986;Suppl 3:226.
45
46
47 428 2. Williams AC de C, Craig KD. Updating the definition of pain. *Pain*.
48
49 429 2016;157(11):2420–3.
50
51
52 430 3. Lavand'homme P. The progression from acute to chronic pain. *Curr Opin*
53
54 431 *Anaesthesiol*. 2011;24(5):545–50.
55
56
57 432 4. Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification
58
59 433 of chronic pain for ICD-11. *Pain*. 2015;156(6):1003–7.
60

- 1
2
3 434 5. Bevan S, Quadrello T, Mcgee R, Mahdon M, Vavrovsky A, Barham L. Fit for
4
5 435 Work pain-European report. 2009.
6
7
8 436 6. Barke A, Schiller J, Rief W, Treede R-D, Falter S, Schäfer P, et al. The IASP
9
10 437 classification of chronic pain for ICD-11. *Pain*. 2018;160(1):88–94.
11
12
13 438 7. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain
14
15 439 in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006
16
17 440 May;10(4):287–333.
18
19
20 441 8. Larsson C, Hansson EE, Sundquist K, Jakobsson U. Chronic pain in older
21
22 442 adults: prevalence, incidence, and risk factors. *Scand J Rheumatol*. 2017
23
24 443 Jul;46(4):317–25.
25
26
27 444 9. Nahin RL. Estimates of pain prevalence and severity in adults: United States,
28
29 445 2012. *J Pain*. 2015 Aug;16(8):769–80.
30
31
32 446 10. Häuser W, Wolfe F, Henningsen P, Schmutz G, Brähler E, Hinz A. Untying
33
34 447 chronic pain: Prevalence and societal burden of chronic pain stages in the
35
36 448 general population - A cross-sectional survey. *BMC Public Health*. 2014;14(1):1–
37
38 449 8.
39
40
41
42 450 11. Miró J, Paredes S, Rull M, Queral R, Miralles R, Nieto R, et al. Pain in older
43
44 451 adults: A prevalence study in the Mediterranean region of Catalonia. *Eur J Pain*.
45
46 452 2007;11(1):83.
47
48
49 453 12. Vincent GE, Velkoff VA. The next four decades the older population in the United
50
51 454 States : 2010 to 2050. Vol. 2011, U.S. Department of Commerce. Economics
52
53 455 and Statistics Administration. U.S. Census Bureau. 2010.
54
55
56 456 13. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic
57
58 457 pain in Europe: The case for strategic prioritisation and action to improve
59
60

- 1
2
3 458 knowledge and availability of appropriate care. BMC Public Health. 2013;13(1).
4
5
6 459 14. Frießem CH, Willweber-Strumpf A, Zenz MW. Chronic pain in primary care.
7
8 460 German figures from 1991 and 2006. BMC Public Health. 2009;9(1):299.
9
10
11 461 15. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global,
12
13 462 regional, and national incidence, prevalence, and years lived with disability for
14
15 463 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a
16
17 464 systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015
18
19 465 Aug;386(9995):743–800.
20
21
22
23 466 16. Blyth FM, Van Der Windt DA, Croft PR. Chronic Disabling Pain. Am J Prev Med.
24
25 467 2015 Jul;49(1):98–101.
26
27
28 468 17. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain
29
30 469 management: past, present, and future. Am Psychol. 2014;69(2):119–30.
31
32
33 470 18. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical
34
35 471 activity and exercise for chronic pain in adults: an overview of Cochrane
36
37 472 Reviews. Cochrane database Syst Rev. 2017 Jan;1:CD011279.
38
39
40
41 473 19. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and
42
43 474 Commitment Therapy (ACT) for Chronic Pain: A Systematic Review and Meta-
44
45 475 Analyses. Clin J Pain. 2017 Jun;33(6):552–68.
46
47
48 476 20. Dansie EJ, Turk DC. Assessment of patients with chronic pain. Br J Anaesth.
49
50 477 2013 Jul;111(1):19–25.
51
52
53 478 21. Suso-Ribera C, Castilla D, Zaragoza I, Ribera-Canudas MV, Botella C, Garcia-
54
55 479 Palacios A. Validity, Reliability, Feasibility, and Usefulness of Pain Monitor: A
56
57 480 Multidimensional Smartphone App for Daily Monitoring of Adults With
58
59 481 Heterogenous Chronic Pain. Clin J Pain. 2018 Oct;34(10):900–8.

- 1
2
3 482 22. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity
4
5 483 measurement in chronic pain patients. *Pain*. 1993 Nov;55(2):195–203.
6
7
8 484 23. Kikuchi H, Yoshiuchi K, Miyasaka N, Ohashi K, Yamamoto Y, Kumano H, et al.
9
10 485 Reliability of recalled self-report on headache intensity: investigation using
11
12 486 ecological momentary assessment technique. *Cephalalgia*. 2006
13
14 487 Nov;26(11):1335–43.
15
16
17 488 24. Kratz AL, Murphy SL, Braley TJ. Ecological Momentary Assessment of Pain,
18
19 489 Fatigue, Depressive, and Cognitive Symptoms Reveals Significant Daily
20
21 490 Variability in Multiple Sclerosis. *Arch Phys Med Rehabil*. 2017 Nov;98(11):2142–
22
23 491 50.
24
25
26 492 25. García-Palacios A, Herrero R, Belmonte MA, Castilla D, Guixeres J, Molinari G,
27
28 493 et al. Ecological momentary assessment for chronic pain in fibromyalgia using a
29
30 494 smartphone: A randomized crossover study. *Eur J Pain*. 2014;18(6):862–72.
31
32
33 495 26. Smyth JM, Stone AA. Ecological Momentary Assessment Research in
34
35 496 Behavioral medicine. *J Happiness Stud*. 2003 Mar;4(1):35–52.
36
37
38 497 27. Shiffman S, Stone AA, Hufford MR. Ecological Momentary Assessment. *Annu*
39
40 498 *Rev Clin Psychol*. 2008;4(1):1–32.
41
42
43 499 28. Lin W-C, Burke L, Schlenk EA, Yeh CH. Use of an Ecological Momentary
44
45 500 Assessment Application to Assess the Effects of Auricular Point Acupressure for
46
47 501 Chronic Low Back Pain. *Comput Inform Nurs*. 2018 Oct; 37(5), 276-82.
48
49
50 502 29. Suso-Ribera C, Mesas Á, Medel J, Server A, Márquez E, Castilla D, et al.
51
52 503 Improving pain treatment with a smartphone app: study protocol for a
53
54 504 randomized controlled trial. *Trials*. 2018 Dec;19(1):145.
55
56
57 505 30. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological Momentary
58
59
60

- 1
2
3 506 Assessment Methodology in Chronic Pain Research: A Systematic Review. J
4
5 507 Pain. 2018;19(7):699–716.
6
7
8 508 31. Moore J. The benefits of mobile apps for patients and providers. Br J Healthc
9
10 509 Manag. 2012 Sep 1;18(9):465–7.
11
12
13 510 32. Reynoldson C, Stones C, Allsop M, Gardner P, Bennett MI, Closs SJ, et al.
14
15 511 Assessing the Quality and Usability of Smartphone Apps for Pain Self-
16
17 512 Management. Pain Med. 2014;15(6):898–909.
18
19
20 513 33. Rosser BA, Eccleston C. Smartphone applications for pain management. J
21
22 514 Telemed Telecare. 2011;17(6):308–12.
23
24
25 515 34. Nieto R, Raichle K a, Jensen MP, Miró J. Changes in pain-related beliefs,
26
27 516 coping, and catastrophizing predict changes in pain intensity, pain interference,
28
29 517 and psychological functioning in individuals with myotonic muscular dystrophy
30
31 518 and facioscapulohumeral dystrophy. Clin J Pain. 2012 Jan;28(1):47–54.
32
33
34 519 35. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power
35
36 520 analysis program for the social, behavioral, and biomedical sciences. Behav Res
37
38 521 Methods. 2007 May;39(2):175–91.
39
40
41 522 36. Kristjansdottir OB, Fors EA, Eide E, Finset A, Stensrud TL, van Dulmen S, et al.
42
43 523 A smartphone-based intervention with diaries and therapist-feedback to reduce
44
45 524 catastrophizing and increase functioning in women with chronic widespread
46
47 525 pain: randomized controlled trial. J Med Internet Res. 2013 Jan;15(1):e5.
48
49
50 526 37. Macea DD, Gajos K, Daglia Calil YA, Fregni F. The efficacy of Web-based
51
52 527 cognitive behavioral interventions for chronic pain: a systematic review and
53
54 528 meta-analysis. J Pain. 2010 Oct;11(10):917–29.
55
56
57 529 38. Urbaniak, GC and Plous S. Research randomizer (version 4.0)[computer
58
59
60

- 1
2
3 530 software]. Social Psychology Network. 2013.
4
5
6 531 39. Kantar World Panel. Smartphone OS sales market share. 2015. Available from:
7
8 532 <http://www.kantarworldpanel.com/global/smartphone-os-market-share>.
9
10 533 Retrieved May 05, 2019.
11
12
13 534 40. Kaiser U, Kopkow C, Deckert S, Neustadt K, Jacobi L, Cameron P, et al.
14
15 535 Developing a core outcome domain set to assessing effectiveness of
16
17 536 interdisciplinary multimodal pain therapy: the VAPAIN consensus statement on
18
19 537 core outcome domains. *Pain*. 2018 Apr;159(4):673–83.
20
21
22
23 538 41. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et
24
25 539 al. Core outcome measures for chronic pain clinical trials: IMMPACT
26
27 540 recommendations. *Pain*. 2005 Jan;113(1–2):9–19.
28
29
30 541 42. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS
31
32 542 guidelines on the pharmacological treatment of neuropathic pain: 2010 revision.
33
34 543 *Eur J Neurol*. 2010 Sep;17(9):1113-e88.
35
36
37 544 43. Varrassi G, Müller-Schwefe G, Pergolizzi J, Orónska A, Morlion B,
38
39 545 Mavrocordatos P, et al. Pharmacological treatment of chronic pain – the need for
40
41 546 CHANGE. *Curr Med Res Opin*. 2010;26(5):1231–45.
42
43
44
45 547 44. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory.
46
47 548 *Ann Acad Med Singapore*. 1994 Mar;23(2):129–38.
48
49
50 549 45. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development
51
52 550 and validation. *Psychol Assess*. 1995 Dec;7(4):524–32.
53
54
55 551 46. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta*
56
57 552 *Psychiatr Scand*. 1983 Jun;67(6):361–70.
58
59
60

- 1
2
3 553 47. Gorin, A. A., & Stone AA. Recall biases and cognitive errors in retrospective self-
4
5 554 reports: A call for momentary assessments. In: Baum A, Revenson T, J. Singer,
6
7 555 editors. Handbook of health psycholog. Mahwah, NJ: Lawrence Erlbaum; 2001.
8
9 556 p. 405–13.
- 11
12 557 48. Schwarz N. Retrospective and Concurrent Self-Reports: The Rationale for Real-
13
14 558 Time Data Capture. In: A. Stone, S. S. Shiffman, A. Atienza & LN, editor. The
15
16 559 science of real-time data capture: Self-reports in health research. New York:
17
18 560 Oxford University Pres; 2007. p. 11–26.
- 21
22 561 49. Alexander JC, Joshi GP. Smartphone applications for chronic pain
23
24 562 management : a critical appraisal. J Pain Res. 2016;9:731–4.
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27 563

30 564 **Author Statement:** All authors were strongly involved in the study conceptualization
31
32 565 and design and have reviewed and discussed the manuscript. IJ and CSR prepared
33
34 566 the first draft of the manuscript, which was then reviewed by AGP, DC, IZ, and JLG.
35
36 567 After changes were incorporated, a final version was approved by all authors. IJ and
37
38 568 JLG are currently in charge of recruitment and IJ and CSR will be in charge of data
39
40 569 analysis.

43
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45
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47
48 572 to IJ. The first grant allowed for the development of the technological systems used in
49
50 573 the study (physician website and link to the app). The second grant serves to pay the
51
52 574 salary of the lead researcher and predoctoral candidate, IJ.

55
56 575 **Competing interests:** The intellectual property of the Pain Monitor app is owned by
57
58 576 co-authors CSR, DC, IZ, and AGP. These authors declare that they do not have any

1
2
3 577 competing interests to declare as they do not receive any financial gain from these
4
5 578 technologies.

7 579 **Ethics and dissemination:** Ethical approval from the Hospital General Universitari de
8
9 580 Castelló was obtained, in accordance with the Declaration of Helsinki. All participants
10
11 581 provided written informed consent to participate in the study. The informed consent
12
13 582 form was approved by the ethics committee of the Hospital General Universitari de
14
15 583 Castelló. The findings of this study will be published in peer-reviewed journals.
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28 586 **FIGURES**

29 587 Figure 1. Study schedule of enrolment, interventions, and assessments.

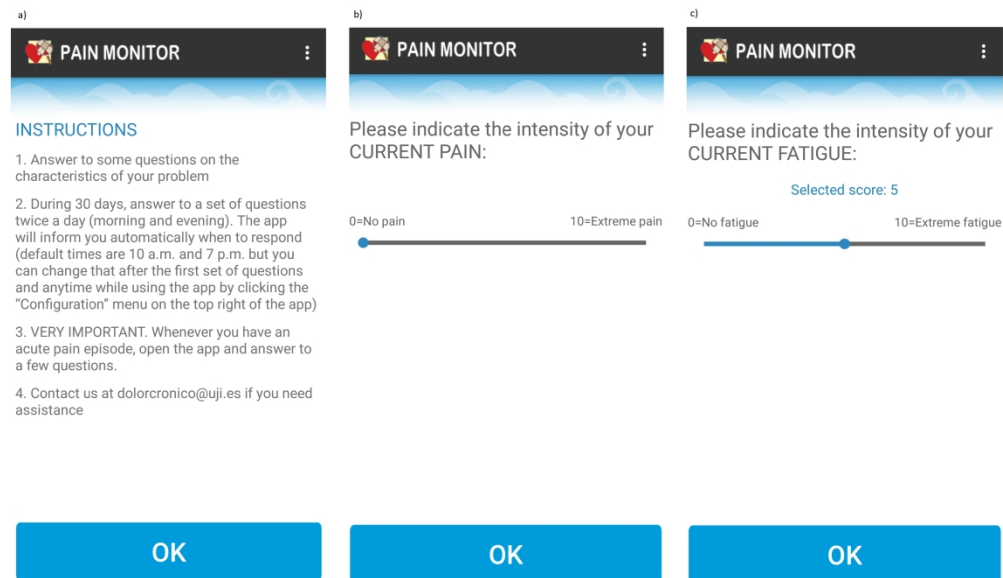
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32 588 Figure 2. a) Pain Monitor Instructions; b) Pain Monitor assessment of pain intensity; c)
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34 589 Pain Monitor assessment of fatigue.

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37 590 Figure 3. Examples of the web for the physician. a) Patient's side effects during 30
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39 591 days. b) Patient morning values on Pain, Fatigue and Interference on sleep. c)
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41 592 Distribution of patient side effects.
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STUDY PERIOD

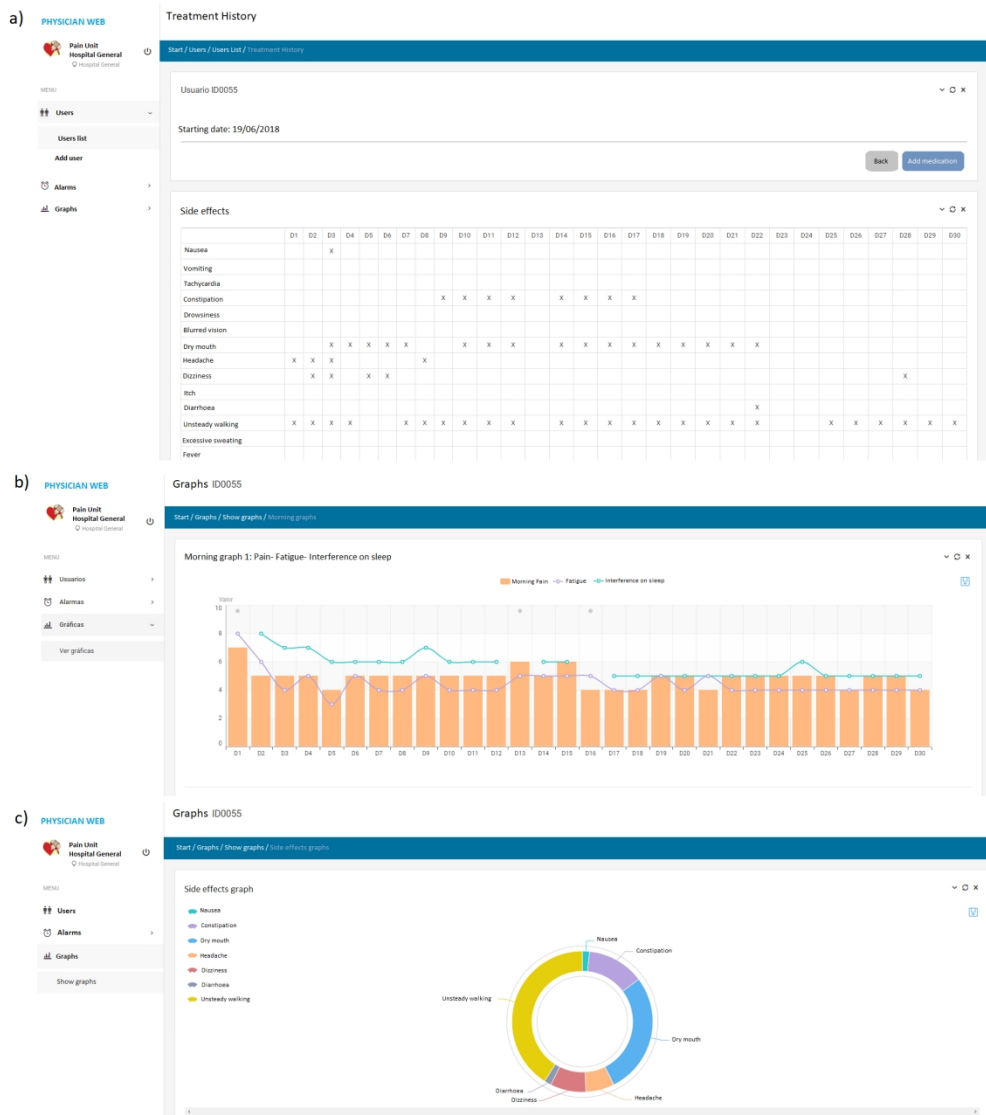
	Pre-intervention	Intervention period	Close-out
TIMEPOINT	0	T_1	T_2
	<i>Pre-Intervention</i>	<i>Between assessments</i>	<i>One month follow-up</i>
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
Allocation	X		
INTERVENTIONS:			
Medical treatment		X	
App use		App condition only	
ASSESSMENTS:			
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)

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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	<p>Inclusion Criteria:</p> <p>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</p> <p>Exclusion Criteria:</p> <p>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</p>

	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.

For peer review only

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 investigación 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 month 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

1
2
3 reduction in the increase in access to health services for a large number of people who
4 do not have access to health services suffer from mental disorders.
5

6 **How will my data be treated?**

7
8 All data relevant to the study will be collected and stored in compliance with data
9 protection regulations in force. These data will only be used anonymously for the
10 purpose of scientific analysis. All persons involved in the study have an obligation to
11 comply with data protection laws. We will make sure that all your information - without
12 restrictions - is treated as in a confidential manner. Any data collected will be deleted as
13 soon as it is not necessary for scientific purposes.
14
15
16

17 **Can I decline or suspend my participation?**

18
19 Yes, you may refuse to participate in this study or terminate your participation at any
20 time. In the event that you decide to discontinue your participation in the study all of
21 your data will be destroyed immediately.
22
23

24 **Who is the researcher responsible for the study?**

25
26 Dr. Azucena García Palacios, Department of Basic Psychology, Clinic and
27 Psychobiology, Universitat Jaume I (Castellón de la Plana), Tel: 964 387 640, E-mail:
28 azucena@uji.es
29

30
31 You may contact the principal investigator if you have any questions, concerns about
32 the study, about the data being collected, or if you wish to make use of your right to
33 suspend your participation.
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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

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3 g. Neurosurgeon
4 h. Neurologist
5 i. Oncologist
6 j. Another professional.
7
8
9 7. When did your current pain start?
10 a. Less than one year ago
11 b. Between 1 and 5 years ago
12 c. Between 5 and 10 years ago
13 d. More than 10 years ago
14
15
16 8. What is your current treatment for pain? You may select more than one option:
17 a. Physiotherapy
18 b. Pharmacotherapy
19 c. Infiltrations
20 d. Psychological treatment
21 e. Natural / alternative treatments
22 f. My pain is not being treated
23
24
25 9. Did you start a new treatment for pain in the last month?
26 a. Yes
27 b. No
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30 10. Please select the treatment/s you started in the last month. You may select more
31 than one option:
32 a. Physiotherapy
33 b. Pharmacotherapy
34 c. Infiltrations
35 d. Psychological treatment
36 e. Natural / alternative treatments
37 f. I have not started a new treatment
38
39
40 11. What is your marital status?
41 a. Single
42 b. Married
43 c. In a relationship
44 d. Divorced
45 e. Separated
46 f. Widowed
47
48
49 12. What is your job status?
50 a. Active worker
51 b. Sick leave
52 c. Permanent disability
53 d. Unemployed
54 e. Homemaker
55 f. Retired
56 g. Student
57
58
59 13. What is the highest level of education you have completed?
60

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- 3 a. No studies
- 4 b. Less than high school
- 5 c. High school graduate
- 6 d. Technical training
- 7 e. University degree
- 8
- 9

10 14. Do you currently have a diagnosis of depression by a physician or a
11 psychologist?

- 12 a. Yes
- 13 b. No
- 14
- 15

16 15. Do you currently have a diagnosis of anxiety by a physician or a psychologist?

- 17 a. Yes
- 18 b. No
- 19
- 20
- 21

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

23 16. Please indicate the intensity of your CURRENT PAIN:

24 0 No pain -----10 Extreme pain

25 17. Please indicate the intensity of your CURRENT FATIGUE:

26 0 No fatigue -----10 Extreme fatigue

27 18. Please indicate the intensity of your CURRENT HAPPINESS:

28 0 No happiness -----10 Extremely happy

29 19. Please indicate the intensity of your CURRENT SADNESS:

30 0 No sadness ----- 10 Extremely sad

31 20. Please indicate the intensity of your CURRENT ANXIETY:

32 0 No anxiety ----- 10 Extremely anxious

33 21. Please indicate the intensity of your CURRENT ANGER:

34 0 No anger ----- 10 Extremely angry

35 22. Does your pain have any of these characteristics? You may select more than one
36 option:

- 37 a. Burning
- 38 b. Painful cold
- 39 c. Electric shocks
- 40 d. Tingling
- 41 e. Pins and needles
- 42 f. Numbness
- 43 g. Itching
- 44 h. Reduced sensitivity to touch
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- 3 i. Pain when brushing against the skin
- 4 j. None of the above
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8 *Items assessed in the morning:*

9

10 23. In general, your HEALTH is:

- 11 1) Very poor
- 12 2) Poor
- 13 3) Average
- 14 4) Good
- 15 5) Very good

16 24. Did your PAIN interfere with the quality of your SLEEP LAST NIGHT?

17 0 No interference ----- 10 Maximum interference

18 25. Indicate your degree of agreement with the following sentence: With my current
19 pain, I should not do my usual job (it includes housework and work outside the
20 home).

- 21 1) Strongly disagree
- 22 2) Disagree
- 23 3) Neither agree nor disagree
- 24 4) Agree
- 25 5) Strongly agree

26 26. Indicate your degree of agreement with the following sentence: Experiencing
27 pain is terrible and I feel that pain is stronger than me.

- 28 1) Strongly disagree
- 29 2) Disagree
- 30 3) Neither agree nor disagree
- 31 4) Agree
- 32 5) Strongly agree

33 27. Indicate your degree of agreement with the following sentence: I need some
34 control over pain before I can make serious plans.

- 35 1) Strongly disagree
- 36 2) Disagree
- 37 3) Neither agree nor disagree
- 38 4) Agree
- 39 5) Strongly agree

40 28. Indicate your degree of agreement with the following sentence: Physical activity
41 aggravates my pain.

- 42 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

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3 35. Indicate your degree of agreement with the following sentence: Today I could
4 not keep my pain out of my mind.

- 5 1) Strongly disagree
6 2) Disagree
7 3) Neither agree nor disagree
8 4) Agree
9 5) Strongly agree
10
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14 36. Please rate your degree of activity TODAY:
15 0%= Completely inactive -100%= Completely active.
16

17
18 37. In which area have you been more active today? You may select more than one
19 option:

- 20 a. Work
21 b. Family
22 c. Couple
23 d. Friends
24 e. Leisure
25 f. Physical activity
26 g. Other.
27
28
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30
31 38. Did you take a rescue medication TODAY (i.e., medication you only use in the
32 event of acute pain)?

- 33 a. Yes
34 b. No
35
36

37
38 39. Did you experience any of these symptoms TODAY? You may select more than
39 one option:

- 40 a. Nausea
41 b. Vomiting
42 c. Tachycardia
43 d. Constipation
44 e. Drowsiness / sedation
45 f. Blurred vision
46 g. Dry mouth
47 h. Headache
48 i. None of the above
49
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53
54 40. Did you experience any of these symptoms TODAY? You may select more than
55 one option:

- 56 a. Dizziness
57 b. Itching
58 c. Diarrhea
59 d. Gait instability
60

- 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

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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:
- Death of a close person
 - Job problem
 - Relationship problem
 - Economic problem
 - Health problem
 - Family problem
 - An event not listed above
 - I have not experienced any major negative event this month
46. Please indicate the location where your pain is more intense:
- Head
 - Shoulder
 - Neck
 - High back
 - Lower back
 - Arm
 - Elbow
 - Wrist
 - Hand
 - Abdomen
 - Chest
 - Buttock
 - Hip
 - Leg
 - Knee
 - Foot
 - Whole body
 - Somewhere not listed
47. What is your current treatment for pain? You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - Psychological treatment
 - Natural / alternative treatments
 - My pain is not being treated
48. Did you start a new treatment for pain in the last month?
- Yes
 - No
49. Please select the treatment/s you started in the last month. You may select more than one option:
- Physiotherapy
 - Pharmacotherapy
 - Infiltrations
 - Psychological treatment

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3 e. Natural / alternative treatments
4 f. I have not started a new treatment
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7 50. What is your marital status?

- 8 a. Single
9 b. Married
10 c. In a relationship
11 d. Divorced
12 e. Separated
13 f. Widowed
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16 51. What is your job status?

- 17 a. Active worker
18 b. Sick leave
19 c. Permanent disability
20 d. Unemployed
21 e. Homemaker
22 f. Retired
23 g. Student
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26 52. Do you currently have a diagnosis of depression by a physician or a
27 psychologist?

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

- 33 a. Yes
34 b. No
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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

1		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
2				
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7	Introduction			
8				
9	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
10				
11				
12		6b	Explanation for choice of comparators	Method, page 6
13				
14	Objectives	7	Specific objectives or hypotheses	Introduction, page 3
15				
16				
17	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
18				
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21				
22	Methods: Participants, interventions, and outcomes			
23				
24	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
25				
26				
27	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
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30	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
31				
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35		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
36				
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38		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Procedure, page 8
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1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions 9-10
2	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
3				
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8	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
9				
10				
11	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
12				
13				
14	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Procedure, Page 8
15				
16				
17	Methods: Assignment of interventions (for controlled trials)			
18	Allocation:			
19				
20	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
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27	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
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31	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Procedure, page 8
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35	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
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38		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
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1 **Methods: Data collection, management, and analysis**

2 3 4 5 6 7 8	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
9 10 11		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
12 13 14 15 16	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
17 18 19 20 21	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
22 23 24 25 26		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 analysis, page 12-13

27 **Methods: Monitoring**

28 29 30 31 32 33 34	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
35 36 37		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
38 39 40 41 42	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

1	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
2				
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4	Ethics and dissemination			
5				
6	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations, page 15
7				
8				
9	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
10				
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14	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
15				
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17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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20	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
21				
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23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, page 15
24				
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26	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
27				
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30	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
31				
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33	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
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38		31b	Authorship eligibility guidelines and any intended use of professional writers	Authors' contributions, page 16
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1	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
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6	Appendices		
7			
8	Informed consent materials	32 Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
9			
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11	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
12			
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*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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