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eVISualisation (eVIS) of Physical Activity and Pain to improve Physical Health in patients with chronic pain participating in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial.

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Title:

eVISualisation (eVIS) of Physical Activity and Pain to improve Physical Health in patients with chronic pain participating in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial.

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Keywords: Chronic pain, Individualized physical activity level, Interdisciplinary Pain Rehabilitation Programs, Internal pilot study, Physical health, Registry-based randomized clinical trial, Study protocol.

ABSTRACT

Introduction: Living with chronic pain often involves negative consequences. Interdisciplinary Pain Rehabilitation Programs (IPRPs), a subset of Interdisciplinary Treatment (IDT) are considered to be superior to single-treatment measures in patients with chronic pain. However, effects emerge sub-optimal and as many as 30% of patients deteriorate in some outcomes. A novel intervention, eVISualisation (eVIS) of physical activity and pain, has been systematically developed to facilitate patients in reaching and maintaining recommended individualized physical activity levels. The aim is to transparently report on methodology, outcome assessments, and processes for a registry-based randomized controlled trial (R-RCT) initiated as an internal pilot study.

Methods and analysis: In the R-RCT, recruitment of approximately 400 patients with chronic pain who are registered at primary and specialized IPRP units (n=15) in Sweden will be performed. Participants will be randomly allocated to either IPRP + eVIS or to control group that will receive IPRP only. eVIS entails objectively measured physical activity (steps) and patient-reported outcomes (pain intensity, affect on daily activities, pharmaceutical consumption) collected and visualized in the web application PATRON. Data from the initial 30 participants completing the study period (6 months) will be included in a pilot study designed to evaluate recruitment- and randomization processes, standardized effect size, sample size, characteristics of outcomes, and follow-up rates of the R-RCT. Outcome variables will be extracted from PATRON and from six national registries. Multivariate statistics and repeated measures analyses will be performed. Quality Adjusted Life Years (QALYs) and Incremental Cost Effectiveness Ratio (ICER) will be calculated for cost effectiveness evaluation.

Ethics/dissemination: The Swedish Ethics Review Board granted approval (Dnr 2021/02109). Results will be disseminated through peer-review journals.

Trial registration number: The trial is registered at ClinicalTrials.gov. At the time of submission, a trial registration number had not yet been assigned due to pending review.

Protocol version: 1 (1)

Strengths and limitations of the study

- The proceeding internal pilot study will enable rare prerequisites to improve the robustness of the R-RCT design, decrease the risk of adverse events, and aid interpretations of the main trial.
- This study will evaluate the effectiveness of a systematically developed health-promoting intervention (eVIS) that targets individualized physical activity levels in patients with chronic pain who are participating in interdisciplinary pain rehabilitation programs in Sweden.
- The intervention is based on objectively measured physical activity levels, patient-reported clinical outcomes, and mechanisms that facilitate behavior change, in accordance with current guidelines that are provided by authorities in the chronic pain management field.
- The nature of the intervention precludes blinding of patients and the IPRP team.

INTRODUCTION

Chronic pain and physical activity

Chronic musculoskeletal pain (>3 months), including neck/shoulder/back pain or widespread pain, is a major global health and socioeconomic burden.¹⁻² Living with chronic pain is often associated with reduced levels of wellbeing and the health-related quality of life of this group has been reported to be among the lowest of any medical condition.³ To date, physical activity (i.e. any bodily movement that requires energy expenditure) and exercise (i.e. structured and planned physical activity aimed to increase fitness)⁴ have been shown to prevent and/or treat several of our noncommunicable diseases including chronic pain,⁵ due to their beneficial effects on general health, pain intensity, physical and psychological functioning, and health-related quality of life.⁵⁻⁸ WHO's physical activity guidelines provide clear outlines for the recommended amount (volume, intensity, type, duration) of physical activity required for adults living with chronic disabilities such as chronic pain.⁹ These recommendations encourage engaging in physical activity for a minimum of 150-300 minutes/week at a moderate intensity level to assimilate health benefits, such as improved functional health and health-related quality of life.⁹ Despite the growing evidence of health benefits related to physical activity, participation and adherence to recommendations are often low in patients living with chronic pain,¹⁰⁻¹¹ which may result in sub-optimal levels of physical activity. This lack of adherence to recommendations may be partly explained by the indicated association between high pain scores and low patient-reported activity levels among patients with chronic pain and/or the documented reports of the negative impact of depression on physical activity levels.¹² In addition, it is well known that behavior change is difficult, and that each individual's own participation is essential.¹³ It has been shown that behavior change towards a beneficial physical activity level may be facilitated by individuals self-monitoring their physical activity.¹⁴ The use of objective measures increases the likelihood of the effectiveness of interventions designed to promote physical activity.¹⁴ By adding goal setting, feedback, and a focus on achieved goals, effectiveness can be further improved.¹⁴⁻¹⁷

Interdisciplinary Pain Rehabilitation Programs

Interdisciplinary pain rehabilitation programs (described as a subset of Interdisciplinary Treatment [IDT]), are defined as “multimodal treatment provided by a multidisciplinary team (including at least 3 professions), collaborating in assessment and treatment using a shared biopsychosocial model and goals”¹⁸. The IPRP approach adopts the principles of behavioral therapy and incorporates not only physical activity and exercise, but also psychological measures, pharmaceutical treatment and patient education.¹⁹ Physical activity and exercise are central measures in IPRPs as they target physical deconditioning by improving levels of physical activity, and also reducing pain severity and improving physical function and quality of life.⁵ Interdisciplinary pain rehabilitation programs are considered to be superior to single-treatment measures for patients with chronic pain.^{19 20} However, their effectiveness is only slightly better and in the majority of cases only a small effect is seen.²⁰⁻²⁴ In addition, up to 30% of patients deteriorate in some outcomes despite completing an IPRP.^{19, 24-25} Sustainable treatment effects seem to vary according to patient clinical features at baseline, such as poor employment status, high pain levels, and low functioning, all of which predict low physical health at follow-up.²²⁻²⁶

Many efforts have been made to find effective interventions that improve the health of chronic pain patients. To facilitate individualized physical activity levels within the Swedish IPRP setting, an eVISualisation (eVIS) of physical activity and pain intervention has been systematically developed in collaboration with patients with chronic pain, clinicians, and researchers in the field. eVIS is designed to target facilitating mechanisms for behavior change, such as outcome expectations, self-monitoring, self-evaluation, and self-efficacy,²⁷⁻²⁹ which are theoretically framed by the Social Cognitive Theory.²⁹ In eVIS, objectively measured physical activity tracking using a wrist-worn activity tracker³⁰ (Fitbit Versa 2) is combined with a daily activity goal (steps/day) and daily patient reports of known important clinical outcome assessments: pain intensity and its affect on daily activities³¹⁻³⁵ and pharmaceutical consumption. Data is collected and visualized in a purpose-developed web application, Pain And TRaining ON-line (PATRON), which can be used by the patient and the IPRP-team to follow and adjust individual physical activity levels.

Despite interventions of this kind having highly promising potential, they are rarely systematically developed specifically for their target patient group and thereafter validated,

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3 meaning that there is a lack of crucial information regarding both their feasibility and true
4 effectiveness. To increase the robustness of this planned R-RCT and to avoid problems such as
5 under-power,³⁶ an internal randomized pilot study will be conducted to evaluate the
6 intervention's feasibility within the IPRP setting by assessment of planned methods and
7 procedures with the specific purpose of improving and strengthening the R-RCT design.³⁶⁻³⁹ In
8 this trial, the UK National Institute for Health Research's (NIHR) definitions of the terms *pilot*
9 *study* (i.e., "a smaller version of the main study") and *feasibility study* (i.e., "evaluation of pieces
10 of research done before the main study") are applied.⁴⁰ The aim of this paper is to transparently
11 clarify and report on the study designs, aims, outcome assessments, and procedures for a
12 planned R-RCT (including an internal randomized pilot study) to prospectively evaluate clinical
13 effectiveness and the cost effectiveness of eVIS as a supplement to IPRPs for patients living
14 with chronic pain compared to standard IPRPs.
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30 METHODS AND ANALYSIS

31 32 33 34 **Trial design and setting**

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36 This two-armed multi-site registry-based randomized controlled clinical trial (R-RCT) will be
37 conducted in specialized and primary IPRPs in Sweden, and include approximately 400 (n=200,
38 n=200) patients (number will be definitively determined after the pilot study is finalized) with
39 chronic musculoskeletal non-malignant pain. As indicated, an internal randomized controlled
40 pilot study (n=15, n=15) will be incorporated as the initial phase of the main trial.^{38, 41} This trial
41 will comply with the Consolidated Standards of Reporting Trials (CONSORT)³⁷ and with the
42 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)⁴². A completed
43 SPIRIT 2013 Checklist can be found in the additional files. See Figure 1 for study design and
44 enrollment details.
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55 *Insert Figure 1 here.*

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57 **Figure 1.** CONSORT 2010 Flow diagram chart of study design and enrollment.
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Eligibility criteria

In this trial, the patient-related, care process- and caregiver-related inclusion criteria for receiving Swedish IPRP will be applied, as patients entering the trial must be accepted for IPRP. Principal IPRP inclusion criteria are: patients of working age with persistent or intermittent pain lasting ≥ 3 months with pain affecting daily activities to a large extent, completed systematic assessment (including screening for psychosocial risk factors and differential diagnosis) and non-pharmacological optimization. Inclusion criteria for Swedish IPRPs is outlined in detail elsewhere.⁴³ Due to the nature of the intervention, patients must be able to hear, see, and comprehend spoken and written Swedish, and have daily access to a computer, smartphone, or tablet. Patients who need to use a walking aid indoors will be excluded, as will patients living with pain caused by systemic disease or malignancies.

Recruitment

Interdisciplinary Pain Rehabilitation Program Units

A balanced distribution of approximately 15 IPRP units in primary and specialized care in Sweden will be included in the trial. IPRP units reporting to the Swedish National Quality Registry for Pain Rehabilitation (SQRP) have been approached by email with study information (aim, rationale, methods etc.) and an invitation to participate in one of several online digital information meetings that will further present the study (planned for August/September 2021). Study representatives will approach healthcare staff at potential IPRP units by telephone or email to formally offer participation. Operation managers at each unit will be asked to provide written consent by e-mail.

Participants

In order to give potential participants additional time to consider taking part in the trial before they visit the IPRP unit, healthcare staff at the units will be encouraged to provide a general information sheet about the trial in the summon to the initial IPRP assessment. Members of IPRP teams (primarily physiotherapists but also occupational therapists, physicians, nurses etc.) will identify potential participants selected for an IPRP based on outlined criteria and provide them with verbal and written details of the study (information sheets and the project's web address). All participants will provide written informed consent prior to joining the study, which will be managed by the IPRP team. Detailed verbal and written information about the voluntary

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3 nature of participation and the indisputable right to discontinue participation in the trial at any
4 time will be provided. Detailed checklists and forms will support these procedures, and these
5 will be easily accessible on the project web site.
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10 11 **Intervention**

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13 Participation in the intervention group involves regular IPRP supplemented with eVIS for a
14 coherent time span of six months, IPRP time included. Participants are not prohibited from
15 taking part of other health care programs during the study period. Interdisciplinary pain
16 rehabilitation programs vary in interventions, duration, composition, and intensity²³⁻²⁴ and can
17 be performed either individually or in group format. In this trial, participation in a an IPRP will
18 be supplemented by eVIS, a health promoting intervention containing three elements designed
19 to facilitate individualized physical activity level.
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26 The data collection element

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28 Outcome assessments of physical activity level (steps/day) will be objectively collected by a
29 wrist-worn population-specifically validated activity tracker, Fitbit Versa 2.³⁰ This data will be
30 combined with activity goal setting (steps/day), daily patient reports of pain intensity (0-10),
31 affect of pain on daily activities (0-10), pharmacological consumption (name, dose, number,
32 and form), and (optional) free-text comments in the web application PATRON that can be
33 accessed via computer, smartphone, or tablet. The data collection element is designed to target
34 facilitating mechanisms for behavior change, such as outcome expectations, self-monitoring,
35 self-evaluation, and self-efficacy.²⁷⁻²⁹
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43 The visualisation element

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45 The outcome assessments described above are graphically visualized in relation to daily activity
46 goals for the patient and the IPRP team in three different graphs (1/7/28 days). The visualisation
47 element provides prerequisites for knowledge acquisition and self-monitoring, and self-
48 evaluation as data is visualized in relation to individual goals to improve patient self-efficacy.
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53 The communication element

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55 The graphs will provide support for the patient and the IPRP team in goal setting, reinforcement,
56 knowledge acquisition, self-monitoring, and self-efficacy by facilitating informed discussions
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3 on physical activity levels in relation to daily patient-reported clinical assessments (described
4 in Data collection element) and daily physical activity goals.
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9 **Control**

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12 Participation in the control group involves taking part in a regular IPRP plus making daily
13 ratings of pain intensity, affect of pain on daily activities, and pharmaceutical consumption
14 (corresponding as in intervention group) in PATRON for six months, including the time that
15 the IPRP is being carried out. The control group will not use the wrist-worn activity tracker or
16 have access to PATRON's visualizing or communication features.
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23 **Patient and Public Involvement Statement**

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26 In an early phase of developing the web application PATRON, patients living with chronic pain
27 and representatives from patient organizations were invited to participate to the development.
28 In this stage, PATRON was presented and carefully discussed with patients and representatives
29 from patient organizations as well as with web application developers and researchers, resulting
30 in important alterations were made in an early phase.
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38 **Outcome assessments**

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40 According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
41 (IMMPACT), physical health, emotional health, and pain intensity are three of six identified
42 core outcome domains that should be considered when designing research studies aiming to
43 evaluate the efficacy and effectiveness of chronic pain treatments.^{31, 44} It is specifically
44 recommended that a health survey such as RAND-36 should be incorporated into treatment as
45 a clinical outcome assessment of physical health in clinical trials.³³⁻³⁴ Outcome assessments for
46 evaluating feasibility will be performed on data from the IPRP baseline and after the study
47 period is completed (six months). In the main trial, assessments of effectiveness will be
48 performed on data from the IPRP baseline and from the 12-month follow-up. The cost
49 effectiveness assessments will be based on data from the IPRP baseline, from the 12-month
50 IPRP follow-up and again 24 and 36 months after the IPRP is completed. A detailed overview
51 of outcome assessments can be found in Table 1.
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Table 1. Overview of study period, measurement time points, outcome assessments (*bold and italics*), instruments, and data sources (*italics*).

	Enrolment	Allocation	Study period				
			Baseline	t1	t2	t3	t4
	-t ₁	0					
Enrolment	X						
Written and verbal study information	X						
Eligibility screen	X						
Informed consent	X						
Allocation/randomization		X					
Interventions							
Intervention, eVIS (6 months)				X			
Control (6 months)				X			
Outcome assessments							
<i>Personal characteristics</i>							
Sex, age, country of origin, family composition, beliefs of restored health (<i>SQRP, ITR</i>)			X				
Disposable-, earned- and net income (<i>ITR</i>)			X		X	X	X
Education level and education orientation (<i>PER, ITR</i>)			X		X	X	X
Diagnosis (<i>PATR</i>)			X		X	X	X
Volume and reason for inpatient care (<i>PATR</i>)			X		X	X	X
<i>Pain characteristics</i>							
Pain intensity (last 7 days), NRS (<i>SQRP-PC and SC</i>)			X		X		
Pain intensity (today), NRS (<i>PATRON</i>)			X	X			
Pain type, location, duration (<i>SQRP-PC and SC</i>)			X				
Pain interference (<i>PATRON</i>)			X				
<i>Multidimensional measures</i>							
Physical health, RAND-36 PCS health survey (<i>PATRON</i>)			X	X	X	X	X
Physical health, RAND-36 PCS health survey (<i>SQRP-SC only</i>)			X		X		
Emotional health, RAND-36 MCS health survey (<i>PATRON</i>)			X	X	X	X	X
Emotional health, RAND-36 MCS health survey (<i>SQRP- SC only</i>)			X		X		

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Overall emotional distress, HAD(S) (<i>SQRP-PC and SC</i>)	X		X		
Pain catastrophizing, PCS (<i>SQRP-PC and SC</i>)	X		X		
Psychosocial consequences, MPI-S (<i>SQRP-PC and SC</i>)	X		X		
Pain acceptance, CPAQ-8 (<i>SQRP-PC only</i>)	X		X		
Perceived life Satisfaction, LiSat (<i>SQRP-PC and SC</i>)	X		X		
Functional level, FRI (<i>SQRP-SC only</i>)	X		X		
Physical activity					
Objective measures of steps per day (<i>Fitbit Versa 2</i>)	X	X			
Patient-reported measures (<i>SQRP- PC and SC</i>)	X		X		
Work					
Return to work (partially or full time) every month (<i>SSIA</i>)			X	X	X
Number of days with sick benefit during study period (<i>SSIA</i>)			X	X	X
Number of days in work before new sick leave during study period (<i>SSIA</i>)			X	X	X
Length of total sick leave during study period (<i>SSIA</i>)			X	X	X
Perceived work ability, WAI (<i>SQRP-PC and SC</i>)	X		X		
Sleep quality , ISI (<i>SQRP-SC only</i>)	X		X		
Pharmaceutical consumption					
Name, dose, size, prize of prescribed pharmaceuticals (<i>PHAR, PATRON [not size, prize]</i>)			X	X	X
Prescribed pharmaceuticals collected from pharmacies, (<i>PHAR</i>)			X	X	X
Cost of prescribed pharmaceuticals included in benefit program (<i>PHAR</i>)			X	X	X
Health care consumption (<i>PATR</i>)			X	X	X
Feasibility outcomes , <i>Questionnaire</i>			X		
Treatment integrity , <i>Questionnaire</i>			X	X	

Abbreviations: -t¹ = pre recruitment period, t¹ = completed study period (6 months), t² = follow-up 12 months after completed Interdisciplinary Pain Rehabilitation Program (IPRP), t³ = 24 months after completed IPRP, t⁴ = 36 months after completed IPRP, eVIS = eVISualisation of physical activity and pain intervention, SQRP = the Swedish national quality registry for pain rehabilitation, SQRP-PC = , the Swedish national quality registry for pain rehabilitation primary care, SQRP-SC = the Swedish national quality registry for pain rehabilitation specialized care, NRS = Numeric Rating Scale, PATRON = Pain and training online (web application), RAND-36 PCS = physical health domain , RAND-36 MCS = mental health domain, HAD(S) = Hospital Anxiety and Depression Scale, PCA = Pain Catastrophizing Scale, MPI-S = Multidimensional Pain Inventory -Swedish Version, CPAQ-8 = The Chronic Pain and Acceptance Questionnaire, LiSat = Life Satisfaction Scale, WAI = Work Ability Index, FRI = Functional rating scale, ISI = Insomnia Severity Index, SSIA = the Swedish Social Insurance Agency's registry, PATR = the Patient registry, PHAR = the Pharmaceutical registry, ITR = the Income- and taxation registry, PER = the Population education registry.

Feasibility outcomes, pilot study

The trial will be initiated as a full-scale registry-based internal randomized controlled pilot study. In this initial step, the recruitment process and more specifically the willingness of clinicians to recruit participants, willingness of patients to be recruited, number of eligible participants, contact ways, procedure of gaining consent, and sufficiency of provided recruitment material etc. will be evaluated. Also, the randomization process and the willingness of participants to be randomized and the type of randomization (block size, cluster, details of restrictions) will be evaluated. Furthermore, the standardized effect size and sample size estimation with Cohen's d , characteristics [mean, SD] of the primary outcome assessment in the main trial will be calculated after completed study period. In addition, follow-up rates (response rates to questionnaires, rates of treatment integrity, fidelity) will contribute with important aspects of the trial's feasibility in the intended setting.^{38, 41}

Primary outcome, main trial

The R-RCT will prospectively evaluate the *clinical effectiveness* of eVIS supplementing IPRPs regarding improvements in our primary outcome assessment *Physical health* collected by the physical health domain in RAND-36 health survey^{3, 45} at the 12-month IPRP follow-up after completing the IPRP. The RAND-36 is, for this population, a valid health survey measuring health-related quality of life in two dimensions, physical health (PCS) and mental health (MCS), mediated by eight subscales.⁴⁵

Secondary outcomes, main trial

In the main trial, secondary outcomes will be extracted from Fitbit Versa 2, PATRON and collapsed with data from six national registries (all listed below) at 6, 12, 24, and 36 months after the IPRP is completed.

Objectively measured secondary outcomes collected using Fitbit Versa 2

Objectively measured physical activity levels will be collected daily during the study period using a wrist-worn activity tracker (Fitbit Versa 2). The Fitbit device measures and estimates a range of physical activity outcomes such as number of steps, heart rate, energy expenditure, floors climbed, physical activity level, and sleep.^{30, 46} In this trial, participants' step count per

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3 day will automatically be synchronized to PATRON during the study period (six months). The
4 use of steps per day is considered to be a valid quantification of physical activity levels and this
5 is acknowledged by the Swedish Health Authority.⁴⁷
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8 9 *Patient-reported secondary outcomes collected through PATRON*

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11 Data on physical and mental health collected using the RAND-36 health survey will be
12 collected through PATRON at 6, 12 and 24 months after IPRP. Pain intensity (“rate your
13 average pain during the last 24 hours”) will be measured daily using the Numeric Rating Scale
14 (NRS 0-10), a 11-point Likert scale⁴⁸ incorporated in the web application PATRON. Pain
15 interference on daily activities is a recommended outcome domain.³² In PATRON, assessments
16 of affect of pain on daily activities (“rate how much your daily activities are affected by pain”) will
17 be measured using an 11-point Likert Scale (0-10). This question in PATRON has been
18 modified based on the Multidimensional Pain Inventory Swedish version and its items on pain
19 interference,⁴⁹ and validated in our previous study (in manuscript). Data on daily
20 pharmaceutical consumption will be collected in PATRON (name, dose, number, and form).
21 Voluntary free text comments will supplement patient reporting by providing additional
22 information regarding perceived mental and physical health (only in the intervention group).
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32 33 *Secondary outcomes collected through the Swedish national quality registry for pain 34 rehabilitation*

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36 In Sweden, 90% of IPRP units routinely collect patient-reported data from standardized
37 questionnaires and report to SQRP, a database initiated in 1998 that contains data from chronic
38 non-malignant pain patients participating in IPRPs.^{23, 50} The registry consists of two parts; the
39 primary care SQRP (SQRP-PC) and the specialized SQRP (SQRP-SC). The primary care SQRP
40 is supplied with data from affiliated primary care IPRP units (n=42, reported data from 505
41 patients in 2020). The specialized care SQRP, receives data from affiliated specialized care
42 IPRP units (n=45, reporting data from 7427 patients in 2020). Data in both registries are
43 collected at baseline, when the IPRP is completed, and at 12-month follow-ups, the content of
44 data collected in the registries differs somewhat. In this trial, registry data from both registries
45 will be collected and used to describe demographics such as age, sex, height, weight, education
46 level, and work.^{23, 50} Participants partaking in an IPRP in SC will also routinely complete the
47 RAND-36 health survey at baseline and at their 12-month follow-up after they have completed
48 their program. Data on pain intensity (“last 7 days”) (NRS 0-10)⁴⁸ will be retrieved from SQRP-
49 PC and SQRP-SC alongside other pain characteristics including pain location (36 anatomical
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3 predefined areas, 18 on the left side, 18 on the right side), pain duration, and pain type
4 (intermittent or continuous). Data on self-rated physical and mental health is collected by the
5 RAND-36 health survey^{3, 45} in SQRP-SC and the EuroQol-5 dimensions (EQ-5D) collected
6 routinely in SQRP-PC and SQRP-SC will be used. The EQ-5D is a standard instrument used in
7 health economic evaluations and contains five items each with three ordered response
8 categories, and a 0-100 index.⁵¹
9

10 Measures of self-rated physical activity are collected in SQRP-PC using the National Board of
11 Health and Welfare's three questions on physical activity (0 - >300 minutes/week), exercise (0
12 - >120 minutes/week), and sedentary behavior (0 - 15 hours/day).⁵² In SQRP-SC, data is
13 collected by the Godin-Shepard leisure-time physical activity questionnaire (number of
14 times/week that strenuous/moderate/light exercise is performed).⁵³ Data on overall emotional
15 distress (0 - 3), pain catastrophizing (0 - 4), and psychosocial consequences (0 - 6) of living
16 with pain are collected in SQRP-PC and SQRP-SC using the Hospital Anxiety and Depression
17 Scale (HADS),^{45, 54} the Pain Catastrophizing Scale (PCS),⁵⁵ and the Multidimensional Pain
18 Inventory Scale Swedish version (MPI-S, 0 - 6).⁴⁹ Level of pain acceptance (0 - 6) is collected
19 in SQRP-PC using the Chronic Pain and Acceptance Questionnaire (CPAQ-8).⁵⁶ Perceived life
20 satisfaction (1-6) is collected by the Life Satisfaction Scale (LiSat)⁵⁷ in both registries. Data on
21 perceived work ability (0 - 10) is collected by the Work Ability Index (WAI)⁵⁸ and functional
22 levels (0 - 4) by the Functional Rating Scale (FRI)⁵⁹ is collected in SQRP-SC only. Data on
23 patient-reported sleep quality (0 - 4) is collected by the Insomnia Severity Index (ISI)⁶⁰ in
24 SQRP-SC.
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40 *Secondary outcomes collected through other national registries*

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43 Data will be collected from the Swedish Social Insurance Agency's registry on diagnosis,
44 reasons for sick leave, type of financial compensation, number of sick days, and sickness benefit
45 (days and hours) during the study period. In addition, data on days in work (partial or full time)
46 per month in total before a new sick leave period and length of total sick leave during the study
47 period will be retrieved from the registry. Data will be retrieved from the Patient registry on
48 diagnosis and healthcare consumption (total number of days in care etc.). Retrieved data from
49 the Pharmaceutical registry will provide information on prescribed pharmaceutical names,
50 doses, sizes, and prices that have been collected from pharmacies, their costs, and whether the
51 pharmaceutical is included in the subsidized pharmaceutical program. Data on disposable and
52 earned income as well as net income will be retrieved from the Income and taxation registry.
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60 In addition, demographic data such as sex, age, marital status, citizenship, education level, and

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3 number of children in the family will be collected. Data on education level and education
4 orientation (focus) in addition to limited demographic data (sex, age) will be collected from the
5 Population registry.
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10 11 **Sample size**

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13 A sample size for the pilot study of at least $n=30$ is considered sufficient for planned pilot study
14 analyses since it will not involve hypothesis testing and sample size calculation *per se*.³⁹ An
15 interim sample size and power calculation was performed and based on data on RAND-36
16 outcomes reported by patients living with chronic pain 12 months after taking part in IPRP
17 treatment.²² A clinically meaningful difference on our primary outcome has previously been
18 reported to be ≥ 3 points.²⁴ In this trial, the null hypothesis is that there will be no difference
19 ($<15\%$ with ≥ 3 points improvement) between the intervention group and the control group with
20 regard to proportional improvement in the PCS domain of RAND-36 health survey when
21 assessed at the 12-month follow-up after the completion of the IPRP. The calculation was
22 performed in R, using a calculation method for simple randomization and for independent
23 observations. The preliminary power calculation allows a dropout rate of 20% and requires a
24 total sample size of approximately $n=400$ to have an 80% power to detect a 15% difference
25 ($\geq 3p$) between the groups regarding our primary outcome Physical health. Physical health is
26 measured using the RAND-36 health survey at the 12-month follow-up measurement point after
27 the completion of the IPRP. The significance level is set to 0.05 and is two-tailed. The sample
28 size calculation may be re-calculated after the pilot study is completed.
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45 **Allocation**

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47 A simple randomization design with a (random) block size of 4 and 6 will be applied and
48 evaluated in the pilot study in order to allocate participants to either the intervention or control
49 group.⁶¹⁻⁶³ A computer-generated randomization schedule will be created using a random
50 number table to allocate participants to one of the two treatment arms; intervention group (IPRP
51 supplemented by eVIS) or control group (IPRP with daily patient reports in PATRON). The
52 schedule will be generated by an experienced researcher, who is not directly involved in the
53 trial. Sequentially numbered opaque sealed envelopes will be used to ensure allocation
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3 concealment. Allocation will take place at the IPRP unit and will be conducted by members of
4 the IPRP team.
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9 **Blinding/masking**

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11 Neither the IPRP team delivering the intervention nor participants will be blinded to
12 allocation to either group due to the nature of the intervention.
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18 **Data collection methods**

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20 Besides objectively measured data of physical activity level, patient-reported data will be
21 collected from PATRON and from six Swedish registries at the IPRP baseline and at 6, 12, and
22 24 months after completed IPRP. In addition, patient-reported data regarding cost effectiveness
23 will be retrieved 36 months after the IPRP is completed. In this trial, data will be retrieved from
24 SQRP, the Swedish social insurance agency's registry, the Patient registry, the Pharmaceutical
25 registry, the Income- and taxation registry, and the Population education registry to enable a
26 broad investigation into the intervention's effectiveness.
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33 To enable sufficient pilot study analyses, as well as assessment of the primary outcome Physical
34 health (PCS) in RAND-36, members of the IPRP team will be asked to provide self-reported
35 data on feasibility outcomes (outlined below) using a purpose-developed questionnaire with
36 specific questions targeting the IPRP-team perspective.³⁸ If deemed required, data collection
37 will be supplemented by individual or group interviews. A detailed overview of assessments,
38 time points, and data sources can be found in Table 1.
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47 **Data management**

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49 In order to connect individual-level data from different registries to PATRON data, we will
50 seek assistance from the National Board of Health and Welfare who will provide a consecutive
51 number key. This key will be stored at the National Board of Health and Welfare for three years
52 (longer if needed). The procedure is initiated by sending PATRON data to the National Board
53 of Health and Welfare and participants' social security numbers will be sent there by SQRP.
54 The National Board of Health and Welfare creates the consecutive number key and connects
55 ordered data with own registry data (the Patient registry and the Pharmaceutical registry). The
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3 National Board of Health and Welfare will then send a data order to the remaining registries
4 (the Swedish Social Insurance Agency's registry, the Income and taxation registry, and the
5 Population education registry) and un-identified data will be sent to the principal investigator
6 to be stored in Dalarna University's secured server.
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10 11 12 13 **Intervention fidelity**

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15 The following measures have been and will be taken to increase intervention fidelity: A
16 systematical intervention development with a clarified theoretical base explaining suggested
17 mechanisms has been undertaken throughout the development process. Healthcare staff at the
18 IPRP units will be provided with comprehensive written information (easily accessed online)
19 that includes step-by-step instructions on how to initiate and deliver the intervention while
20 maintaining a high level of integrity. Before the study starts, all participating healthcare staff at
21 the IPRP units will take part in a standardized provider training session online. Also, recurring
22 web-based meeting opportunities will be provided, where IPRP-team members will be
23 encouraged to discuss experienced or perceived difficulties, and a questionnaire will be sent out
24 after the study period with the aim of assessing treatment fidelity (treatment integrity and
25 treatment differentiation) by gathering data on how treatment was delivered (manner *versus*
26 treatment manual, intervention's alignment to intended theoretical base). This will allow results
27 to be interpreted and will facilitate practical implementation.⁶⁴⁻⁶⁵ During the on-going study
28 period, researchers will be automatically notified of non-wear time (Fitbit Versa 2) and any
29 absence of patient reports in PATRON. In these cases, researchers will contact the relevant
30 participant via email or telephone to ask if they need help or support. If a participant decides to
31 discontinue the trial, he or she will be asked if they are willing to grant permission for the
32 collected data up to that point to be used in the trial.
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50 51 **Statistical methods**

52 A statistical analysis plan (SAP) will expand on statistical principles, statistical analyses, the
53 planned handling of missing data, possible additional analyses (subgroups etc.), and interim
54 analyses. In both the pilot study and the R-RCT, descriptive statistical analyses will be
55 performed to provide transparent reporting of characteristics of both participants and
56 participating IPRP units. In addition, IPRP units will be prompted to register the number of
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3 patients they ask to participate, those excluded based on eligibility criteria, and those who
4 decline participation. Analyses of pilot outcomes and primary and secondary outcomes will be
5 performed based on PATRON data and registry data. The clinical effectiveness of eVIS will be
6 analyzed for each outcome using multivariate statistical and repeated measures analyses as a
7 preliminary plan. Both the intention-to-treat and the per-protocol sample will be analyzed, but
8 the intention-to-treat analysis will be considered as the primary analysis. All p-values will be
9 presented. If a p-value is <0.05 , the null hypothesis will be rejected and eVIS will be considered
10 effective according to the outlined hypothesis. To perform cost-effectiveness calculations, data
11 on health-related quality of life measured by EQ-5D will be retrieved from SQRP. EQ-5D is
12 the standard instrument used to evaluate health costs and cost effectiveness. Calculations of
13 quality-adjusted life-years (QALYs) will be performed by multiplying health-state utility
14 (measured using the EQ-5D Index score) by time spent in this specific health state.⁶⁶⁻⁶⁷ In
15 addition, calculations of the incremental cost effectiveness ratio (ICER) will be made as the
16 difference in the cost of two interventions divided by their effect.⁶⁸
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30 **Data monitoring**

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32 Trial data will be monitored and regularly assessed for integrity and errors. All data monitoring
33 will be performed completely independently from sponsors and competing interests. An
34 independent data monitoring committee (DMC) will be appointed to critically review data
35 safety in the trial. Veronica Sjöberg (VS) will be responsible for the monitoring of all data
36 collected in the internal pilot study. A data management plan (DMP) will be outlined by the
37 first author (VS) and implemented by the principal investigator (LV) to ensure sound data
38 structure (folder structure, file naming, organization), and data storing.
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48 **Harms and adverse events**

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50 Participating patients and healthcare staff at the participating IPRP units will be encouraged to
51 report any adverse events such as unexpected side effects or symptom deterioration,⁶⁹ which
52 will also be reported to the Swedish Ethical Board Review.
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Ethics and dissemination

The trial is registered in ClinicalTrials.gov and was approved by the Swedish Ethics Review Board in May 2021 (Dnr 2021/02109). The trial will be conducted in compliance to the Helsinki Declaration.⁷⁰ Important protocol modifications will be communicated to the Swedish Ethics Review Board as well as to all participating IPRP units and participants. To protect confidentiality, all data will be coded by an individual code, and the encryption key will be stored separately. Data will be stored at an intended project server at Dalarna University, which is secured by regular backups and only accessible by researchers in the trial after approval from the principal investigator. Results of the internal pilot study and the main trial will be submitted for publication in peer-reviewed journals and communicated in national and international research networks, as well as in relevant clinical settings, including patient associations.

CONCLUSION

This trial has been designed to provide robust data on the feasibility and effectiveness of a systematically developed intervention named eVIS. eVIS is designed to facilitate patients in IPRP reaching and maintaining individualized levels of physical activity recommended to them by involving both objective and patient-reported data, as well as mitigating behavior-change mechanisms.

Author contribution statement

LV and BÄ are responsible for the conception of the trial. LV is the principal investigator and is involved in all methodological decisions. VS, ET, AM, JW, RLM, BÄ, MH, MB, and LV all contributed to study design and were all involved in the development processes (the evaluation of criterion validity of the wrist-worn activity tracker and the evaluations of the content validity and clinical feasibility) of the intervention. RLM performed the preliminary power and sample size calculations and was involved in all associated decisions. VS wrote the first draft of the manuscript and was responsible for revising the manuscript's intellectual content based on all co-authors conscientious input. All authors read and approved the final version of the manuscript. For this article, no ghost authors, guest authors, or professional writers have or will

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3 be used. Author eligibility is and will be based upon the ICMJE Recommendations for the
4 Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.
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7 **Trial status**

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9 The recruitment process of IPRP units have been initiated in June 2021. Recruitment of
10 participants are anticipated to start in September 2021 and the trial is planned to be completed
11 on 31 December 2024.
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17 **Funding**

18 This trial is funded by the Swedish Research Council for Health, Working Life and Welfare
19 (2017-00491), the Research Council (2018-02455), the Swedish Association for Survivors of
20 Polio, Accident, and Injury (2020-03), and research funding from Dalarna University (No grant
21 number). The funders had no role in study design and will have no role in any part of the
22 implementation of the study or the reporting of its results.
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32 **Competing interests**

33 None declared.
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39 **Access to data**

40 This is a protocol describing a trial design. No data collection has yet been initiated. All
41 authors will have access to the final trial dataset.
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48 **Additional files:**

- 49 - Completed SPIRIT 2013 Checklist
- 50 - Patient consent form (in Swedish)
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8 [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)
9 [medical-research-involving-human-subjects/](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Access date 2018-05-22.
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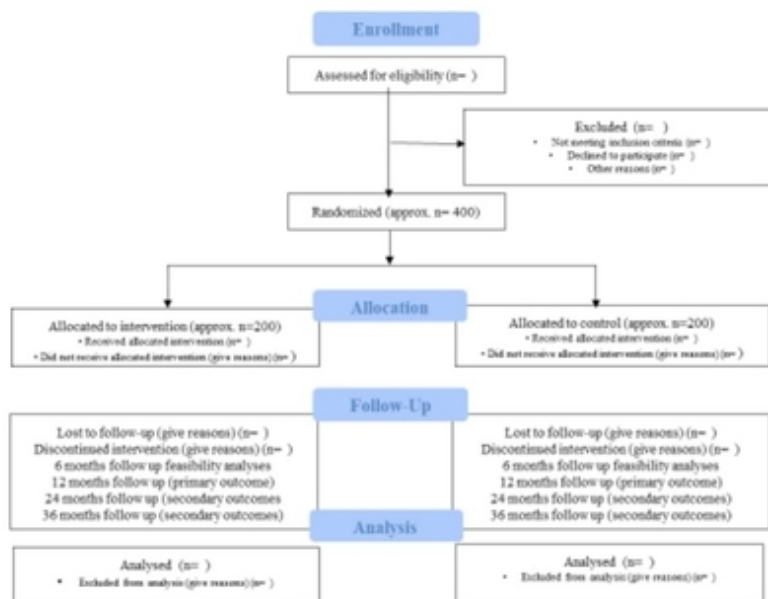


Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.

21x17mm (600 x 600 DPI)

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3 SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related
4 documents*
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Section/ item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 18
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19
	5b	Name and contact information for the trial sponsor	20 (not contact info)
	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	20
	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)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6

	6b	Explanation for choice of comparators	17-18
Objectives	7	Specific objectives or hypotheses	6, 17-18
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)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	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)	18-19
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9-14 Table 1
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)	Table 1, 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	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			15
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	17-18
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	17-18
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18

	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	17
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	16
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	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	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)	17-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	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	17-18
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	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
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)	18-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	20
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	No
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	18-19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary files [In Swedish]
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	NA

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BMJ Open

Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial

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Title:

Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial

Authors:

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Keywords: Chronic pain, Individualized physical activity level, Interdisciplinary Pain Rehabilitation Programs, pilot study, Physical health, Registry-based randomized clinical trial, Study protocol.

ABSTRACT

Introduction: Living with chronic pain often involves negative consequences. Interdisciplinary Pain Rehabilitation Programs (IPRPs), a subset of Interdisciplinary Treatment is considered superior to single-treatment measures in patients with chronic pain. Despite this, effects emerge sub-optimal and more than 20% of patients deteriorate in patient reported physical health outcomes after IPRP. A novel e-Health intervention, eVISualisation (eVIS) of physical activity and pain, has been systematically developed to facilitate patients in reaching and maintaining recommended individualized physical activity levels. The aim is to transparently report on methodology, outcome assessments, and processes for a registry-based randomized controlled trial (R-RCT) initiated as a pilot study.

Methods and analysis: In the R-RCT, recruitment of approximately 400 patients with chronic pain at primary and specialized IPRP units (n=15) in Sweden will be performed. Participants will be randomly allocated to either IPRP + eVIS or to control group that will receive IPRP only. eVIS entails objectively measured physical activity (steps) and patient-reported outcomes (pain intensity, interference of pain on daily activities, pharmaceutical consumption) collected and visualized in the web application PATRON. Data from the initial 30 participants completing the study period (6 months) will be included in a pilot study designed to evaluate key feasibility outcomes (recruitment- and randomization processes, implementation process, treatment integrity, data collection procedure, and preliminary outcome measures). Outcome variables will be extracted from PATRON and from six national registries. Multivariate statistics and repeated measures analyses will be performed. Quality Adjusted Life Years (QALYs) and Incremental Cost Effectiveness Ratio (ICER) will be calculated for cost effectiveness evaluation.

Ethics/dissemination: The Swedish Ethics Review Board granted approval (Dnr 2021/02109). Results will be disseminated through peer-review journals.

Trial registration number: The trial was prospectively registered at ClinicalTrials.gov with trial registration number NCT05009459.

Protocol version: 1

Strengths and limitations of the study

- A proceeding pilot study will enable improvements of design and feasibility of subsequent R-RCT.
- The eVIS-intervention has been developed, evaluated, and improved, based on data provided from patients, clinicians, and researchers in different fields.
- The intervention targets physical activity modalities in IPRP and is designed to enable a more individualized IPRP treatment.
- The intervention is based on objectively measured physical activity levels, patient-reported clinical outcomes, and mechanisms that facilitate behavior change, in accordance with current guidelines that are provided by authorities in the chronic pain management field.
- The nature of the intervention precludes blinding of patients and the IPRP team.

INTRODUCTION

Chronic musculoskeletal pain (>3 months), including neck/shoulder/back pain or widespread pain, is a major global health and socioeconomic burden.^{1 2} Living with chronic pain is often associated with reduced levels of wellbeing and the health-related quality of life of this group has been reported to be among the lowest of any medical condition.³ To date, physical activity (i.e. any bodily movement that requires energy expenditure) and exercise (i.e. structured and planned physical activity aimed to increase fitness)⁴ have been shown to prevent and/or treat several of our noncommunicable diseases including chronic pain,⁵ due to their beneficial effects on general health, pain intensity, physical and psychological functioning, and health-related quality of life.⁵⁻⁸ Despite the growing evidence of health benefits related to physical activity, participation and adherence to physical activity recommendations, such as WHO's physical activity guidelines, are often low in patients living with chronic pain.⁹⁻¹² This may partly be explained by the indicated association between high pain scores and low patient-reported activity levels among patients with chronic pain and/or the documented reports of the negative impact of depression on physical activity levels.¹³ In addition, it is well known that behavior change is difficult, and that each individual's own participation is essential.¹⁴ It has been shown that behavior change towards a beneficial physical activity level may be facilitated by individuals self-monitoring their physical activity.¹⁵ The use of objective measures increases the likelihood of the effectiveness of interventions designed to promote physical activity.¹⁵ By adding goal setting, feedback, and a focus on achieved goals, effectiveness can be further improved.¹⁵⁻¹⁸

Interdisciplinary pain rehabilitation programs (described as a subset of Interdisciplinary Treatment [IDT]), is defined as "multimodal treatment provided by a multidisciplinary team (at least 3 professions), collaborating in assessment and treatment using a shared biopsychosocial model and goals"¹⁹. The IPRP approach adopts the principles of behavioral therapy and incorporates besides physical activity and exercise, also psychological measures, pharmaceutical treatment and patient education.²⁰ Physical activity and exercise are central measures in IPRPs as it targets the physical deconditioning by improving levels of physical activity, and also reduces pain severity and improved physical function and quality of life, without causing any severe adverse events.⁵ Interdisciplinary pain rehabilitation programs are considered to be superior to single-treatment measures (e.g., physical treatments, education interventions, surgery, etc.) for patients with chronic pain supporting positive effects on pain intensity and activity disability.^{20 21} However, IPRP effectiveness is only slightly better and in

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3 the majority of cases only a small effect is seen.²¹⁻²⁵ In addition, up to 25% of patients report
4 deterioration in physical health after completing IPRP and after 12 months follow up, regardless
5 of duration of IPRP.^{20 25 26} Sustainable treatment affects seem to vary according to patient
6 clinical features at baseline, such as poor employment status, high pain levels, and low
7 functioning, all of which predict low physical health at follow-up.^{23 27} Many efforts have been
8 made to find effective interventions that improve the health of chronic pain patients. To
9 facilitate individualized physical activity levels within the Swedish IPRP setting, an
10 eVISualisation (eVIS) of physical activity and pain intervention has been systematically
11 developed according to the Medical Research Council's recently updated framework for
12 development and evaluation of complex interventions.^{28 29} In accordance with the framework,
13 the eVIS-interventions were designed and planned in close collaboration with stakeholders.
14 eVIS is designed to target facilitating mechanisms for behavior change, such as outcome
15 expectations, self-monitoring, self-evaluation, and self-efficacy,³⁰⁻³² which are theoretically
16 framed by the Social Cognitive Theory.³² In eVIS, objectively measured physical activity
17 tracking using a wrist-worn activity tracker³³ (Fitbit Versa 2) is combined with a daily activity
18 goal (steps/day) and daily patient reports of known important clinical outcome assessments:
19 pain intensity and its interference on daily activities³⁴⁻³⁸ and pharmaceutical consumption. Data
20 is collected and visualized in a purpose-developed web application, Pain And TRaining ON-
21 line (PATRON), which can be used by the patient and the IPRP-team to follow and adjust
22 individual physical activity levels. Despite interventions of this kind having highly promising
23 potential to relive pain and improve disability in this patient group,³⁹ interventions are rarely
24 systematically developed and validated specifically for their target patient group, leaving
25 crucial information of feasibility and true effectiveness unknown. To increase the robustness
26 of this planned R-RCT and to avoid an underpowered trial and gain knowledge of population
27 variation,⁴⁰ an randomized pilot study will be conducted to evaluate the intervention's
28 feasibility within the IPRP setting with the specific purpose of improving and strengthening the
29 R-RCT design.⁴⁰⁻⁴³ In this trial, the UK National Institute for Health Research's (NIHR)
30 definitions of the terms *pilot study* (i.e., "a smaller version of the main study") and *feasibility*
31 *study* (i.e., "evaluation of pieces of research done before the main study") are applied.⁴⁴ The
32 aim of this paper is to transparently clarify and report on study designs, aims, outcome
33 assessments, and procedures for a planned R-RCT (including an randomized pilot study) which
34 prospectively will evaluate clinical effectiveness and cost effectiveness of eVIS supplement to
35 IPRPs for patients living with chronic pain compared to standard IPRPs.
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METHODS AND ANALYSIS

Trial design and setting

This two-armed pragmatic multi-site registry-based randomized controlled clinical trial (R-RCT) will be conducted in specialized and primary IPRPs in Sweden, and include approximately 400 (n=200, n=200) patients (number will be definitively determined after the pilot study is finalized) with chronic musculoskeletal non-malignant pain. As indicated, an randomized controlled pilot study (n=15, n=15) will be incorporated as the initial phase of the main trial in order to evaluate the intervention's methodology and design.^{29 42 45} This trial will comply with the Consolidated Standards of Reporting Trials (CONSORT)⁴¹ and with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)⁴⁶. A completed SPIRIT 2013 Checklist can be found in the additional files. See Figure 1 for study design and enrollment details.

Insert Figure 1 here.

Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.

Eligibility criteria

In this trial, the patient-related, care process and caregiver-related inclusion criteria for receiving Swedish IPRP will be applied, as patients entering the trial must be accepted for IPRP. Principal IPRP inclusion criteria are patients in working age with persistent or intermittent pain lasting ≥ 3 months with pain affecting daily activities to a large extent, completed systematic assessment (including screening for psychosocial risk factors and differential diagnosis) and non-pharmacological optimization. Inclusion criteria for Swedish IPRPs is outlined in detail elsewhere.⁴⁷ Due to the nature of the intervention, patients must be able to hear, see, and comprehend spoken and written Swedish, and have daily access to a computer, smartphone, or tablet. Patients who need to use a walking aid indoors will be excluded.

Recruitment

Interdisciplinary Pain Rehabilitation Units

Approximately 15 IPRP units in primary and specialized care in Sweden will be included in the trial. IPRP units reporting to the Swedish National Quality Registry for Pain Rehabilitation (SQRP) have been approached by email with study information (aim, rationale, methods etc.) and an invitation to participate in one of several online digital information meetings that will further present the study (planned from August 2021). Study representatives will approach healthcare staff at potential IPRP units by telephone or email to formally offer participation. Operation managers at each unit will be asked to provide written consent by e-mail.

Participants

In order to give potential participants additional time to consider taking part in the trial before they visit the IPRP unit, healthcare staff at the units will be encouraged to provide a general information sheet about the trial in the summon to the IPRP assessment. Members of IPRP teams (primarily physiotherapists but also occupational therapists, physicians, nurses etc.) will identify potential participants selected for IPRP based on outlined criteria and provide them with verbal and written details of the study (information sheets and the project's web address). All participants will provide written informed consent (see supplementary file) prior to joining the study, which will be managed by the IPRP team. Detailed verbal and written information about the voluntary nature of participation and the indisputable right to discontinue participation in the trial at any time will be provided. Detailed checklists and forms will support these procedures, and these will be easily accessible on the project web site.

Intervention

Participation in the intervention group involves regular IPRP supplemented with eVIS for a coherent time span of six months, IPRP time included. As the duration and intensity of IPRPs greatly vary from a couple of weeks up to four months²⁵, a six month study period ensures time of independent use of eVIS after completed IPRP. Participants are not prohibited to take part of other health care during study period. Interdisciplinary pain rehabilitation programs vary in interventions, duration, composition, intensity^{24 25} and can be performed either individually or in group format. In this trial, participation in a IPRP will be supplemented by eVIS, a health

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3 promoting intervention containing three elements designed to facilitate individualized physical
4 activity level (Figure 2).
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6 7 The data collection element 8

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10 Outcome assessments of physical activity level (steps/day) will be objectively collected by a
11 wrist-worn activity tracker, Fitbit Versa 2. This device has been population-specifically
12 validated and the measurement of step rate is indicated as valid for measurement in this
13 population.³³ Data on step rate will be automatically synchronized to the web application
14 PATRON where pain intensity (0-10),⁴⁸ interference of pain on daily activities (0-10),⁴⁹
15 pharmacological consumption (name, dose, number, and form), and (optional) free-text
16 comments will be reported by the patient daily. The web application can be accessed via
17 computer, smartphone, or tablet. A daily activity goal (steps/day) is formulated by the patient
18 in collaboration with the IPRP-team and revised accordingly.
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26 The data collection element is designed to target facilitating mechanisms for behavior change,
27 such as outcome expectations, self-monitoring, self-evaluation, and self-efficacy.³⁰⁻³² The
28 visualisation element
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31 Objectively measured physical activity levels, patient-report on pain intensity and interference
32 of pain on daily activity are graphically visualized in relation to patient daily activity goal.
33 Three different graphs (1/7/28 days) are available. The visualisation element provides
34 prerequisites for increased knowledge acquisition, self-monitoring, and self-evaluation as data
35 is visualized over time and in relation to each other and to the individual daily activity goal in
36 order to improve patient self-efficacy.
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42 43 The communication element 44

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46 The graphs in the visualisation element together with compiled data on pharmacological
47 consumption will provide novel support for the patient and the IPRP team towards an
48 individualized goal setting process by reinforcement, knowledge acquisition, self-monitoring,
49 and self-efficacy. The support is facilitated by objectively measured physical activity levels
50 visualized in relation known factors important in pain rehabilitation. Based on data in eVIS,
51 patient and IPRP-team get unique information of factors affecting physical activity levels. This
52 addition to IPRP provides possibilities to investigate barriers to physical activity and fine-tune
53 individualized treatment.
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8 **Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of**
9 **physical activity level (steps/day), patient-reports of interference of pain on daily activities, pain intensity**
10 **and pharmacological consumption, ii) the visualisation element of collected data in different graphs and**
11 **compilations of data, and iii) the communication element.**
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16 **Control**

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19 Participation in the control group involves taking part in regular IPRP plus making daily ratings
20 of pain intensity, interference of pain on daily activities, and pharmaceutical consumption
21 (corresponding as in intervention group) in PATRON for six months, including the time that
22 the IPRP is being carried out. The control group will not use the wrist-worn activity tracker or
23 have access to PATRON's visualizing or communication features.
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30 **Patient and Public Involvement Statement**

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33 In an early developing phase, stakeholders (patients living with chronic pain, representatives
34 from patient organizations and clinicians experienced in pain rehabilitation) were invited to
35 contribute to the intervention development. In this phase, the web application PATRON and
36 eVIS was presented and carefully discussed with stakeholders as well as with web application
37 developers and researchers. Several needs for improvement were identified, such as a need of
38 an addition of pharmaceutical report function, designated web pages and graphical changes in
39 planned interfaces.
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48 **Outcome assessments**

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50 According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
51 (IMMPACT), physical health, emotional health, and pain intensity are three of six identified
52 core outcome domains that should be considered when designing research studies aiming to
53 evaluate effectiveness of chronic pain treatments.^{34 50} It is specifically recommended that a
54 health survey such as RAND-36 should be incorporated into treatment as a clinical outcome
55 assessment of physical health in clinical trials.^{36 37} Outcome assessments for evaluating
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3 feasibility will be performed on data from the IPRP baseline and after the study period is
4 completed (six months) for the first 30 participants (n=15 +, n=15). In the main trial,
5 assessments of effectiveness will be performed on data from the IPRP baseline and from the
6 12-month follow-up. The cost effectiveness assessments will be based on data from the IPRP
7 baseline, from the 12-month IPRP follow-up and again 24 and 36 months after the IPRP is
8 completed. A detailed overview of outcome assessments can be found in Table 1.
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Table 1. Overview of study period, measurement time points, outcome assessments (*bold and italics*), instruments, and data sources (*italics*).

	Enrolment	Allocation	Study period				
			Baseline	t1	t2	t3	t4
	-t ₁	0					
Enrolment	X						
Written and verbal study information	X						
Eligibility screen	X						
Informed consent	X						
Allocation/randomization		X					
Interventions							
Intervention, eVIS (6 months)				X			
Control (6 months)				X			
Outcome assessments							
<i>Personal characteristics</i>							
Sex, age, country of origin, family composition, beliefs of restored health (<i>SQRP, SS</i>)			X				
Disposable-, earned- and net income (<i>SS</i>)			X		X	X	X
Education level and education orientation (<i>SPR, SS</i>)			X		X	X	X
Diagnosis (<i>NPR</i>)			X		X	X	X
Volume and reason for inpatient care (<i>NPR</i>)			X		X	X	X
<i>Pain characteristics</i>							
Pain intensity (last 7 days), NRS (<i>SQRP-PC and SC</i>)			X		X		
Pain intensity (today), NRS (<i>PATRON</i>)			X	X			
Pain type, location, duration (<i>SQRP-PC and SC</i>)			X				
Pain interference (<i>PATRON</i>)			X				
<i>Multidimensional measures</i>							
Physical health, RAND-36 PCS health survey (<i>PATRON</i>)			X	X	X	X	X
Physical health, RAND-36 PCS health survey (<i>SQRP-SC only</i>)			X		X		
Emotional health, RAND-36 MCS health survey (<i>PATRON</i>)			X	X	X	X	X
Emotional health, RAND-36 MCS health survey (<i>SQRP- SC only</i>)			X		X		

Overall emotional distress, HAD(S) (<i>SQRP-PC and SC</i>)	X		X		
Pain catastrophizing, PCS (<i>SQRP-PC and SC</i>)	X		X		
Psychosocial consequences, MPI-S (<i>SQRP-PC and SC</i>)	X		X		
Pain acceptance, CPAQ-8 (<i>SQRP-PC only</i>)	X		X		
Perceived life Satisfaction, LiSat (<i>SQRP-PC and SC</i>)	X		X		
Functional level, FRI (<i>SQRP-SC only</i>)	X		X		
Physical activity					
Objective measures of steps per day (<i>Fitbit Versa 2</i>)	X	X			
Patient-reported measures (<i>SQRP- PC and SC</i>)	X		X		
Work					
Return to work (partially or full time) every month (<i>SSIA</i>)			X	X	X
Number of days with sick benefit during study period (<i>SSIA</i>)			X	X	X
Number of days in work before new sick leave during study period (<i>SSIA</i>)			X	X	X
Length of total sick leave during study period (<i>SSIA</i>)			X	X	X
Perceived work ability, WAI (<i>SQRP-PC and SC</i>)	X		X		
Sleep quality , ISI (<i>SQRP-SC only</i>)	X		X		
Pharmaceutical consumption					
Name, dose, size, prize of prescribed pharmaceuticals (<i>SPDR, PATRON [not size, prize]</i>)			X	X	X
Prescribed pharmaceuticals collected from pharmacies, (<i>SPDR</i>)			X	X	X
Cost of prescribed pharmaceuticals included in benefit program (<i>SPDR</i>)			X	X	X
Health care consumption (NPR)					
Feasibility outcomes, Questionnaire			X		
Treatment integrity, Questionnaire			X	X	

Abbreviations: -t¹ = pre recruitment period, t¹ = completed study period (6 months), t² = follow-up 12 months after completed Interdisciplinary Pain Rehabilitation Program (IPRP), t³ = 24 months after completed IPRP, t⁴ = 36 months after completed IPRP, eVIS = eVISualisation of physical activity and pain intervention, SQRP = the Swedish national quality registry for pain rehabilitation, SQRP-PC = , the Swedish national quality registry for pain rehabilitation primary care, SQRP-SC = the Swedish national quality registry for pain rehabilitation specialized care, NRS = Numeric Rating Scale, PATRON = Pain and training online (web application), RAND-36 PCS = physical health domain , RAND-36 MCS = mental health domain, HAD(S) = Hospital Anxiety and Depression Scale, PCA = Pain Catastrophizing Scale, MPI-S = Multidimensional Pain Inventory -Swedish Version, CPAQ-8 = The Chronic Pain and Acceptance Questionnaire, LiSat = Life Satisfaction Scale, WAI = Work Ability Index, FRI = Functional rating scale, ISI = Insomnia Severity Index, SSIA = the Swedish Social Insurance Agency's registry, NPR = the National Patient Register, SPDR = the Swedish Prescribed Drug Register, SS = Statistics Sweden, SPR = the Swedish Population Register.

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3 1 Feasibility outcomes, pilot study
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5
6 2 The trial will be initiated as a full-scale registry-based randomized controlled pilot study. In
7
8 3 this initial step, feasibility will be evaluated from data provided from the first 30 participants
9
10 4 completing the study period and in the following key areas: the unit's recruitment capabilities,
11
12 5 the randomization process, implementation process, participant response to intervention which
13
14 6 is outlined in Table 2. In addition, the data collection procedure and the preliminary outcome
15
16 7 measures (standardized effect size, sample size estimation with Cohen's *d*, characteristics
17
18 8 [mean, SD]) in main trial will be evaluated.^{42 45} In addition to feasibility outcomes,
19
20 9 characteristics of the units IPRP will be collected
21

22 11 **Table 2.** Overview of key feasibility outcomes in pilot study.
23

24 12

Key feasibility outcomes	
25 13	Recruitment capability
26	Volume of total eligible patients
27	Number recruited/week
28	Eligibility screening procedure
29 14	Proportion accepted/declined
30	Personal characteristics of included and excluded participants
31	Pain characteristics of included and excluded participants
32 15	Procedure of collecting consent
33	Randomization process
34 16	Delivery envelopes
35	Storage of envelopes
36	Procedure of opening envelopes
37 17	Patients' reaction to allocation
38	Implementation process
39 18	Response rate RAND-36 PCS
40	Compliance rate (use of Fitbit Versa 2, intervention group only)
41	Compliance rate (patient reported outcomes in PATRON)
42 19	Treatment integrity
43	Reported adverse events
44 20	Data collection procedure
45	Access to PATRON data
46	Access to RAND-36 data
47 21	Preliminary outcome measures
48	Characteristics primary outcome
49	Missing data
50 22	Changes from baseline to finalized study period

51 23 **Abbreviations:** RAND-36 PCS = physical health domain in RAND-36, PATRON = Pain and training online (web
52 24 application).
53

54 25
55
56 26 Primary outcome, main trial
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3 27 The R-RCT will prospectively evaluate the clinical effectiveness of eVIS supplementing IPRPs
4
5 28 regarding improvements in our primary outcome assessment Physical health collected by the
6
7 29 physical health domain in RAND-36 health survey^{3 51} at the 12-month IPRP follow-up after
8
9 30 completing the IPRP. The RAND-36 is, for this population, a valid health survey measuring
10
11 31 health-related quality of life in two dimensions, physical health (PCS) and mental health (MCS),
12
13 32 mediated by eight subscales.⁵¹

14 33 Secondary outcomes, main trial

15
16 34 In the main trial, secondary outcomes will be extracted from Fitbit Versa 2, PATRON and
17
18 35 collapsed with data from six national registries (all listed below) at 12, 24, 36 months after the
19
20 36 IPRP is completed.

21 22 37 *Objectively measured secondary outcomes collected using Fitbit Versa 2*

23
24
25 38 Objectively measured physical activity levels will be collected daily during the study period
26
27 39 using a wrist-worn activity tracker (Fitbit Versa 2). The Fitbit device measures and estimates a
28
29 40 range of physical activity outcomes such as number of steps, heart rate, energy expenditure,
30
31 41 floors climbed, physical activity level, and sleep.^{33 52} In this trial, participants' step count per
32
33 42 day will automatically be synchronized to PATRON during the study period (six months). The
34
35 43 use of steps per day is considered to be a valid quantification of physical activity levels and this
36
37 44 is acknowledged by the Swedish Health Authority.⁵³

37 45 *Patient-reported secondary outcomes collected through PATRON*

38
39
40 46 Data on physical and mental health collected by RAND-36 health survey will be collected
41
42 47 through PATRON at 6, 12 and 24 months after IPRP. Pain intensity (“rate your average pain
43
44 48 during the last 24 hours”) will be measured daily using the Numeric Rating Scale (NRS 0 = no
45
46 49 pain at all to 10 = pain as bad as it could be), a 11-point Likert scale⁴⁸ incorporated in the web
47
48 50 application PATRON. Pain interference on daily activities is a recommended outcome
49
50 51 domain.³⁵ In PATRON, assessments of interference of pain on daily activities will be measured
51
52 52 by the question “rate how much your daily activities are affected by pain” using an 11-point
53
54 53 Likert Scale (0 = not at all to 10 = to a very large extent). This question in PATRON has been
55
56 54 modified based on the Multidimensional Pain Inventory Swedish version and its items on pain
57
58 55 interference,⁴⁹ and validated in our previous study (in manuscript). Data on daily
59
60 56 pharmaceutical consumption will be collected in PATRON (name, dose, number, and form).

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2
3 57 Voluntary free text comments will supplement patient reporting by providing additional
4 58 information regarding perceived mental and physical health (only in the intervention group).

59 *Secondary outcomes collected through the Swedish national quality registry for pain*
60 *rehabilitation*

61 In Sweden, 90% of IPRP units routinely collect patient-reported data from standardized
62 questionnaires and report to SQRP, a database initiated in 1998 that contains data from chronic
63 non-malignant pain patients participating in IPRPs.^{24 54} The registry consists of two parts; the
64 primary care SQRP (SQRP-PC) and the specialized SQRP (SQRP-SC). The primary care SQRP
65 is supplied with data from affiliated primary care IPRP units (n=42, reported data from 505
66 patients in 2020). The specialized care SQRP, receives data from affiliated specialized care
67 IPRP units (n=45, reporting data from 7427 patients in 2020). Data in both registries are
68 collected at baseline, when the IPRP is completed, and at 12-month follow-ups, the content of
69 data collected in the registries differs somewhat. In this trial, registry data from both registries
70 will be collected used to describe demographics such as age, sex, height, weight, education
71 level, and work.^{24 54} Participants partaking in an IPRP in SC will also routinely complete the
72 RAND-36 health survey at baseline and at their 12-month follow-up after they have completed
73 their program. Data on pain intensity (“last 7 days”) (NRS 0-10)⁴⁸ will be retrieved from SQRP-
74 PC and SQRP-SC alongside other pain characteristics including pain location (36 anatomical
75 predefined areas, 18 on the left side, 18 on the right side), pain duration, and pain type
76 (intermittent or continuous). Data on self-rated physical and mental health is collected by the
77 RAND-36 health survey^{3 51} in SQRP-SC and the EuroQol-5 dimensions (EQ-5D) collected
78 routinely in SQRP-PC and SQRP-SC will be used. The EQ-5D is a standard instrument used in
79 health economic evaluations and contains five items each with three ordered response
80 categories, and a 0-100 index.⁵⁵

81 Measures of self-rated physical activity is collected in SQRP-PC and SC using the National
82 Board of Health and Welfare’s three questions on physical activity (0 - >300 minutes/week),
83 exercise (0 - >120 minutes/week), and sedentary behavior (0 - 15 hours/day).⁵⁶ and in SQRP-
84 PC by the Godin-Shepard leisure-time physical activity questionnaire (number of times/week
85 that strenuous/moderate/light exercise.⁵⁷ Data on overall emotional distress (0 - 3), pain
86 catastrophizing (0 - 4), and psychosocial consequences (0 - 6) of living with pain are collected
87 in SQRP-PC and SQRP-SC using the Hospital Anxiety and Depression Scale (HADS),^{51 58} the
88 Pain Catastrophizing Scale (PCS),⁵⁹ and the Multidimensional Pain Inventory Scale Swedish
89 version (MPI-S, 0 - 6).⁴⁹ Level of pain acceptance (0 - 6) is collected in SQRP-PC using the

1
2
3 90 Chronic Pain and Acceptance Questionnaire (CPAQ-8).⁶⁰ Perceived life satisfaction (1-6) is
4 91 collected by the Life Satisfaction Scale (LiSat)⁶¹ in both registries. Data on perceived work
5 92 ability (0 - 10) is collected by the Work Ability Index (WAI)⁶² and functional levels (0 - 4) by
6 93 the Functional Rating Scale (FRI)⁶³ is collected in SQRP-SC only. Data on patient-reported
7 94 sleep quality (0 - 4) is collected by the Insomnia Severity Index (ISI)⁶⁴ in SQRP-SC.

95 *Secondary outcomes collected through other national registries*

96 Data will be collected from the Swedish Social Insurance Agency's registry on diagnosis,
97 reasons for sick leave, type of financial compensation, number of sick days, and sickness benefit
98 (days and hours) during the study period. In addition, data on days in work (partial or full time)
99 per month in total before new sick leave period and length of total sick leave during the study
100 period will be retrieved from the registry. Data will be retrieved from the Patient registry on
101 diagnosis and healthcare consumption (total number of days in care etc.). Retrieved data from
102 the Swedish Prescribed Drug Register will provide information on prescribed pharmaceutical
103 names, doses, sizes, and prices that have been collected from pharmacies, their costs, and
104 whether the pharmaceutical is included in the subsidized pharmaceutical program. Data on
105 disposable and earned income as well as net income will be retrieved from Statistics Sweden.
106 In addition, demographic data such as sex, age, marital status, citizenship, education level, and
107 number of children in the family will be collected. From the Swedish Population Register, data
108 on education level and education orientation (focus) in addition to limited demographic data
109 (sex, age) will be collected.

110

111 **Sample size**

112 A sample size for the pilot study of at least n=30 is considered sufficient for planned feasibility
113 analyses since it will not involve hypothesis testing and sample size calculation *per se*.^{43 65 66}
114 For the main trial, a preliminary power calculation are based on assumptions from previous
115 research reporting on proportions of patients that report a clinically meaningful difference of
116 ≥ 3 points in the physical health domain in RAND-36, 12-months after completed IPRP.²⁵ The
117 calculation was performed in R, using a calculation method for simple randomization and for
118 independent observations. The preliminary power calculation allows a dropout rate of 20% and
119 requires a total sample size of approximately n=400 to have an 80% power to detect a 15%
120 difference ($\geq 3p$) between the groups in the outcome physical health. Physical health is measured
121 by the RAND-36 health survey at the 12-month follow-up measurement point after the

1
2
3 122 completion of the IPRP. The significance level is set to 0.05 and is two-tailed. The sample size
4
5 123 calculation may be re-calculated after the pilot study is completed. In this trial, the null
6
7 124 hypothesis is that there will be no difference between the intervention group and the control
8
9 125 group (<15% with ≥ 3 points improvement) with regard to proportional improvement in the PCS
10
11 126 domain of RAND-36 health survey when assessed at the 12-month follow-up after the
12
127 completion of the IPRP.

13
14 128

15 16 129 **Allocation**

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18
19 130 A permuted block randomization design with a random block size of 4 and 6 and an 1:1
20
21 131 allocation ratio will be applied and evaluated in the pilot study in order to allocate participants
22
23 132 to either the intervention or control group.⁶⁷⁻⁶⁹ A computer-generated randomization schedule
24
25 133 will be created using a random number table to allocate participants to one of the two treatment
26
27 134 arms; intervention group (IPRP supplemented by eVIS) or control group (IPRP with daily
28
29 135 patient reports in PATRON). The schedule will be generated by an experienced researcher, who
30
31 136 is not directly involved in the trial. Sequentially numbered opaque sealed envelopes will be
32
33 137 used to ensure allocation concealment. Allocation will take place at the IPRP unit and will be
34
35 138 conducted by members of the IPRP team after initial assessment.

36
37 139

38 140 **Blinding/masking**

39
40 141 Neither the IPRP team delivering the intervention nor participants will be blinded to
41
42 142 allocation to either group due to the nature of the intervention.

43
44 143

45 46 144 **Data collection methods**

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48
49 145 Besides objectively measured data of physical activity level, patient-reported data will be
50
51 146 collected from PATRON and from six Swedish registries at the IPRP baseline and at 6, 12 and
52
53 147 24 months after completed IPRP. In addition, patient-reported data regarding cost effectiveness
54
55 148 will be retrieved 36 months after the IPRP is completed. In this trial, data will be retrieved from
56
57 149 SQRP, the Swedish social insurance agency's registry, the Patient registry, the Pharmaceutical
58
59 150 registry, the Income- and taxation registry, and the Population education registry to enable a
60
151 broad investigation into the intervention's effectiveness.

1
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3 152 To enable sufficient pilot study analyses, as well as assessment of the primary outcome Physical
4
5 153 health (PCS) in RAND-36, members of the IPRP team will be asked to provide self-reported
6
7 154 data on feasibility outcomes (outlined below) using a purpose-developed questionnaire with
8
9 155 specific questions targeting the IPRP-team perspective.⁴² If deemed required, data collection
10
11 156 will be supplemented by individual or group interviews. A detailed overview of assessments,
12
13 157 time points, and data sources can be found in Table 1.

14 158

159 **Data management**

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19 160 In order to link individual-level data from different registries to PATRON data, we will seek
20
21 161 assistance from the National Board of Health and Welfare who will provide a consecutive
22
23 162 number key. This key will be stored at the National Board of Health and Welfare for three years
24
25 163 (longer if needed). The procedure is initiated by sending PATRON data to the National Board
26
27 164 of Health and Welfare and participants' social security numbers will be sent there by SQRP.
28
29 165 The National Board of Health and Welfare creates the consecutive number key and connects
30
31 166 ordered data with own registry data (the Patient registry and the Pharmaceutical registry). The
32
33 167 National Board of Health and Welfare will then send a data order to the remaining registries
34
35 168 (the Swedish Social Insurance Agency's registry, Statistics Sweden, and the Population
36
37 169 education registry) and encoded data will be sent to the principal investigator to be stored in
38
39 170 Dalarna University's secured server.

40 171

41 172 **Intervention fidelity**

42
43 173 The following measures have been and will be taken to increase intervention fidelity: A
44
45 174 systematical intervention development with a clarified theoretical base explaining suggested
46
47 175 mechanisms has been undertaken throughout the development process.²⁹ Healthcare staff at the
48
49 176 IPRP units will be provided with comprehensive written information (easily accessed online)
50
51 177 that includes step-by-step instructions on how to initiate and deliver the intervention while
52
53 178 maintaining a high level of integrity. Before the study starts, all participating healthcare staff at
54
55 179 the IPRP units will take part in a standardized provider training session online. Also, recurring
56
57 180 web-based meeting opportunities will be provided, where IPRP-team members will be
58
59 181 encouraged to discuss experienced or perceived difficulties, and a questionnaire will be sent out
60
182 after the study period with the aim of assessing treatment fidelity (treatment integrity and

1
2
3 183 treatment differentiation) by gathering data on how treatment was delivered (manner *versus*
4 184 treatment manual, intervention's alignment to intended theoretical base). This will allow results
5 185 to be interpreted and will facilitate practical implementation.^{70 71} During the on-going study
6 186 period, researchers will be automatically notified of non-wear time (Fitbit Versa 2) and any
7 187 absence of patient reports in PATRON. In these cases, researchers will contact the relevant
8 188 participant via email or telephone to ask if they need help or support. If a participant decides to
9 189 discontinue the trial, he or she will be asked if they are willing to grant permission for the
10 190 collected data up to that point to be used in the trial.
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20 192 **Statistical methods**

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22 193 A statistical analysis plan (SAP) will expand on statistical principles, statistical analyses, the
23 194 planned handling of missing data, possible additional analyses (subgroups etc.) and interim
24 195 analyses. In both the pilot study and the R-RCT, descriptive statistical analyses will be
25 196 performed to provide transparent reporting of characteristics of both participants and
26 197 participating IPRP units. In addition, IPRP units will be prompted to register the number of
27 198 patients they ask to participate, those excluded based on eligibility criteria, and those who
28 199 decline participation. Analyses of pilot data (ratings of key feasibility outcomes) made by IPRP-
29 200 teams on a four-point Likert scale (i.e. 1= strongly disagree, 2= disagree, 3= agree, 4= strongly
30 201 agree) will be calculated as proportions in four categories for each item. Ratings ≥ 3 will be
31 202 considered as acceptable feasibility. Analyses of primary and secondary outcomes in main trial
32 203 will be performed based on PATRON data and registry data. The clinical effectiveness of eVIS
33 204 will be analyzed for each outcome using multivariate statistical and repeated measures analyses
34 205 as a preliminary plan. Both the intention-to-treat and the per-protocol sample will be analyzed,
35 206 but the intention-to-treat analysis will be considered as the primary analysis. All p-values will
36 207 be presented. If a p-value is ≤ 0.05 , the null hypothesis will be rejected and eVIS will be
37 208 considered effective according to the outlined hypothesis. To perform cost-effectiveness
38 209 calculations, data on health-related quality of life measured by EQ-5D will be retrieved from
39 210 SQRP. EQ-5D is the standard instrument used to evaluate health costs and cost effectiveness.
40 211 Calculations of quality-adjusted life-years (QALYs) will be performed by multiplying health-
41 212 state utility (measured using the EQ-5D Index score) by time spent in this specific health state.⁷²
42 213 ⁷³ In addition, calculations of the incremental cost effectiveness ratio (ICER) will be made as
43 214 the difference in the cost of two interventions divided by their affect.⁷⁴
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216 **Data monitoring**

217 Trial data will be monitored and regularly assessed for integrity and errors. All data monitoring
218 will be performed completely independently from sponsors and competing interests. An
219 independent data monitoring committee (DMC) will be appointed to critically review data
220 safety in the trial. Veronica Sjöberg (VS) will be responsible for the monitoring of all data
221 collected in the pilot study. A data management plan (DMP) will be outlined by the first author
222 (VS) and implemented by the principal investigator (LV) to ensure sound data structure (folder
223 structure, file naming, organization), and data storing.

224

225

226

DISCUSSION

227 This article describes a protocol for a R-RCT trial of a novel e-Health intervention. The trial
228 will contribute to establish evidence for the effectiveness of individualized physical activity and
229 exercise among patients living with chronic pain and participating in IPRP. The methodology
230 and feasibility of the trial will be evaluated in an early phase by a pilot study, which will
231 contribute to optimized robustness of the subsequent R-RCT-trial and enable further refinement
232 of the intervention. Despite many efforts have been taken to develop health promoting
233 interventions for this patient group, it is rare that such interventions are systematically
234 developed and includes both objective and patient reported outcomes. The eVIS-intervention is
235 developed according to MRC's framework for development and evaluation of complex
236 interventions.²⁹ It consists of both objectively measured physical activity level (steps/day), and
237 patients own reports on pain intensity, interference on daily activities and individual daily
238 activity goal, all joint in the web application named PATRON. This enables known facilitating
239 mechanisms for behavior change (e.g., as self-monitoring etc.)³² whilst including several core
240 outcome domains.^{34 75} The agile development process has enabled continuous evaluation and
241 improvement of the intervention based on data provided from patients, clinicians, and
242 researchers in different fields. Objectively measured constructs of physical activity by Fitbit
243 devices have been criticized due to lack of accuracy of measurements of time spent in moderate
244 to vigorous physical activity (MVPA) where various devices overestimate the measurement⁷⁶.
245 Preceding this study, our research group performed an evaluation of Fitbit Versa's criterion
246 validity of measuring energy expenditure, heart rate and step count among patients living with
247 chronic pain. Results confirmed previous study results in adjacent patient groups reporting that

248 Fitbit Versa systematically overestimated energy expenditure, however, measurements of step
249 count both in laboratory and in free-living setting were valid.³³

250 In this trial participants will be recruited at IPRP units nationally distributed. All units adopt to
251 core IPRP content regarding modalities, but it is well-known that both duration and intensity
252 greatly vary which may limit generalization of the results.²⁵ To achieve maximum external
253 validity, we will collect data on the specific characteristics of all participating units and include
254 this in the final analyses. Unknown engagement in other out-patient treatments under study
255 period, may be a potential source of bias, though data on in-patient engagement will be known
256 through registry data from the Patient registry. Non-adherence to daily self-report in PATRON
257 can be expected and may differ between intervention- and control group (differential missing).
258 Measures will be taken to optimize adherence in both groups such as regular auditing of
259 registrations in PATRON followed by personal emails with encouragement to follow protocol.
260 To minimize the risk of contamination between groups, and to ensure that the study will be
261 carried out in compliance with the study protocol, all participating staff at the IPRP-units will
262 participate in a study-specific course including sessions regarding Good Clinical Practice prior
263 entering the trial. Results generated from the pilot study and the subsequent effectiveness trial
264 will inform pain management field with new knowledge on eVIS's potential to increase pain
265 rehabilitation program's effectiveness by individualized physical activity levels among patients
266 living with chronic pain.

267

268 **Harms and adverse events**

269 Participating patients and healthcare staff at the participating IPRP units will be encouraged to
270 report any adverse events such as unexpected side effects or symptom deterioration,⁷⁷ which
271 will also be reported to the Swedish Ethical Board Review.

272

273 **Ethics and dissemination**

274 The trial is prospectively registered in ClinicalTrials.gov (trial registration number
275 NCT05009459) and was approved by the Swedish Ethics Review Board in May 2021 (Dnr
276 2021/02109). The trial will be conducted in compliance to the Helsinki Declaration.⁷⁹ Important
277 protocol modifications will be communicated to the Swedish Ethics Review Board as well as
278 to all participating IPRP units and participants. To protect confidentiality, all data will be coded

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3 279 by an individual code, and the encryption key will be stored separately. Data will be stored at
4
5 280 an intended project server at Dalarna University, which is secured by regular backups. No
6
7 281 unauthorized persons will have access to data, e.g., data will only be accessible by researchers
8
9 282 in the trial after approval from the principal investigator. Results of the pilot study and the main
10
11 283 trial will be submitted for publication in peer-reviewed journals and communicated in national
12
13 284 and international research networks, as well as in relevant clinical settings, including patient
14
15 285 associations.

16 286

17 18 287 **Author contribution statement**

19
20 288 LV and BÄ are responsible for the conception of the trial. LV is the principal investigator and
21
22 289 is involved in all methodological decisions. VS, ET, AM, JW, RLM, BÄ, MH, MB, and LV all
23
24 290 contributed to study design and were all involved in the development processes (the evaluation
25
26 291 of criterion validity of the wrist-worn activity tracker and the evaluations of the content validity
27
28 292 and clinical feasibility) of the intervention. RLM performed the preliminary power and sample
29
30 293 size calculations and was involved in all associated decisions. VS wrote the first draft of the
31
32 294 manuscript, was responsible for revising the manuscript's intellectual content based on all co-
33
34 295 authors conscientious input and conducted manuscript revision according to peer-reviewer's
35
36 296 comments. All authors read and approved the final version of the manuscript. For this article,
37
38 297 no ghost authors, guest authors, or professional writers have or will be used. Author eligibility
39
40 298 is and will be based upon the ICMJE Recommendations for the Conduct, Reporting, Editing,
41
42 299 and Publication of Scholarly work in Medical Journals.

43 300

44 301 **Trial status**

45
46 302 Recruitment of participants was initiated late October 2021 and the trial is planned to be
47
48 303 completed on 31 December 2024.

49 304

50 51 305 **Funding**

52
53 306 This trial is funded by the Swedish Research Council for Health, Working Life and Welfare
54
55 307 (2017-00491), the Research Council (2018-02455), the Swedish Association for Survivors of
56
57 308 Polio, Accident, and Injury (2020-03), and research funding from Dalarna University (No grant
58
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2
3 309 number). The funders had no role in study design and will have no role in any part of the
4
5 310 implementation of the study or the reporting of its results.
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12 313 **Competing interests**

13
14 314 None declared.
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19 316 **Access to data**

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21 317 This is a protocol describing a trial design. All authors will have access to the final trial
22
23 318 dataset.
24
25 319

26
27
28 320 **Supplementary files:**

- 29
30
31 321 - Completed SPIRIT 2013 Checklist
32
33 322 - Patient consent form (in Swedish)
34
35 323

36
37 324 **REFERENCES**

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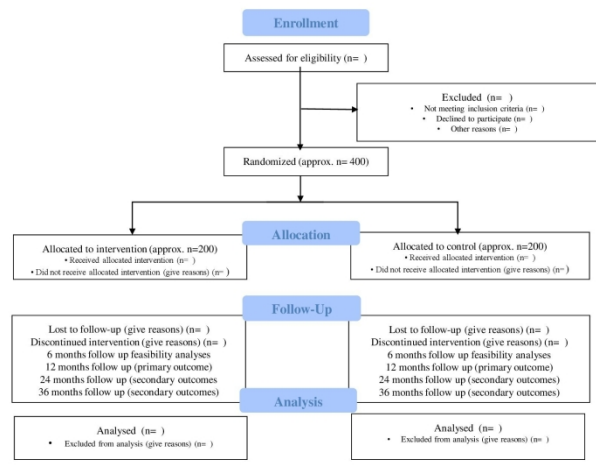


Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.

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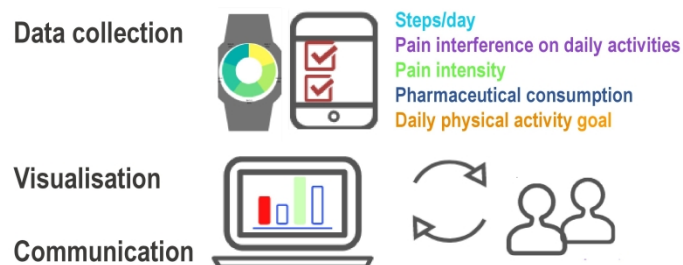


Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of physical activity level (steps/day), patient-report of pain interference on daily activities, pain intensity and pharmacological consumption, ii) the visualisation element of collected data in different graphs and compilations of data, and iii) the communication element.

338x190mm (300 x 300 DPI)



HÖGSKOLAN
DALARNA

Deltagarkod _____

Samtycke till att delta i projektet

Jag har fått muntlig och skriftlig informationen om projektet och har haft möjlighet att ställa frågor. Jag får behålla den skriftliga informationen.

- Jag samtycker till att delta i projektet **Utvärdering av eVISualisering av fysisk aktivitet och smärta (eVIS) som tillägg till multimodal smärtrehabilitering**
- Jag samtycker till att Socialstyrelsen sammanför data från de i forskningspersonsinformationerna nämnda svenska register med den data som samlas in via forskningsprojektet (PATRON, aktivitetsklockan och hälsoenkäten RAND36)
- Jag samtycker till att uppgifter om mig behandlas på det sätt som beskrivs i forskningspersonsinformationerna.

Ort och datum

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

Section/ item	Item No	Description	Page number in Main document (clean copy)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 21
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	22 (not contact info)
	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	22
	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)	19
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	16-17
Objectives	7	Specific objectives or hypotheses	5-6, 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)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11 a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11 b	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)	18-19
	11 c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	18-19
	11 d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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	9-16 Table 1 Table 2

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)	Table 1 Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 18-19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			15
Sequence generation	16 a	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	17-18
Allocation concealment mechanism	16 b	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	17
Implementation	16 c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	17 a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17 b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18 a	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	Table 1 9-16
	18 b	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	18-19
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	20
Statistical methods	20 a	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	19
	20 b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20 c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring	21 a	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	20
	21 b	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	19
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	21

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
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)	21-22
Consent or assent	26 a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26 b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	20
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	No
Dissemination policy	31 a	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	21-22
	31 b	Authorship eligibility guidelines and any intended use of professional writers	22
	31 c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary files [In Swedish]
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	NA

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Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial

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Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial.

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Keywords: Chronic pain, Individualized physical activity level, Interdisciplinary Pain Rehabilitation Programs, Pilot study, Physical health, Registry-based randomized clinical trial, Study protocol.

ABSTRACT

Introduction: Living with chronic pain often involves negative consequences. Interdisciplinary Pain Rehabilitation Programs (IPRPs) is considered superior to single-treatment measures in patients with chronic pain. Despite this, effects emerge sub-optimal and more than 20% of patients deteriorate in patient reported physical health outcomes after IPRP. A novel e-Health intervention, eVISualisation of physical activity and pain (eVIS), was systematically developed to facilitate individualization of physical activity levels. By adding elements of data collection, visualization, and communication of objectively measured physical activity and patient-reported outcomes (pain intensity, interference of pain, pharmaceutical consumption) to existing treatment modalities in IPRP, the IPRP team acquires prerequisites to adapt advice and physical activity prescriptions and to evaluate set activity goals. The overall aim is two-fold. First, the aim is to evaluate the feasibility of the subsequent registry-based randomized controlled clinical trial (R-RCT). Secondly, the aim is to prospectively evaluate the effectiveness of the eVIS-intervention as a supplement to IPRP on our defined primary (physical health) and secondary outcomes.

Methods and analysis: In the R-RCT, recruitment of 400 patients with chronic pain will be performed at 15 IPRP units . A random allocation to either IPRP + eVIS or to control group that will receive IPRP only will be performed. . Data from the initial 30 participants completing the study period (6 months) will be included in a pilot study where key feasibility outcomes (recruitment, randomization, , implementation, , treatment integrity, data collection procedure, preliminary outcome measures) will be evaluated. Outcome variables will be extracted from PATRON and from six national registries. Multivariate statistics and repeated measures analyses will be performed. Quality Adjusted Life Years (QALYs) and Incremental Cost Effectiveness Ratio (ICER) will be calculated for cost effectiveness evaluation.

Ethics/dissemination: The Swedish Ethics Review Board granted approval (Dnr 2021/02109). Results will be disseminated through peer-review journals.

Trial registration number: NCT05009459.

Protocol version: 1

Strengths and limitations of the study

- A proceeding pilot study will enable improvements of design and feasibility of a subsequent R-RCT
- The eVIS-intervention has been developed, evaluated, and improved, based on data provided from patients, clinicians, and researchers in different fields.
- The intervention targets physical activity modalities in IPRP and is designed to enable a more individualized IPRP treatment.
- The intervention is based on objectively measured physical activity levels, patient-reported clinical outcomes, and mechanisms that facilitate behavior change, in accordance with current guidelines that are provided by authorities in the chronic pain management field.
- The nature of the intervention precludes blinding of patients and the IPRP team.

INTRODUCTION

Chronic musculoskeletal pain (>3 months), including neck/shoulder/back pain or widespread pain, is a major global health and socioeconomic burden.^{1 2} Living with chronic pain is often associated with reduced levels of wellbeing and the health-related quality of life of this group has been reported to be among the lowest of any medical condition.³ To date, physical activity (i.e. any bodily movement that requires energy expenditure) and exercise (i.e. structured and planned physical activity aimed to increase fitness)⁴ have been shown to prevent and/or treat several of our noncommunicable diseases including chronic pain,⁵ due to their beneficial effects on general health, pain intensity, physical and psychological functioning, and health-related quality of life.⁵⁻⁸ Despite the growing evidence of health benefits related to physical activity, participation and adherence to physical activity recommendations, such as WHO's physical activity guidelines, are often low in patients living with chronic pain.⁹⁻¹² This may partly be explained by the indicated association between high pain scores and low patient-reported activity levels among patients with chronic pain and/or the documented reports of the negative impact of depression on physical activity levels.¹³ In addition, it is well known that behavior change is difficult, and that each individual's own participation is essential.¹⁴ It has been shown that behavior change towards a beneficial physical activity level may be facilitated by individuals self-monitoring their physical activity.¹⁵ The use of objective measures increases the likelihood of the effectiveness of interventions designed to promote physical activity.¹⁵ By adding goal setting, feedback, and a focus on achieved goals, effectiveness can be further improved.¹⁵⁻¹⁸

Interdisciplinary pain rehabilitation programs (described as a subset of Interdisciplinary Treatment), is defined as "multimodal treatment provided by a multidisciplinary team (at least 3 professions), collaborating in assessment and treatment using a shared biopsychosocial model and goals"¹⁹. The IPRP approach adopts the principles of behavioral therapy and incorporates besides physical activity and exercise, also psychological measures, pharmaceutical treatment and patient education.²⁰ Physical activity and exercise are central measures in IPRPs as it targets the physical deconditioning by improving levels of physical activity, and also reduces pain severity and improved physical function and quality of life, without causing any severe adverse events.⁵ Interdisciplinary pain rehabilitation programs are considered to be superior to single-treatment measures (e.g., physical treatments, education interventions, surgery, etc.) for patients with chronic pain supporting positive effects on pain intensity and activity disability.^{20 21}

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3 However, IPRP effectiveness is only slightly better and in the majority of cases only a small
4 effect is seen.²¹⁻²⁵ In addition, up to 25% of patients report deterioration in physical health after
5 completing IPRP and after 12 months follow up, regardless of duration of IPRP.^{20 25 26}
6 Sustainable treatment affects seem to vary according to patient clinical features at baseline,
7 such as poor employment status, high pain levels, and low functioning, all of which predict low
8 physical health at follow-up.^{23 27} Many efforts have been made to find effective interventions
9 that improve the health of chronic pain patients. To facilitate individualized physical activity
10 levels within the Swedish IPRP setting, an eVISualisation (eVIS) of physical activity and pain
11 intervention has been systematically developed according to the Medical Research Council's
12 recently updated framework for development and evaluation of complex interventions.^{28 29} In
13 accordance with the framework, the eVIS-interventions was designed and planned in close
14 collaboration with stakeholders. eVIS is designed to target facilitating mechanisms for behavior
15 change, such as outcome expectations, self-monitoring, self-evaluation, and self-efficacy,³⁰⁻³²
16 which are theoretically framed by the Social Cognitive Theory.³² In eVIS, objectively measured
17 physical activity tracking using a wrist-worn activity tracker³³ (Fitbit Versa 2) is combined with
18 a daily activity goal (steps/day) and daily patient reports of known important clinical outcome
19 assessments: pain intensity and its interference on daily activities³⁴⁻³⁸ and pharmaceutical
20 consumption. Data is collected and visualized in a purpose-developed web application, Pain
21 And TRaining ON-line (PATRON), which can be used by the patient and the IPRP team to
22 follow and adjust individual physical activity levels. Despite interventions of this kind having
23 highly promising potential to relive pain and improve disability in this patient
24 group,³⁹ interventions are rarely systematically developed and validated specifically for their
25 target patient group, leaving crucial information of feasibility and true effectiveness unknown.
26 Therefore, the overall aim of this study is two-fold. First, the aim is to evaluate the feasibility
27 (recruitment capability, eligibility screening procedure, randomization, implementation process,
28 response rate, compliance rate, changes in primary- and secondary outcomes from start to end
29 of study period, differences between treatment groups in primary outcome) of a subsequent
30 registry-based randomized controlled clinical trial (R-RCT) within the IPRP setting in order to
31 gain knowledge of population variation, increase robustness and to avoid underpower.⁴⁰⁻⁴³
32 Secondly, the aim is to prospectively evaluate the effectiveness of the eVIS-intervention as a
33 supplement to IPRP on our defined primary (physical health) and secondary outcomes, 12
34 months after completed IPRP compared to IPRP as usually provided. In addition, the aim is to
35 evaluate the cost effectiveness of eVIS supplementing IPRP at 12 and 36 months follow up
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3 after completed IPRP, and to prospectively evaluate differences in opioid consumption at start
4 of IPRP compared to six months after completed IPRP.
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7 ⁴²⁴⁰⁻⁴³In this trial, the UK National Institute for Health Research's (NIHR) definitions of the
8 terms *pilot study* (i.e., "a smaller version of the main study") and *feasibility study* (i.e.,
9 "evaluation of pieces of research done before the main study") are applied.⁴⁴ The aim of this
10 paper is to transparently clarify and report on study designs, aims, outcome assessments, and
11 procedures for a planned R-RCT (including an randomized pilot study) which prospectively
12 will evaluate clinical effectiveness and cost effectiveness of eVIS as a supplement to IPRPs for
13 patients living with chronic pain compared to standard IPRPs.
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25 **METHODS AND ANALYSIS**

26 **Trial design and setting**

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32 This two-armed pragmatic multi-site R-RCT will be conducted in specialized and primary
33 IPRPs in Sweden, and include approximately 400 (n=200, n=200) patients (number will be
34 definitively determined after the pilot study is finalized) with chronic musculoskeletal non-
35 malignant pain. As indicated, an randomized controlled pilot study (n=15, n=15) will be
36 incorporated as the initial phase of the main trial in order to evaluate the intervention's
37 methodology and design.^{29 41 45} This trial will comply with the Consolidated Standards of
38 Reporting Trials (CONSORT)⁴⁰ and with the Standard Protocol Items: Recommendations for
39 Interventional Trials (SPIRIT)⁴⁶. A completed SPIRIT 2013 Checklist can be found in the
40 additional files. See Figure 1 for study design and enrollment details.
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48 *Insert Figure 1 here.*
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53 **Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.**

54 **Eligibility criteria**

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57 In this trial, the patient-related, care process and caregiver-related inclusion criteria for
58 receiving Swedish IPRP will be applied, as patients entering the trial must be accepted for IPRP.
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3 Principal IPRP inclusion criteria are patients in working age with persistent or intermittent pain
4 lasting ≥ 3 months with pain affecting daily activities to a large extent, completed systematic
5 assessment (including screening for psychosocial risk factors and differential diagnosis) and
6 non-pharmacological optimization. Inclusion criteria for Swedish IPRPs is outlined in detail
7 elsewhere.⁴⁷ Due to the nature of the intervention, patients must be able to hear, see, and
8 comprehend spoken and written Swedish, and have daily access to a computer, smartphone, or
9 tablet. Patients who need to use a walking aid indoors will be excluded.
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18 **Recruitment**

19 Interdisciplinary Pain Rehabilitation Units

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23 Approximately 15 IPRP units in primary and specialized care in Sweden will be included in the
24 trial. IPRP units reporting to the Swedish National Quality Registry for Pain Rehabilitation
25 (SQRP) have been approached by email with study information (aim, rationale, methods etc.)
26 and an invitation to participate in one of several online digital information meetings that will
27 further present the study (initiated August 2021). Study representatives will approach healthcare
28 staff at potential IPRP units by telephone or email to formally offer participation. Operation
29 managers at each unit will be asked to provide written consent by e-mail.
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36 Participants

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38 In order to give potential participants additional time to consider taking part in the trial before
39 they visit the IPRP unit, healthcare staff at the units will be encouraged to provide a general
40 information sheet about the trial in the summon to the IPRP assessment. Members of IPRP
41 teams (primarily physiotherapists but also occupational therapists, physicians, nurses etc.) will
42 identify potential participants selected for IPRP based on outlined criteria and provide them
43 with verbal and written details of the study (information sheets and the project's web address).
44 All participants will provide written informed consent (see supplementary file) prior to joining
45 the study, which will be managed by the IPRP team. Detailed verbal and written information
46 about the voluntary nature of participation and the indisputable right to discontinue participation
47 in the trial at any time will be provided. Detailed checklists and forms will support these
48 procedures, and these will be easily accessible on the project web site.
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Intervention

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3 Participation in the intervention group involves regular IPRP supplemented with eVIS for a
4 coherent time span of six months, IPRP time included. As the duration and intensity of IPRPs
5 greatly vary from a couple of weeks up to four months²⁵, a six month study period ensures time
6 of independent use of eVIS after completed IPRP. Participants are not prohibited to take part
7 of other health care during study period. Interdisciplinary pain rehabilitation programs vary in
8 interventions, duration, composition, intensity^{24 25} and can be performed either individually or
9 in group format. In this trial, participation in a IPRP will be supplemented by eVIS, a health
10 promoting intervention containing three elements designed to facilitate individualized physical
11 activity level (Figure 2).
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19 The data collection element

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21 Outcome assessments of physical activity level (steps/day) will be objectively collected by a
22 wrist-worn activity tracker, Fitbit Versa 2. This device has been population-specifically
23 validated and the measurement of step rate is indicated as valid for measurement in this
24 population.³³ Data on patient's physical activity level quantified as steps/day, will be
25 automatically synchronized to the web application PATRON where pain intensity (0-10),⁴⁸
26 interference of pain on daily activities (0-10),⁴⁹ pharmacological consumption (name, dose,
27 number, and form), and (optional) free-text comments will be reported by the patient daily. The
28 web application can be accessed via computer, smartphone, or tablet. A daily activity goal
29 (steps/day) is formulated by the patient in close collaboration with the IPRP team and revised
30 accordingly. The daily activity goal in eVIS is individually set based on patient's individual
31 prerequisites and re-evaluated regularly as part of the communication element (described
32 below). In the process of setting a daily activity goal, the IPRP team are encouraged to consider
33 international guidelines of step rate as a quantification of beneficial physical activity levels⁵⁰
34 as well as patient's personal barriers and resources to perform physical activity. The data
35 collection element is designed to target facilitating mechanisms for behavior change, such as
36 outcome expectations, self-monitoring, self-evaluation, and self-efficacy.³⁰⁻³²
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50 The visualisation element

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52 Objectively measured physical activity levels, patient-report on pain intensity and interference
53 of pain on daily activity are graphically visualized separately or alongside each other, in relation
54 to the daily activity goal. Three different graphs (1/7/28 days) are available. The visualisation
55 element provides additional prerequisites for increased knowledge acquisition, self-monitoring,
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3 and self-evaluation as data is visualized over time and in relation to each other and to the
4 individual daily activity goal in order to improve patient self-efficacy.
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7 The communication element
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10 The graphs in the visualisation element together with compiled data on pharmacological
11 consumption will provide a novel decision basis for the patient and the IPRP team. This
12 addition to existing treatment modalities traditionally provided in Swedish IPRP (e.g. physical
13 activity, cardio training, weight training, mobility training, stability training, motivating
14 conversation education, advice etc.). enables prerequisites for the IPRP team to integrate
15 behavioral changing techniques (e.g. reinforcement, knowledge acquisition, self-monitoring,
16 self-efficacy) into existing treatment options. By such integration, knowledge of patient's
17 personal barriers and resources in factors important in pain rehabilitation may be visualized and
18 if necessary, assessed. The IPRP team as well as the patients are encouraged to explore the
19 visualisation element of eVIS at each visit at the IPRP unit. This in order to utilize data into the
20 treatment by adjusting advise or prescriptions.
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36 **Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of**
37 **physical activity level (steps/day), patient-reports of interference of pain on daily activities, pain intensity**
38 **and pharmacological consumption, ii) the visualisation element of collected data in different graphs and**
39 **compilations of data, and iii) the communication element.**
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45 **Control**

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47 Participation in the control group involves taking part in regular IPRP plus making daily ratings
48 of pain intensity, interference of pain on daily activities, and pharmaceutical consumption
49 (corresponding as in intervention group) in PATRON for six months, including the time that
50 the IPRP is being carried out. The control group will not use the wrist-worn activity tracker as
51 this may affect their physical activity behavior⁵¹. Nor will they have access to PATRON's
52 visualizing or communication features.
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Patient and Public Involvement Statement

In an early developing phase, stakeholders (patients living with chronic pain, representatives from patient organizations and clinicians experienced in pain rehabilitation) were invited to contribute to the intervention development. In this phase, the web application PATRON and eVIS was presented and carefully discussed with stakeholders as well as with web application developers and researchers. Several needs for improvement were identified, such as a need of an addition of pharmaceutical report function, designated web pages and graphical changes in planned interfaces.

Outcome assessments

According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), physical health, emotional health, and pain intensity are three of six identified core outcome domains that should be considered when designing research studies aiming to evaluate effectiveness of chronic pain treatments.³⁵⁻³⁷ It is specifically recommended that a health survey such as RAND-36 should be incorporated into treatment as a clinical outcome assessment of physical health in clinical trials.^{36,37} Outcome assessments for evaluating feasibility will be performed on data from the IPRP baseline and after the study period is completed (six months) for the first 30 participants (n=15 +, n=15). In the main trial, assessments of effectiveness will be performed on data from the IPRP baseline and from the 12-month follow-up. The cost effectiveness assessments will be based on data from the IPRP baseline, from the 12-month IPRP follow-up and again 24 and 36 months after the IPRP is completed. A detailed overview of outcome assessments can be found in Table 1.

Table 1. Overview of study period, measurement time points, outcome assessments (*bold and italics*), instruments, and data sources (*italics*).

	Enrolment	Allocation	Study period				
			Baseline	t1	t2	t3	t4
	-t ₁	0					
Enrolment	X						
Written and verbal study information	X						
Eligibility screen	X						
Informed consent	X						
Allocation/randomization		X					
Interventions							
Intervention, eVIS (6 months)				X			
Control (6 months)				X			
Outcome assessments							
<i>Personal characteristics</i>							
Sex, age, country of origin, family composition, beliefs of restored health (<i>SQRP, SS</i>)			X				
Disposable-, earned- and net income (<i>SS</i>)			X		X	X	X
Education level and education orientation (<i>SPR, ITR</i>)			X		X	X	X
Diagnosis (<i>NPR</i>)			X		X	X	X
Volume and reason for inpatient care (<i>NPR</i>)			X		X	X	X
<i>Pain characteristics</i>							
Pain intensity (last 7 days), NRS (<i>SQRP-PC and SC</i>)			X		X		
Pain intensity (today), NRS (<i>PATRON</i>)			X	X			
Pain type, location, duration (<i>SQRP-PC and SC</i>)			X				
Pain interference (<i>PATRON</i>)			X				
<i>Multidimensional measures</i>							
Physical health, RAND-36 PCS health survey (<i>PATRON</i>)			X	X	X	X	X
Physical health, RAND-36 PCS health survey (<i>SQRP-SC only</i>)			X		X		
Emotional health, RAND-36 MCS health survey (<i>PATRON</i>)			X	X	X	X	X
Emotional health, RAND-36 MCS health survey (<i>SQRP- SC only</i>)			X		X		

Overall emotional distress, HAD(S) (<i>SQRP-PC and SC</i>)	X	X		
Pain catastrophizing, PCS (<i>SQRP-PC and SC</i>)	X		X	
Psychosocial consequences, MPI-S (<i>SQRP-PC and SC</i>)	X		X	
Pain acceptance, CPAQ-8 (<i>SQRP-PC only</i>)	X		X	
Perceived life Satisfaction, LiSat (<i>SQRP-PC and SC</i>)	X		X	
Functional level, FRI (<i>SQRP-SC only</i>)	X		X	
Physical activity				
Objective measures of steps per day (<i>Fitbit Versa 2</i>)	X	X		
Patient-reported measures (<i>SQRP- PC and SC</i>)	X		X	
Work				
Return to work (partially or full time) every month (<i>SSIA</i>)			X	X X
Number of days with sick benefit during study period (<i>SSIA</i>)			X	X X
Number of days in work before new sick leave during study period (<i>SSIA</i>)			X	X X
Length of total sick leave during study period (<i>SSIA</i>)			X	X X
Perceived work ability, WAI (<i>SQRP-PC and SC</i>)	X		X	
Sleep quality , ISI (<i>SQRP-SC only</i>)	X		X	
Pharmaceutical consumption				
Name, dose, size, prize of prescribed pharmaceuticals (<i>SPDR, PATRON [not size, prize]</i>)			X	X X
Prescribed pharmaceuticals collected from pharmacies, (<i>SPDR</i>)			X	X X
Cost of prescribed pharmaceuticals included in benefit program (<i>SPDR</i>)			X	X X
Health care consumption (NPR)				
Feasibility outcomes, Questionnaire			X	
Treatment integrity, Questionnaire			X	X

Abbreviations: -t¹ = pre recruitment period, t¹ = completed study period (6 months), t² = follow-up 12 months after completed Interdisciplinary Pain Rehabilitation Program (IPRP), t³ = 24 months after completed IPRP, t⁴ = 36 months after completed IPRP, eVIS = eVISualisation of physical activity and pain intervention, SQRP = the Swedish national quality registry for pain rehabilitation, SQRP-PC = , the Swedish national quality registry for pain rehabilitation primary care, SQRP-SC = the Swedish national quality registry for pain rehabilitation specialized care, NRS = Numeric Rating Scale, PATRON = Pain and training online (web application), RAND-36 PCS = physical health domain , RAND-36 MCS = mental health domain, HAD(S) = Hospital Anxiety and Depression Scale, PCA = Pain Catastrophizing Scale, MPI-S = Multidimensional Pain Inventory -Swedish Version, CPAQ-8 = The Chronic Pain and Acceptance Questionnaire, LiSat = Life Satisfaction Scale, WAI = Work Ability Index, FRI = Functional rating scale, ISI = Insomnia Severity Index, SSIA = the Swedish Social Insurance Agency's registry, NPR = the National Patient Register, SPDR = the Swedish Prescribed Drug Register, SS = Statistics Sweden, SPR = the Swedish Population Register.

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1 Feasibility outcomes, pilot study

2 The trial will be initiated as a full-scale registry-based randomized controlled pilot study. In
 3 this initial step, feasibility will be evaluated from data provided from the first 30 participants
 4 completing the study period and in the following key areas: the unit's recruitment capabilities,
 5 the randomization process, implementation process, participant response to intervention which
 6 is outlined in Table 2. In addition, the data collection procedure and the preliminary outcome
 7 measures (standardized effect size, sample size estimation with Cohen's *d*, characteristics
 8 [mean, SD]) in main trial will be evaluated.^{41 45} In addition to feasibility outcomes,
 9 characteristics of the IPRP units will be collected

11 Table 2. Overview of key feasibility outcomes in pilot study.

12 Key feasibility outcomes	
13 Recruitment capability	
	14 Volume of total eligible patients
	15 Number recruited/week
16 Eligibility screening procedure	
	17 Proportion accepted/declined
	18 Personal characteristics of accepted and declined participants
	19 Pain characteristics of accepted and declined participants
	20 Procedure of collecting consent
21 Randomization process	
	22 Delivery envelopes
	23 Storage of envelopes
	24 Procedure of opening envelopes
	25 Patients' reaction to allocation
26 Implementation process	
	27 Response rate RAND-36 PCS
	28 Compliance rate (use of Fitbit Versa 2, intervention group only)
	29 Compliance rate (patient reported outcomes in PATRON)
30 Treatment integrity	
	31 Reported adverse events
32 Data collection procedure	
	33 Access to PATRON data
	34 Access to registry data
	35 Access to RAND-36 data
36 Preliminary outcome measures	
	37 Characteristics, mean (SD)
	38 Missing data
	39 Changes from baseline to finalized study period

40 Abbreviations: RAND-36 PCS = physical health domain in RAND-36, PATRON = Pain and training online (web application).

41 Primary outcome, main trial

42 The R-RCT will prospectively evaluate the *clinical effectiveness* of eVIS supplementing IPRPs
 43 regarding improvements in our primary outcome assessment *Physical health* collected by the

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3 28 physical health domain in RAND-36 health survey^{3 52} at the 12-month IPRP follow-up after
4 29 completing the IPRP. The RAND-36 is, for this population, a valid health survey measuring
5 30 health-related quality of life in two dimensions, physical health (PCS) and mental health (MCS),
6 31 mediated by eight subscales.⁵²
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10 32 Secondary outcomes, main trial

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13 33 In the main trial, secondary outcomes will be extracted from Fitbit Versa 2, PATRON and
14 34 collapsed with data from six national registries (all listed below) at 12, 24, 36 months after the
15 35 IPRP is completed.
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18 36 *Objectively measured secondary outcomes collected using Fitbit Versa 2*

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21 37 Objectively measured physical activity levels will be collected daily during the study period
22 38 using a wrist-worn activity tracker (Fitbit Versa 2). The Fitbit device measures and estimates a
23 39 range of physical activity outcomes such as number of steps, heart rate, energy expenditure,
24 40 floors climbed, physical activity level, and sleep.^{33 53} In this trial, participants' step count per
25 41 day will automatically be synchronized to PATRON during the study period (six months). The
26 42 use of steps per day is considered to be a valid quantification of physical activity levels and this
27 43 is acknowledged by the Swedish Health Authority.⁵⁴
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34 44 *Patient-reported secondary outcomes collected through PATRON*

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36 45 Data on physical and mental health collected by RAND-36 health survey will be collected
37 46 through PATRON at 6, 12 and 24 months after IPRP. Pain intensity (“rate your average pain
38 47 during the last 24 hours”) will be measured daily using the Numeric Rating Scale (NRS, 0 =
39 48 no pain at all to 10 = pain as bad as it could be), a 11-point Likert scale⁴⁸ incorporated in the
40 49 web application PATRON. Pain interference on daily activities is a recommended outcome
41 50 domain.³⁵ In PATRON, assessments of interference of pain on daily activities will be measured
42 51 by the question “rate how much your daily activities are affected by pain” using an 11-point
43 52 Likert Scale (0 = not at all to 10 = to a very large extent). This question in PATRON has been
44 53 modified based on the Multidimensional Pain Inventory Swedish version and its items on pain
45 54 interference,⁴⁹ and validated in our previous study (in manuscript). Data on daily
46 55 pharmaceutical consumption will be collected in PATRON (name, dose, number, and form).
47 56 Voluntary free text comments will supplement patient reporting by providing additional
48 57 information regarding perceived mental and physical health (only in the intervention group).
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3 58 *Secondary outcomes collected through the Swedish national quality registry for pain*
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5 59 *rehabilitation*
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7 60 In Sweden, 90% of IPRP units routinely collect patient-reported data from standardized
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9 61 questionnaires and report to SQRP, a database initiated in 1998 that contains data from chronic
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11 62 non-malignant pain patients participating in IPRPs.^{24 55} The registry consists of two parts; the
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13 63 primary care SQRP (SQRP-PC) and the specialized SQRP (SQRP-SC). The primary care SQRP
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15 64 is supplied with data from affiliated primary care IPRP units (n=42, reported data from 505
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17 65 patients in 2020). The specialized care SQRP, receives data from affiliated specialized care
18
19 66 IPRP units (n=45, reporting data from 7427 patients in 2020). Data in both registries are
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21 67 collected at baseline, when the IPRP is completed, and at 12-month follow-ups, the content of
22
23 68 data collected in the registries differs somewhat. In this trial, registry data from both registries
24
25 69 will be collected used to describe demographics such as age, sex, height, weight, education
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27 70 level, and work.^{24 55} Participants partaking in an IPRP in SC will also routinely complete the
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29 71 RAND-36 health survey at baseline and at their 12-month follow-up after they have completed
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31 72 their program. Data on pain intensity (“last 7 days”) (NRS 0-10)⁴⁸ will be retrieved from SQRP-
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33 73 PC and SQRP-SC alongside other pain characteristics including pain location (36 anatomical
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35 74 predefined areas, 18 on the left side, 18 on the right side), pain duration, and pain type
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37 75 (intermittent or continuous). Data on self-rated physical and mental health is collected by the
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39 76 RAND-36 health survey^{3 52} in SQRP-SC and the EuroQol-5 dimensions (EQ-5D) collected
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41 77 routinely in SQRP-PC and SQRP-SC will be used. The EQ-5D is a standard instrument used in
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43 78 health economic evaluations and contains five items each with three ordered response
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45 79 categories, and a 0-100 index.⁵⁶

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47 80 Measures of self-rated physical activity is collected in SQRP-PC and SC using the National
48
49 81 Board of Health and Welfare’s three questions on physical activity (0 - >300 minutes/week),
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51 82 exercise (0 - >120 minutes/week), and sedentary behavior (0 – 15 hours/day).⁵⁷ and in SQRP-
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53 83 PC by the Godin-Shepard leisure-time physical activity questionnaire (number of times/week
54
55 84 that strenuous/moderate/light exercise.⁵⁸ Data on overall emotional distress (0 – 3), pain
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57 85 catastrophizing (0 – 4), and psychosocial consequences (0 – 6) of living with pain are collected
58
59 86 in SQRP-PC and SQRP-SC using the Hospital Anxiety and Depression Scale (HADS),^{52 59} the
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61 87 Pain Catastrophizing Scale (PCS),⁶⁰ and the Multidimensional Pain Inventory Scale Swedish
62
63 88 version (MPI-S, 0 – 6).⁴⁹ Level of pain acceptance (0 – 6) is collected in SQRP-PC using the
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65 89 Chronic Pain and Acceptance Questionnaire (CPAQ-8).⁶¹ Perceived life satisfaction (1-6) is
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67 90 collected by the Life Satisfaction Scale (LiSat)⁶² in both registries. Data on perceived work

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3 91 ability (0 – 10) is collected by the Work Ability Index (WAI)⁶³ and functional levels (0 – 4) by
4 92 the Functional Rating Scale (FRI)⁶⁴ is collected in SQRP-SC only. Data on patient-reported
5 93 sleep quality (0 – 4) is collected by the Insomnia Severity Index (ISI)⁶⁵ in SQRP-SC.
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9 94 *Secondary outcomes collected through other national registries*

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11 95 Data will be collected from the Swedish Social Insurance Agency's registry on diagnosis,
12 96 reasons for sick leave, type of financial compensation, number of sick days, and sickness benefit
13 97 (days and hours) during the study period. In addition, data on days in work (partial or full time)
14 98 per month in total before new sick leave period and length of total sick leave during the study
15 99 period will be retrieved from the registry. Data will be retrieved from the National Patient
16 100 Register on diagnosis and healthcare consumption (total number of days in care etc.). Retrieved
17 101 data from the Swedish Prescribed Drug Register will provide information on prescribed
18 102 pharmaceutical names, doses, sizes, and prices that have been collected from pharmacies, their
19 103 costs, and whether the pharmaceutical is included in the subsidized pharmaceutical program.
20 104 Data on disposable and earned income as well as net income will be retrieved from Statistics
21 105 Sweden. In addition, demographic data such as sex, age, marital status, citizenship, education
22 106 level, and number of children in the family will be collected. From the Population registry, data
23 107 on education level and education orientation (focus) in addition to limited demographic data
24 108 (sex, age) will be collected.
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38 110 **Sample size**

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41 111 A sample size for the pilot study of at least $n=30$ is considered sufficient for planned feasibility
42 112 analyses since it will not involve hypothesis testing and sample size calculation *per se*.^{43 66 67}
43 113 For the main trial, a preliminary power calculation are based on assumptions from previous
44 114 research reporting on proportions of patients that report a clinically meaningful difference of
45 115 ≥ 3 points in the physical health domain in RAND-36, 12-months after completed IPRP.²⁵ The
46 116 calculation was performed in R, using a calculation method for simple randomization and for
47 117 independent observations. The preliminary power calculation allows a dropout rate of 20% and
48 118 requires a total sample size of approximately $n=400$ to have an 80% power to detect a 15%
49 119 difference ($\geq 3p$) between the groups in the outcome physical health. Physical health is measured
50 120 by the RAND-36 health survey at the 12-month follow-up measurement point after the
51 121 completion of the IPRP. The significance level is set to 0.05 and is two-tailed. The sample size
52 122 calculation may be re-calculated after the pilot study is completed. In this trial, the null
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3 123 hypothesis is that there will be no difference between the intervention group and the control
4 124 group (<15% with ≥ 3 points improvement) with regard to proportional improvement in the PCS
5 125 domain of RAND-36 health survey when assessed at the 12-month follow-up after the
6 126 completion of the IPRP.
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11 128 **Allocation**

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15 129 A permuted block randomization design with a random block size of 4 and 6 and an 1:1
16 130 allocation ratio will be applied and evaluated in the pilot study in order to allocate participants
17 131 to either the intervention or control group.⁶⁸⁻⁷⁰ A computer-generated randomization schedule
18 132 will be created using a random number table to allocate participants to one of the two treatment
19 133 arms; intervention group (IPRP supplemented by eVIS) or control group (IPRP with daily
20 134 patient reports in PATRON). The schedule will be generated by an experienced researcher, who
21 135 is not directly involved in the trial. Sequentially numbered opaque sealed envelopes will be
22 136 used to ensure allocation concealment. Allocation will take place at the IPRP unit and will be
23 137 conducted by members of the IPRP team after initial assessment.
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32 139 **Blinding/masking**

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34 140 Neither the IPRP team delivering the intervention nor participants will be blinded to
35 141 allocation to either group due to the nature of the intervention.
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41 143 **Data collection methods**

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45 144 Besides objectively measured data of physical activity level, patient-reported data will be
46 145 collected from PATRON and from six Swedish registries at the IPRP baseline and at 6, 12 and
47 146 24 months after completed IPRP. In addition, patient-reported data regarding cost effectiveness
48 147 will be retrieved 36 months after the IPRP is completed. In this trial, data will be retrieved from
49 148 SQRP, the Swedish social insurance agency's registry, the Patient registry, the Swedish
50 149 Prescribed Drug Register, the Income- and taxation registry, and the Swedish Population
51 150 Register to enable a broad investigation into the intervention's effectiveness.
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58 151 To enable sufficient pilot study analyses, as well as assessment of the primary outcome Physical
59 152 health (PCS) in RAND-36, members of the IPRP team will be asked to provide self-reported

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3 153 data on feasibility outcomes (outlined below) using a purpose-developed questionnaire with
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5 154 specific questions targeting the IPRP team perspective.⁴¹ If deemed required, data collection
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7 155 will be supplemented by individual or group interviews. A detailed overview of assessments,
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9 156 time points, and data sources can be found in Table 1.

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12 13 158 **Data management**

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15 159 In order to link individual-level data from different registries to PATRON data, we will seek
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17 160 assistance from the National Board of Health and Welfare who will provide a consecutive
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19 161 number key. This key will be stored at the National Board of Health and Welfare for three years
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21 162 (longer if needed). The procedure is initiated by sending PATRON data to the National Board
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23 163 of Health and Welfare and participants' social security numbers will be sent there by SQRP.
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25 164 The National Board of Health and Welfare creates the consecutive number key and connects
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27 165 ordered data with own registry data (the National Patient Register and the Swedish Prescribed
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29 166 Drug Register). The National Board of Health and Welfare will then send a data order to the
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31 167 remaining registries (the Swedish Social Insurance Agency's registry, Statistics Sweden, and
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33 168 the Swedish Population Register) and encoded data will be sent to the principal investigator to
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35 169 be stored in Dalarna University's secured server.

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38 171 **Intervention fidelity**

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40 172 The following measures have been and will be taken to increase intervention fidelity: A
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42 173 systematical intervention development with a clarified theoretical base explaining suggested
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44 174 mechanisms has been undertaken throughout the development process.²⁹ Healthcare staff at the
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46 175 IPRP units will be provided with comprehensive written information (easily accessed online)
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48 176 that includes step-by-step instructions on how to initiate and deliver the intervention while
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50 177 maintaining a high level of integrity. Before the study starts, all participating healthcare staff at
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52 178 the IPRP units will take part in a standardized provider training session online. Also, recurring
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54 179 web-based meeting opportunities will be provided, where IPRP team members will be
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56 180 encouraged to discuss experienced or perceived difficulties, and a questionnaire will be sent out
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58 181 after the study period with the aim of assessing treatment fidelity (treatment integrity and
59
60 182 treatment differentiation) by gathering data on how treatment was delivered (manner *versus*
183 treatment manual, intervention's alignment to intended theoretical base). This will allow results

184 to be interpreted and will facilitate practical implementation.^{71 72} During the on-going study
185 period, researchers will be automatically notified of non-wear time (Fitbit Versa 2) and any
186 absence of patient reports in PATRON. In these cases, researchers will contact the relevant
187 participant via email or telephone to ask if they need help or support. If a participant decides to
188 discontinue the trial, he or she will be asked if they are willing to grant permission for the
189 collected data up to that point to be used in the trial.

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191 **Statistical methods**

192 A statistical analysis plan (SAP) will expand on statistical principles, statistical analyses, the
193 planned handling of missing data, possible additional analyses (subgroups etc.) and interim
194 analyses. In both the pilot study and the R-RCT, descriptive statistical analyses will be
195 performed to provide transparent reporting of characteristics of both participants and
196 participating IPRP units. In addition, IPRP units will be prompted to register the number of
197 patients they ask to participate, those excluded based on eligibility criteria, and those who
198 decline participation. Analyses of pilot data (ratings of key feasibility outcomes) made by IPRP
199 teams on a four-point Likert scale (i.e. 1= strongly disagree, 2= disagree, 3= agree, 4= strongly
200 agree) will be calculated as proportions in four categories for each item. Ratings ≥ 3 will be
201 considered as acceptable feasibility. Analyses of primary and secondary outcomes in main trial
202 will be performed based on PATRON data and registry data. The clinical effectiveness of eVIS
203 will be analyzed for each outcome using multivariate statistical and repeated measures analyses
204 as a preliminary plan. Both the intention-to-treat and the per-protocol sample will be analyzed,
205 but the intention-to-treat analysis will be considered as the primary analysis. All p-values will
206 be presented. If a p-value is ≤ 0.05 , the null hypothesis will be rejected and eVIS will be
207 considered effective according to the outlined hypothesis. To perform cost-effectiveness
208 calculations, data on health-related quality of life measured by EQ-5D will be retrieved from
209 SQRP. EQ-5D is the standard instrument used to evaluate health costs and cost effectiveness.
210 Calculations of quality-adjusted life-years (QALYs) will be performed by multiplying health-
211 state utility (measured using the EQ-5D Index score) by time spent in this specific health state.⁷³
212 ⁷⁴ In addition, calculations of the incremental cost effectiveness ratio (ICER) will be made as
213 the difference in the cost of two interventions divided by their affect.⁷⁵

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215 **Data monitoring**

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3 216 Trial data will be monitored and regularly assessed for integrity and errors. All data monitoring
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5 217 will be performed completely independently from sponsors and competing interests. An
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7 218 independent data monitoring committee (DMC) will be appointed to critically review data
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9 219 safety in the trial. Veronica Sjöberg (VS) will be responsible for the monitoring of all data
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11 220 collected in the pilot study. A data management plan (DMP) will be outlined by the first author
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13 221 (VS) and implemented by the principal investigator (LV) to ensure sound data structure (folder
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15 222 structure, file naming, organization), and data storing.
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20 225 **DISCUSSION**

23 226 This article describes a protocol for a R-RCT trial of a novel e-Health intervention. The trial
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25 227 will contribute to establish evidence for the effectiveness of individualized physical activity and
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27 228 exercise among patients living with chronic pain and participating in IPRP. The methodology
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29 229 and feasibility of the trial will be evaluated in an early phase by a pilot study, which will
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31 230 contribute to optimized robustness of the subsequent R-RCT-trial and enable further refinement
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33 231 of the intervention. Despite many efforts have been taken to develop health promoting
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35 232 interventions for this patient group, it is rare that such interventions are systematically
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37 233 developed and includes both objective and patient reported outcomes. The eVIS-intervention is
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39 234 developed according to MRC's framework for development and evaluation of complex
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41 235 interventions.²⁹ It consists of both objectively measured physical activity level (steps/day), and
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43 236 patients own reports on pain intensity, interference on daily activities and individual daily
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45 237 activity goal, all joint in the web application named PATRON. This enables known facilitating
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47 238 mechanisms for behavior change (e.g., as self-monitoring etc.)³² whilst including several core
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49 239 outcome domains.^{34 76} The agile development process has enabled continuous evaluation and
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51 240 improvement of the intervention based on data provided from patients, clinicians and
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53 241 researchers in different fields. Objectively measured constructs of physical activity by Fitbit
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55 242 devices have been criticized due to lack of accuracy of measurements of time spent in moderate
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57 243 to vigorous physical activity (MVPA) where various devices overestimate the measurement⁷⁷.
58
59 244 Preceding this study, our research group performed an evaluation of Fitbit Versa's criterion
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245 validity of measuring energy expenditure, heart rate and step count among patients living with
246 chronic pain. Results confirmed previous study results in adjacent patient groups reporting that

247 Fitbit Versa systematically overestimated energy expenditure, however, measurements of step
248 count both in laboratory and in free-living setting were valid.³³

249 In this trial participants will be recruited at IPRP units nationally distributed. All units adopt to
250 core IPRP content regarding modalities, but it is well-known that both duration and intensity
251 greatly vary which may limit generalization of the results.²⁵ To achieve maximum external
252 validity, we will collect data on the specific characteristics of all participating units and include
253 this in the final analyses. Unknown engagement in other out-patient treatments under study
254 period, may be a potential source of bias, though data on in-patient engagement will be known
255 through registry data from the National Patient register. Non-adherence to daily self-report in
256 PATRON can be expected and may differ between intervention- and control group (differential
257 missing). Measures will be taken to optimize adherence in both groups such as regular auditing
258 of registrations in PATRON followed by personal emails with encouragement to follow
259 protocol. To minimize the risk of contamination between groups, and to ensure that the study
260 will be carried out in compliance with the study protocol, all participating staff at the IPRP units
261 will participate in a study-specific course prior entering the trial. Results generated from the
262 pilot study and the subsequent effectiveness trial will inform pain management field with new
263 knowledge on eVIS's potential to increase pain rehabilitation program's effectiveness by
264 individualized physical activity levels among patients living with chronic pain.

265

266 **Harms and adverse events**

267 Participating patients and healthcare staff at the participating IPRP units will be encouraged to
268 report any adverse events such as unexpected side effects or symptom deterioration,⁷⁸ which
269 will also be reported to the Swedish Ethical Board Review.

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271 **Ethics and dissemination**

272 The trial is prospectively registered in ClinicalTrials.gov (trial registration number
273 NCT05009459) and was approved by the Swedish Ethics Review Board in May 2021 (Dnr
274 2021/02109). The trial will be conducted in compliance to the Helsinki Declaration.⁷⁹ Important
275 protocol modifications will be communicated to the Swedish Ethics Review Board as well as
276 to all participating IPRP units and participants. To protect confidentiality, all data will be coded
277 by an individual code, and the encryption key will be stored separately. Data will be stored at

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3 278 an intended project server at Dalarna University, which is secured by regular backups. No
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5 279 unauthorized persons will have access to data, e.g., data will only be accessible by researchers
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7 280 in the trial after approval from the principal investigator. Results of the pilot study and the main
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9 281 trial will be submitted for publication in peer-reviewed journals and communicated in national
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11 282 and international research networks, as well as in relevant clinical settings, including patient
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13 283 associations.

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16 285 **Author contribution statement**

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19 286 LV and BÄ are responsible for the conception of the trial. LV is the principal investigator and
20
21 287 is involved in all methodological decisions. VS, ET, AM, JW, RLM, BÄ, MH, MB, and LV all
22
23 288 contributed to study design and were all involved in the development processes (the evaluation
24
25 289 of criterion validity of the wrist-worn activity tracker and the evaluations of the content validity
26
27 290 and clinical feasibility) of the intervention. RLM performed the preliminary power and sample
28
29 291 size calculations and was involved in all associated decisions. VS wrote the first draft of the
30
31 292 manuscript, was responsible for revising the manuscript's intellectual content based on all co-
32
33 293 authors conscientious input and conducted manuscript revisions according to peer-reviewer's
34
35 294 comments. All authors read and approved the final version of the manuscript. For this article,
36
37 295 no ghost authors, guest authors, or professional writers have or will be used. Author eligibility
38
39 296 is and will be based upon the ICMJE Recommendations for the Conduct, Reporting, Editing,
40
41 297 and Publication of Scholarly work in Medical Journals.

42 298

43 299 **Trial status**

44
45 300 Recruitment of participants was initiated late October 2021 and the trial is planned to be
46
47 301 completed on 31 December 2024.

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49 302

51 303 **Funding**

52
53
54 304 This trial is funded by the Swedish Research Council for Health, Working Life and Welfare
55
56 305 (2017-00491), the Research Council (2018-02455), the Swedish Association for Survivors of
57
58 306 Polio, Accident, and Injury (2020-03), and research funding from Dalarna University (No grant
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2
3 307 number). The funders had no role in study design and will have no role in any part of the
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5 308 implementation of the study or the reporting of its results.
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10 310 **Competing interests**

11 311 None declared.
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17 313 **Access to data**

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19 314 This is a protocol describing a trial design. All authors will have access to the final trial
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21 315 dataset.
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26 317 **Supplementary files:**

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28 318 - Completed SPIRIT 2013 Checklist
29 319 - Patient consent form (in Swedish)
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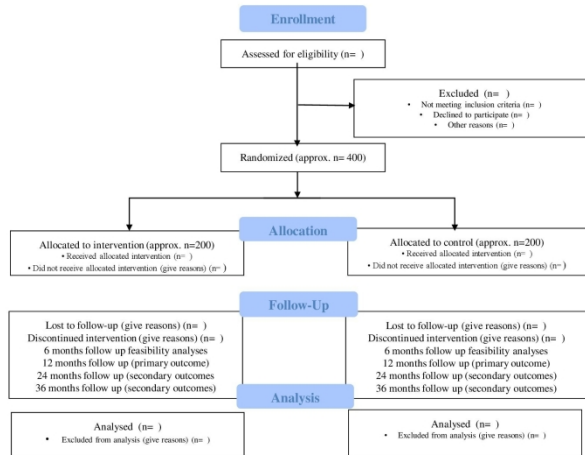


Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.

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Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of physical activity level (steps/day), patient-report of pain interference on daily activities, pain intensity and pharmacological consumption, ii) the visualisation element of collected data in different graphs and compilations of data, and iii) the communication element.

338x190mm (300 x 300 DPI)

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

Section/ item	Item No	Description	Page number in Main document (clean copy)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 21
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	22 (not contact info)
	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	22
	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)	19
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	16-17
Objectives	7	Specific objectives or hypotheses	5-6, 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)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11 a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11 b	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)	18-19
	11 c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	18-19
	11 d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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	9-16 Table 1 Table 2

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)	Table 1 Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 18-19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			15
Sequence generation	16 a	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	17-18
Allocation concealment mechanism	16 b	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	17
Implementation	16 c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	17 a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17 b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18 a	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	Table 1 9-16
	18 b	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	18-19
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	20
Statistical methods	20 a	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	19
	20 b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20 c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring	21 a	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	20
	21 b	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	19
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	21

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
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)	21-22
Consent or assent	26 a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26 b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	20
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	No
Dissemination policy	31 a	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	21-22
	31 b	Authorship eligibility guidelines and any intended use of professional writers	22
	31 c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary files [In Swedish]
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	NA

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BMJ Open

Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized controlled clinical trial

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7 3 **Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish**
8 4 **Interdisciplinary Pain Rehabilitation Programs: study protocol for a registry-based randomized**
9 5 **controlled clinical trial**
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54 28 **Keywords:** Chronic pain, Individualized physical activity level, Interdisciplinary Pain
55 29 Rehabilitation Programs, Pilot study, Physical health, Registry-based randomized clinical trial,
56 30 Study protocol
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ABSTRACT

Introduction: Living with chronic pain often involves negative consequences. Interdisciplinary Pain Rehabilitation Programs (IPRPs) is considered superior to single-treatment measures in patients with chronic pain. Despite this, effects emerge sub-optimal and more than 20% of patients deteriorate in patient reported physical health outcomes after IPRP. A novel e-Health intervention, eVISualisation of physical activity and pain (eVIS), was systematically developed to facilitate individualization of physical activity levels. By adding elements of data collection, visualization, and communication of objectively measured physical activity and patient-reported outcomes (pain intensity, interference of pain, pharmaceutical consumption) to existing treatment modalities in IPRP, the IPRP team acquires prerequisites to adapt advice and physical activity prescriptions and to evaluate set activity goals. The overall aim is two-fold. First, the aim is to evaluate the feasibility of the subsequent registry-based randomized controlled clinical trial (R-RCT). Secondly, the aim is to prospectively evaluate the effectiveness of the eVIS-intervention as a supplement to IPRP on our defined primary (physical health) and secondary outcomes.

Methods and analysis: In the R-RCT, recruitment of 400 patients with chronic pain will be performed at 15 IPRP units. A random allocation to either IPRP + eVIS or to control group that will receive IPRP only will be performed. Data from the initial 30 participants completing the study period (6 months) will be included in a pilot study where key feasibility outcomes (recruitment, randomization, , implementation, treatment integrity, data collection procedure, preliminary outcome measures) will be evaluated. Outcome variables will be extracted from PATRON and from six national registries. Multivariate statistics and repeated measures analyses will be performed. Quality Adjusted Life Years (QALYs) and Incremental Cost Effectiveness Ratio (ICER) will be calculated for cost effectiveness evaluation.

Ethics/dissemination: The Swedish Ethics Review Board granted approval (Dnr 2021/02109). Results will be disseminated through peer-review journals.

Trial registration number: NCT05009459.

Protocol version: 1

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3 63 **Strengths and limitations of the study**
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6 64 • A proceeding pilot study will enable improvements of design and feasibility of a
7 65 subsequent R-RCT
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9 66 • The eVIS-intervention has been developed, evaluated, and improved, based on data
10 67 provided from patients, clinicians, and researchers in different fields.
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12 68 • The intervention targets physical activity modalities in IPRP and is designed to enable
13 69 a more individualized IPRP treatment.
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15 70 • The intervention is based on objectively measured physical activity levels, patient-
16 71 reported clinical outcomes, and mechanisms that facilitate behavior change, in
17 72 accordance with current guidelines that are provided by authorities in the chronic pain
18 73 management field.
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20 74 • The nature of the intervention precludes blinding of patients and the IPRP team.
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INTRODUCTION

Chronic musculoskeletal pain (>3 months), including neck/shoulder/back pain or widespread pain, is a major global health and socioeconomic burden.^{1 2} Living with chronic pain is often associated with reduced levels of wellbeing and the health-related quality of life of this group has been reported to be among the lowest of any medical condition.³ To date, physical activity (i.e. any bodily movement that requires energy expenditure) and exercise (i.e. structured and planned physical activity aimed to increase fitness)⁴ have been shown to prevent and/or treat several of our noncommunicable diseases including chronic pain,⁵ due to their beneficial effects on general health, pain intensity, physical and psychological functioning, and health-related quality of life.⁵⁻⁸ Despite the growing evidence of health benefits related to physical activity, participation and adherence to physical activity recommendations, such as WHO's physical activity guidelines, are often low in patients living with chronic pain.⁹⁻¹² This may partly be explained by the indicated association between high pain scores and low patient-reported activity levels among patients with chronic pain and/or the documented reports of the negative impact of depression on physical activity levels.¹³ In addition, it is well known that behavior change is difficult, and that each individual's own participation is essential.¹⁴ It has been shown that behavior change towards a beneficial physical activity level may be facilitated by individuals self-monitoring their physical activity.¹⁵ The use of objective measures increases the likelihood of the effectiveness of interventions designed to promote physical activity.¹⁵ By adding goal setting, feedback, and a focus on achieved goals, effectiveness can be further improved.¹⁵⁻¹⁸

Interdisciplinary pain rehabilitation programs (described as a subset of Interdisciplinary Treatment), is defined as "multimodal treatment provided by a multidisciplinary team (at least 3 professions), collaborating in assessment and treatment using a shared biopsychosocial model and goals"¹⁹. The IPRP approach adopts the principles of behavioral therapy and incorporates besides physical activity and exercise, also psychological measures, pharmaceutical treatment and patient education.²⁰ Physical activity and exercise are central measures in IPRPs as it targets the physical deconditioning by improving levels of physical activity, and also reduces pain severity and improved physical function and quality of life, without causing any severe adverse events.⁵ Interdisciplinary pain rehabilitation programs are considered to be superior to single-treatment measures (e.g., physical treatments, education interventions, surgery, etc.) for patients with chronic pain supporting positive effects on pain intensity and activity disability.^{20 21}

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3 123 However, IPRP effectiveness is only slightly better and in the majority of cases only a small
4 124 effect is seen.²¹⁻²⁵ In addition, up to 25% of patients report deterioration in physical health after
5 125 completing IPRP and after 12 months follow up, regardless of duration of IPRP.^{20 25 26}
6 126 Sustainable treatment affects seem to vary according to patient clinical features at baseline,
7 127 such as poor employment status, high pain levels, and low functioning, all of which predict low
8 128 physical health at follow-up.^{23 27} Many efforts have been made to find effective interventions
9 129 that improve the health of chronic pain patients. To facilitate individualized physical activity
10 130 levels within the Swedish IPRP setting, an eVISualisation (eVIS) of physical activity and pain
11 131 intervention has been systematically developed according to the Medical Research Council's
12 132 recently updated framework for development and evaluation of complex interventions.^{28 29} In
13 133 accordance with the framework, the eVIS-interventions was designed and planned in close
14 134 collaboration with stakeholders. eVIS is designed to target facilitating mechanisms for behavior
15 135 change, such as outcome expectations, self-monitoring, self-evaluation, and self-efficacy,³⁰⁻³²
16 136 which are theoretically framed by the Social Cognitive Theory.³² In eVIS, objectively measured
17 137 physical activity tracking using a wrist-worn activity tracker³³ (Fitbit Versa 2) is combined with
18 138 a daily activity goal (steps/day) and daily patient reports of known important clinical outcome
19 139 assessments: pain intensity and its interference on daily activities³⁴⁻³⁸ and pharmaceutical
20 140 consumption. Data is collected and visualized in a purpose-developed web application, Pain
21 141 And TRaining ON-line (PATRON), which can be used by the patient and the IPRP team to
22 142 follow and adjust individual physical activity levels. Despite interventions of this kind having
23 143 highly promising potential to relive pain and improve disability in this patient
24 144 group,³⁹ interventions are rarely systematically developed and validated specifically for their
25 145 target patient group, leaving crucial information of feasibility and true effectiveness unknown.
26 146 Therefore, the overall aim of this study is two-fold. First, the aim is to evaluate the feasibility
27 147 (recruitment capability, eligibility screening procedure, randomization, implementation process,
28 148 response rate, compliance rate, changes in primary- and secondary outcomes from start to end
29 149 of study period, differences between treatment groups in primary outcome) of a subsequent
30 150 registry-based randomized controlled clinical trial (R-RCT) within the IPRP setting in order to
31 151 gain knowledge of population variation, increase robustness and to avoid underpower.⁴⁰⁻⁴³
32 152 Secondly, the aim is to prospectively evaluate the effectiveness of the eVIS-intervention as a
33 153 supplement to IPRP on our defined primary (physical health) and secondary outcomes, 12
34 154 months after completed IPRP compared to IPRP as usually provided. In addition, the aim is to
35 155 evaluate the cost effectiveness of eVIS supplementing IPRP at 12 and 36 months follow up
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3 156 after completed IPRP, and to prospectively evaluate differences in opioid consumption at start
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5 157 of IPRP compared to six months after completed IPRP.

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7 158 ⁴²⁴⁰⁻⁴³In this trial, the UK National Institute for Health Research's (NIHR) definitions of the
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9 159 terms *pilot study* (i.e., "a smaller version of the main study") and *feasibility study* (i.e.,
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11 160 "evaluation of pieces of research done before the main study") are applied.⁴⁴ The aim of this
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13 161 paper is to transparently clarify and report on study designs, aims, outcome assessments, and
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15 162 procedures for a planned R-RCT (including an randomized pilot study) which prospectively
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17 163 will evaluate clinical effectiveness and cost effectiveness of eVIS as a supplement to IPRPs for
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19 164 patients living with chronic pain compared to standard IPRPs.

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23 24 25 167 **METHODS AND ANALYSIS**

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28 29 169 **Trial design and setting**

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32 170 This two-armed pragmatic multi-site R-RCT will be conducted in specialized and primary
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34 171 IPRPs in Sweden, and include approximately 400 (n=200, n=200) patients (number will be
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36 172 definitively determined after the pilot study is finalized) with chronic musculoskeletal non-
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38 173 malignant pain. As indicated, an randomized controlled pilot study (n=15, n=15) will be
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40 174 incorporated as the initial phase of the main trial in order to evaluate the intervention's
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42 175 methodology and design.^{29 41 45} This trial will comply with the Consolidated Standards of
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44 176 Reporting Trials (CONSORT)⁴⁰ and with the Standard Protocol Items: Recommendations for
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46 177 Interventional Trials (SPIRIT)⁴⁶. A completed SPIRIT 2013 Checklist can be found in the
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48 178 additional files. See Figure 1 for study design and enrollment details.

49 179 *Insert Figure 1 here.*

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53 181 **Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.**

54 55 182 **Eligibility criteria**

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57 183 In this trial, the patient-related, care process and caregiver-related inclusion criteria for
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59 184 receiving Swedish IPRP will be applied, as patients entering the trial must be accepted for IPRP.

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3 185 Principal IPRP inclusion criteria are patients in working age with persistent or intermittent
4 186 musculoskeletal and or generalized pain lasting ≥ 3 months with pain affecting daily activities
5 187 to a large extent, completed systematic assessment (including screening for psychosocial risk
6 188 factors and differential diagnosis) and non-pharmacological optimization. Inclusion criteria for
7 189 Swedish IPRPs is outlined in detail elsewhere.⁴⁷ Due to the nature of the intervention, patients
8 190 must be able to hear, see, and comprehend spoken and written Swedish, and have daily access
9 191 to a computer, smartphone, or tablet. Patients who need to use a walking aid indoors will be
10 192 excluded.

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194 **Recruitment**

195 Interdisciplinary Pain Rehabilitation Units

196 Approximately 15 IPRP units in primary and specialized care in Sweden will be included in the
197 trial. IPRP units reporting to the Swedish National Quality Registry for Pain Rehabilitation
198 (SQRP) have been approached by email with study information (aim, rationale, methods etc.)
199 and an invitation to participate in one of several online digital information meetings that will
200 further present the study (initiated August 2021). Study representatives will approach
201 healthcare staff at potential IPRP units by telephone or email to formally offer participation.
202 Operation managers at each unit will be asked to provide written consent by e-mail.

203 Participants

204 In order to give potential participants additional time to consider taking part in the trial before
205 they visit the IPRP unit, healthcare staff at the units will be encouraged to provide a general
206 information sheet about the trial in the summon to the IPRP assessment. Members of IPRP
207 teams (primarily physiotherapists but also occupational therapists, physicians, nurses etc.) will
208 identify potential participants selected for IPRP based on outlined criteria and provide them
209 with verbal and written details of the study (information sheets and the project's web address).
210 All participants will provide written informed consent (see supplementary file) prior to joining
211 the study, which will be managed by the IPRP team. Detailed verbal and written information
212 about the voluntary nature of participation and the indisputable right to discontinue participation
213 in the trial at any time will be provided. Detailed checklists and forms will support these
214 procedures, and these will be easily accessible on the project web site.

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216 **Intervention**

217 Participation in the intervention group involves regular IPRP supplemented with eVIS for a
218 coherent time span of six months, IPRP time included. As the duration and intensity of IPRPs
219 greatly vary from a couple of weeks up to four months²⁵, a six month study period ensures time
220 of independent use of eVIS after completed IPRP. Participants are not prohibited to take part
221 of other health care during study period. Interdisciplinary pain rehabilitation programs vary in
222 interventions, duration, composition, intensity^{24 25} and can be performed either individually or
223 in group format. In this trial, participation in a IPRP will be supplemented by eVIS, a health
224 promoting intervention containing three elements designed to facilitate individualized physical
225 activity level (Figure 2).

226 The data collection element

227 Outcome assessments of physical activity level (steps/day) will be objectively collected by a
228 wrist-worn activity tracker, Fitbit Versa 2. This device has been population-specifically
229 validated and the measurement of step rate is indicated as valid for measurement in this
230 population.³³ Data on patient's physical activity level quantified as steps/day, will be
231 automatically synchronized to the web application PATRON where pain intensity (0-10),⁴⁸
232 interference of pain on daily activities (0-10),⁴⁹ pharmacological consumption (name, dose,
233 number, and form), and (optional) free-text comments will be reported by the patient daily. The
234 web application can be accessed via computer, smartphone, or tablet. A daily activity goal
235 (steps/day) is formulated by the patient in close collaboration with the IPRP team and revised
236 accordingly. The daily activity goal in eVIS is individually set based on patient's individual
237 prerequisites and re-evaluated regularly as part of the communication element (described
238 below). In the process of setting a daily activity goal, the IPRP team are encouraged to consider
239 international guidelines of step rate as a quantification of beneficial physical activity levels⁵⁰
240 as well as patient's personal barriers and resources to perform physical activity. The data
241 collection element is designed to target facilitating mechanisms for behavior change, such as
242 outcome expectations, self-monitoring, self-evaluation, and self-efficacy.³⁰⁻³²

243 The visualisation element

244 Objectively measured physical activity levels, patient-report on pain intensity and interference
245 of pain on daily activity are graphically visualized separately or alongside each other, in relation
246 to the daily activity goal. Three different graphs (1/7/28 days) are available. The visualisation
247 element provides additional prerequisites for increased knowledge acquisition, self-monitoring,

248 and self-evaluation as data is visualized over time and in relation to each other and to the
249 individual daily activity goal in order to improve patient self-efficacy.

250 The communication element

251 The graphs in the visualisation element together with compiled data on pharmacological
252 consumption will provide a novel decision basis for the patient and the IPRP team. This
253 addition to existing treatment modalities traditionally provided in Swedish IPRP (e.g. physical
254 activity, cardio training, weight training, mobility training, stability training, motivating
255 conversation education, advice etc.). enables prerequisites for the IPRP team to integrate
256 behavioral changing techniques (e.g. reinforcement, knowledge acquisition, self-monitoring,
257 self-efficacy) into existing treatment options. By such integration, knowledge of patient's
258 personal barriers and resources in factors important in pain rehabilitation may be visualized and
259 if necessary, assessed. The IPRP team as well as the patients are encouraged to explore the
260 visualisation element of eVIS at each visit at the IPRP unit. This in order to utilize data into the
261 treatment by adjusting advise or prescriptions.

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263 *Insert Figure 2 here*

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265 **Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of**
266 **physical activity level (steps/day), patient-reports of interference of pain on daily activities, pain intensity**
267 **and pharmacological consumption, ii) the visualisation element of collected data in different graphs and**
268 **compilations of data, and iii) the communication element.**

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270 **Control**

271 Participation in the control group involves taking part in regular IPRP plus making daily ratings
272 of pain intensity, interference of pain on daily activities, and pharmaceutical consumption
273 (corresponding as in intervention group) in PATRON for six months, including the time that
274 the IPRP is being carried out. The control group will not use the wrist-worn activity tracker as
275 this may affect their physical activity behavior⁵¹. Nor will they have access to PATRON's
276 visualizing or communication features.

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278 **Patient and Public Involvement Statement**

279 In an early developing phase, stakeholders (patients living with chronic pain, representatives
280 from patient organizations and clinicians experienced in pain rehabilitation) were invited to
281 contribute to the intervention development. In this phase, the web application PATRON and
282 eVIS was presented and carefully discussed with stakeholders as well as with web application
283 developers and researchers. Several needs for improvement were identified, such as a need of
284 an addition of pharmaceutical report function, designated web pages and graphical changes in
285 planned interfaces.

287 **Outcome assessments**

288 According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
289 (IMMPACT), physical health, emotional health, and pain intensity are three of six identified
290 core outcome domains that should be considered when designing research studies aiming to
291 evaluate effectiveness of chronic pain treatments.³⁵⁻³⁷ It is specifically recommended that a
292 health survey such as RAND-36 should be incorporated into treatment as a clinical outcome
293 assessment of physical health in clinical trials.^{36,37} Outcome assessments for evaluating
294 feasibility will be performed on data from the IPRP baseline and after the study period is
295 completed (six months) for the first 30 participants (n=15 +, n=15). In the main trial,
296 assessments of effectiveness will be performed on data from the IPRP baseline and from the
297 12-month follow-up. The cost effectiveness assessments will be based on data from the IPRP
298 baseline, from the 12-month IPRP follow-up and again 24 and 36 months after the IPRP is
299 completed. A detailed overview of outcome assessments can be found in Table 1.

Table 1. Overview of study period, measurement time points, outcome assessments (*bold and italics*), instruments, and data sources (*italics*).

	Enrolment	Allocation	Study period				
			Baseline	t1	t2	t3	t4
	-t ₁	0					
Enrolment	X						
Written and verbal study information	X						
Eligibility screen	X						
Informed consent	X						
Allocation/randomization		X					
Interventions							
Intervention, eVIS (6 months)				X			
Control (6 months)				X			
Outcome assessments							
<i>Personal characteristics</i>							
Sex, age, country of origin, family composition, beliefs of restored health (<i>SQRP, SS</i>)			X				
Disposable-, earned- and net income (<i>SS</i>)			X		X	X	X
Education level and education orientation (<i>SPR, ITR</i>)			X		X	X	X
Diagnosis (<i>NPR</i>)			X		X	X	X
Volume and reason for inpatient care (<i>NPR</i>)			X		X	X	X
<i>Pain characteristics</i>							
Pain intensity (last 7 days), NRS (<i>SQRP-PC and SC</i>)			X		X		
Pain intensity (today), NRS (<i>PATRON</i>)			X	X			
Pain type, location, duration (<i>SQRP-PC and SC</i>)			X				
Pain interference (<i>PATRON</i>)			X				
<i>Multidimensional measures</i>							
Physical health, RAND-36 PCS health survey (<i>PATRON</i>)			X	X	X	X	X
Physical health, RAND-36 PCS health survey (<i>SQRP-SC only</i>)			X		X		
Emotional health, RAND-36 MCS health survey (<i>PATRON</i>)			X	X	X	X	X
Emotional health, RAND-36 MCS health survey (<i>SQRP- SC only</i>)			X		X		

Overall emotional distress, HAD(S) (<i>SQRP-PC and SC</i>)	X		X		
Pain catastrophizing, PCS (<i>SQRP-PC and SC</i>)	X		X		
Psychosocial consequences, MPI-S (<i>SQRP-PC and SC</i>)	X		X		
Pain acceptance, CPAQ-8 (<i>SQRP-PC only</i>)	X		X		
Perceived life Satisfaction, LiSat (<i>SQRP-PC and SC</i>)	X		X		
Functional level, FRI (<i>SQRP-SC only</i>)	X		X		
Physical activity					
Objective measures of steps per day (<i>Fitbit Versa 2</i>)	X	X			
Patient-reported measures (<i>SQRP- PC and SC</i>)	X		X		
Work					
Return to work (partially or full time) every month (<i>SSIA</i>)			X	X	X
Number of days with sick benefit during study period (<i>SSIA</i>)			X	X	X
Number of days in work before new sick leave during study period (<i>SSIA</i>)			X	X	X
Length of total sick leave during study period (<i>SSIA</i>)			X	X	X
Perceived work ability, WAI (<i>SQRP-PC and SC</i>)	X		X		
Sleep quality , ISI (<i>SQRP-SC only</i>)	X		X		
Pharmaceutical consumption					
Name, dose, size, prize of prescribed pharmaceuticals (<i>SPDR, PATRON [not size, prize]</i>)			X	X	X
Prescribed pharmaceuticals collected from pharmacies, (<i>SPDR</i>)			X	X	X
Cost of prescribed pharmaceuticals included in benefit program (<i>SPDR</i>)			X	X	X
Health care consumption (NPR)					
Feasibility outcomes, Questionnaire			X		
Treatment integrity, Questionnaire			X	X	

Abbreviations: -t¹ = pre recruitment period, t¹ = completed study period (6 months), t² = follow-up 12 months after completed Interdisciplinary Pain Rehabilitation Program (IPRP), t³ = 24 months after completed IPRP, t⁴ = 36 months after completed IPRP, eVIS = eVISualisation of physical activity and pain intervention, SQRP = the Swedish national quality registry for pain rehabilitation, SQRP-PC = , the Swedish national quality registry for pain rehabilitation primary care, SQRP-SC = the Swedish national quality registry for pain rehabilitation specialized care, NRS = Numeric Rating Scale, PATRON = Pain and training online (web application), RAND-36 PCS = physical health domain , RAND-36 MCS = mental health domain, HAD(S) = Hospital Anxiety and Depression Scale, PCA = Pain Catastrophizing Scale, MPI-S = Multidimensional Pain Inventory -Swedish Version, CPAQ-8 = The Chronic Pain and Acceptance Questionnaire, LiSat = Life Satisfaction Scale, WAI = Work Ability Index, FRI = Functional rating scale, ISI = Insomnia Severity Index, SSIA = the Swedish Social Insurance Agency's registry, NPR = the National Patient Register, SPDR = the Swedish Prescribed Drug Register, SS = Statistics Sweden, SPR = the Swedish Population Register.

300 Feasibility outcomes, pilot study

301 The trial will be initiated as a full-scale registry-based randomized controlled pilot study. In
 302 this initial step, feasibility will be evaluated from data provided from the first 30 participants
 303 completing the study period and in the following key areas: the unit's recruitment capabilities,
 304 the randomization process, implementation process, participant response to intervention which
 305 is outlined in Table 2. In addition, the data collection procedure, and the preliminary outcome
 306 measures (standardized effect size, sample size estimation with Cohen's *d*, characteristics
 307 [mean, SD]) in main trial will be evaluated.^{41 45} In addition to feasibility outcomes,
 308 characteristics of the IPRP units will be collected

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310 Table 2. Overview of key feasibility outcomes in pilot study.

311 Key feasibility outcomes	
312 Recruitment capability	
	312 Volume of total eligible patients
	312 Number recruited/week
313 Eligibility screening procedure	
	313 Proportion accepted/declined
	313 Personal characteristics of accepted and declined participants
	313 Pain characteristics of accepted and declined participants
314 Procedure of collecting consent	
315 Randomization process	
	315 Delivery envelopes
	315 Storage of envelopes
	315 Procedure of opening envelopes
316 Patients' reaction to allocation	
317 Implementation process	
	317 Response rate RAND-36 PCS
	317 Compliance rate (use of Fitbit Versa 2, intervention group only)
	317 Compliance rate (patient reported outcomes in PATRON)
318 Treatment integrity	
	318 Reported adverse events
319 Data collection procedure	
	319 Access to PATRON data
	319 Access to registry data
	319 Access to RAND-36 data
320 Preliminary outcome measures	
	320 Characteristics, mean (SD)
	321 Missing data
	321 Changes from baseline to finalized study period

322 Abbreviations: RAND-36 PCS = physical health domain in RAND-36, PATRON = Pain and training online (web application).

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324 Primary outcome, main trial

325 The R-RCT will prospectively evaluate the *clinical effectiveness* of eVIS supplementing IPRPs
 326 regarding improvements in our primary outcome assessment *Physical health* collected by the

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3 327 physical health domain in RAND-36 health survey^{3 52} at the 12-month IPRP follow-up after
4 328 completing the IPRP. The RAND-36 is, for this population, a valid health survey measuring
5 329 health-related quality of life in two dimensions, physical health (PCS) and mental health (MCS),
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7 330 mediated by eight subscales.⁵²
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10 331 Secondary outcomes, main trial

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13 332 In the main trial, secondary outcomes will be extracted from Fitbit Versa 2, PATRON and
14 333 collapsed with data from six national registries (all listed below) at 12, 24, 36 months after the
15 334 IPRP is completed.

16 335 *Objectively measured secondary outcomes collected using Fitbit Versa 2*

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19 336 Objectively measured physical activity levels will be collected daily during the study period
20 337 using a wrist-worn activity tracker (Fitbit Versa 2). The Fitbit device measures and estimates a
21 338 range of physical activity outcomes such as number of steps, heart rate, energy expenditure,
22 339 floors climbed, physical activity level, and sleep.^{33 53} In this trial, participants' step count per
23 340 day will automatically be synchronized to PATRON during the study period (six months). The
24 341 use of steps per day is considered to be a valid quantification of physical activity levels and this
25 342 is acknowledged by the Swedish Health Authority.⁵⁴
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34 343 *Patient-reported secondary outcomes collected through PATRON*

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36 344 Data on physical and mental health collected by RAND-36 health survey will be collected
37 345 through PATRON at 6, 12 and 24 months after IPRP. Pain intensity (“rate your average pain
38 346 during the last 24 hours”) will be measured daily using the Numeric Rating Scale (NRS, 0 =
39 347 no pain at all to 10 = pain as bad as it could be), a 11-point Likert scale⁴⁸ incorporated in the
40 348 web application PATRON. Pain interference on daily activities is a recommended outcome
41 349 domain.³⁵ In PATRON, assessments of interference of pain on daily activities will be measured
42 350 by the question “rate how much your daily activities are affected by pain” using an 11-point
43 351 Likert Scale (0 = not at all to 10 = to a very large extent). This question in PATRON has been
44 352 modified based on the Multidimensional Pain Inventory Swedish version and its items on pain
45 353 interference,⁴⁹ and validated in our previous study (in manuscript). Data on daily
46 354 pharmaceutical consumption will be collected in PATRON (name, dose, number, and form).
47 355 Voluntary free text comments will supplement patient reporting by providing additional
48 356 information regarding perceived mental and physical health (only in the intervention group).
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3 357 *Secondary outcomes collected through the Swedish national quality registry for pain*
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5 358 *rehabilitation*

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7 359 In Sweden, 90% of IPRP units routinely collect patient-reported data from standardized
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9 360 questionnaires and report to SQRP, a database initiated in 1998 that contains data from chronic
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11 361 non-malignant pain patients participating in IPRPs.^{24 55} The registry consists of two parts; the
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13 362 primary care SQRP (SQRP-PC) and the specialized SQRP (SQRP-SC). The primary care SQRP
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15 363 is supplied with data from affiliated primary care IPRP units (n=42, reported data from 505
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17 364 patients in 2020). The specialized care SQRP, receives data from affiliated specialized care
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19 365 IPRP units (n=45, reporting data from 7427 patients in 2020). Data in both registries are
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21 366 collected at baseline, when the IPRP is completed, and at 12-month follow-ups, the content of
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23 367 data collected in the registries differs somewhat. In this trial, registry data from both registries
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25 368 will be collected used to describe demographics such as age, sex, height, weight, education
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27 369 level, and work.^{24 55} Participants partaking in an IPRP in SC will also routinely complete the
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29 370 RAND-36 health survey at baseline and at their 12-month follow-up after they have completed
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31 371 their program. Data on pain intensity (“last 7 days”) (NRS 0-10)⁴⁸ will be retrieved from SQRP-
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33 372 PC and SQRP-SC alongside other pain characteristics including pain location (36 anatomical
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35 373 predefined areas, 18 on the left side, 18 on the right side), pain duration, and pain type
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37 374 (intermittent or continuous). Data on self-rated physical and mental health is collected by the
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39 375 RAND-36 health survey^{3 52} in SQRP-SC and the EuroQol-5 dimensions (EQ-5D) collected
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41 376 routinely in SQRP-PC and SQRP-SC will be used. The EQ-5D is a standard instrument used in
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43 377 health economic evaluations and contains five items each with three ordered response
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45 378 categories, and a 0-100 index.⁵⁶

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47 379 Measures of self-rated physical activity is collected in SQRP-PC and SC using the National
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49 380 Board of Health and Welfare’s three questions on physical activity (0 - >300 minutes/week),
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51 381 exercise (0 - >120 minutes/week), and sedentary behavior (0 – 15 hours/day).⁵⁷ and in SQRP-
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53 382 PC by the Godin-Shepard leisure-time physical activity questionnaire (number of times/week
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55 383 that strenuous/moderate/light exercise.⁵⁸ Data on overall emotional distress (0 – 3), pain
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57 384 catastrophizing (0 – 4), and psychosocial consequences (0 – 6) of living with pain are collected
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59 385 in SQRP-PC and SQRP-SC using the Hospital Anxiety and Depression Scale (HADS),^{52 59} the
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386 Pain Catastrophizing Scale (PCS),⁶⁰ and the Multidimensional Pain Inventory Scale Swedish
387 version (MPI-S, 0 – 6).⁴⁹ Level of pain acceptance (0 – 6) is collected in SQRP-PC using the
388 Chronic Pain and Acceptance Questionnaire (CPAQ-8).⁶¹ Perceived life satisfaction (1-6) is
389 collected by the Life Satisfaction Scale (LiSat)⁶² in both registries. Data on perceived work

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3 390 ability (0 – 10) is collected by the Work Ability Index (WAI)⁶³ and functional levels (0 – 4) by
4 391 the Functional Rating Scale (FRI)⁶⁴ is collected in SQRP-SC only. Data on patient-reported
5 392 sleep quality (0 – 4) is collected by the Insomnia Severity Index (ISI)⁶⁵ in SQRP-SC.
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8 9 393 *Secondary outcomes collected through other national registries*

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11 394 Data will be collected from the Swedish Social Insurance Agency's registry on diagnosis,
12 395 reasons for sick leave, type of financial compensation, number of sick days, and sickness benefit
13 396 (days and hours) during the study period. In addition, data on days in work (partial or full time)
14 397 per month in total before new sick leave period and length of total sick leave during the study
15 398 period will be retrieved from the registry. Data will be retrieved from the National Patient
16 399 Register on diagnosis and healthcare consumption (total number of days in care etc.). Retrieved
17 400 data from the Swedish Prescribed Drug Register will provide information on prescribed
18 401 pharmaceutical names, doses, sizes, and prices that have been collected from pharmacies, their
19 402 costs, and whether the pharmaceutical is included in the subsidized pharmaceutical program.
20 403 Data on disposable and earned income as well as net income will be retrieved from Statistics
21 404 Sweden. In addition, demographic data such as sex, age, marital status, citizenship, education
22 405 level, and number of children in the family will be collected. From the Population registry, data
23 406 on education level and education orientation (focus) in addition to limited demographic data
24 407 (sex, age) will be collected.
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36 408

37 38 409 **Sample size**

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41 410 A sample size for the pilot study of at least n=30 is considered sufficient for planned feasibility
42 411 analyses since it will not involve hypothesis testing and sample size calculation *per se*.^{43 66 67}
43 412 For the main trial, a preliminary power calculation are based on assumptions from previous
44 413 research reporting on proportions of patients that report a clinically meaningful difference of
45 414 ≥ 3 points in the physical health domain in RAND-36, 12-months after completed IPRP.²⁵ The
46 415 calculation was performed in R, using a calculation method for simple randomization and for
47 416 independent observations. The preliminary power calculation allows a dropout rate of 20% and
48 417 requires a total sample size of approximately n=400 to have an 80% power to detect a 15%
49 418 difference ($\geq 3p$) between the groups in the outcome physical health. Physical health is measured
50 419 by the RAND-36 health survey at the 12-month follow-up measurement point after the
51 420 completion of the IPRP. The significance level is set to 0.05 and is two-tailed. The sample size
52 421 calculation may be re-calculated after the pilot study is completed. In this trial, the null
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3 422 hypothesis is that there will be no difference between the intervention group and the control
4 423 group (<15% with ≥ 3 points improvement) with regard to proportional improvement in the PCS
5 424 domain of RAND-36 health survey when assessed at the 12-month follow-up after the
6 425 completion of the IPRP.
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11 427 **Allocation**

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15 428 A permuted block randomization design with a random block size of 4 and 6 and an 1:1
16 429 allocation ratio will be applied and evaluated in the pilot study in order to allocate participants
17 430 to either the intervention or control group.⁶⁸⁻⁷⁰ A computer-generated randomization schedule
18 431 will be created using a random number table to allocate participants to one of the two treatment
19 432 arms; intervention group (IPRP supplemented by eVIS) or control group (IPRP with daily
20 433 patient reports in PATRON). The schedule will be generated by an experienced researcher, who
21 434 is not directly involved in the trial. Sequentially numbered opaque sealed envelopes will be
22 435 used to ensure allocation concealment. Allocation will take place at the IPRP unit and will be
23 436 conducted by members of the IPRP team after initial assessment.
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32 438 **Blinding/masking**

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34 439 Neither the IPRP team delivering the intervention nor participants will be blinded to
35 440 allocation to either group due to the nature of the intervention.
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41 442 **Data collection methods**

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43 443 Besides objectively measured data of physical activity level, patient-reported data will be
44 444 collected from PATRON and from six Swedish registries at the IPRP baseline and at 6, 12 and
45 445 24 months after completed IPRP. In addition, patient-reported data regarding cost effectiveness
46 446 will be retrieved 36 months after the IPRP is completed. In this trial, data will be retrieved from
47 447 SQRP, the Swedish social insurance agency's registry, the Patient registry, the Swedish
48 448 Prescribed Drug Register, the Income- and taxation registry, and the Swedish Population
49 449 Register to enable a broad investigation into the intervention's effectiveness.
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58 450 To enable sufficient pilot study analyses, as well as assessment of the primary outcome Physical
59 451 health (PCS) in RAND-36, members of the IPRP team will be asked to provide self-reported

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3 452 data on feasibility outcomes (outlined below) using a purpose-developed questionnaire with
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5 453 specific questions targeting the IPRP team perspective.⁴¹ If deemed required, data collection
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7 454 will be supplemented by individual or group interviews. A detailed overview of assessments,
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9 455 time points, and data sources can be found in Table 1.

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13 457 **Data management**

15 458 In order to link individual-level data from different registries to PATRON data, we will seek
16 459 assistance from the National Board of Health and Welfare who will provide a consecutive
17 460 number key. This key will be stored at the National Board of Health and Welfare for three years
18 461 (longer if needed). The procedure is initiated by sending PATRON data to the National Board
19 462 of Health and Welfare and participants' social security numbers will be sent there by SQRP.
20 463 The National Board of Health and Welfare creates the consecutive number key and connects
21 464 ordered data with own registry data (the National Patient Register and the Swedish Prescribed
22 465 Drug Register). The National Board of Health and Welfare will then send a data order to the
23 466 remaining registries (the Swedish Social Insurance Agency's registry, Statistics Sweden, and
24 467 the Swedish Population Register) and encoded data will be sent to the principal investigator to
25 468 be stored in Dalarna University's secured server.

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37 470 **Intervention fidelity**

39 471 The following measures have been and will be taken to increase intervention fidelity: A
40 472 systematical intervention development with a clarified theoretical base explaining suggested
41 473 mechanisms has been undertaken throughout the development process.²⁹ Healthcare staff at the
42 474 IPRP units will be provided with comprehensive written information (easily accessed online)
43 475 that includes step-by-step instructions on how to initiate and deliver the intervention while
44 476 maintaining a high level of integrity. Before the study starts, all participating healthcare staff at
45 477 the IPRP units will take part in a standardized provider training session online. Data on each
46 478 participant's number of entries in PATRON will be available throughout the study in order to
47 479 collect data on treatment fidelity. During the on-going study period, researchers will be
48 480 automatically notified of non-wear time (Fitbit Versa 2) and any absence of patient reports in
49 481 PATRON. In these cases, researchers will contact the relevant participant via email or telephone
50 482 to ask if they need help or support. If a participant decides to discontinue the trial, he or she will

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3 483 be asked if they are willing to grant permission for the collected data up to that point to be used
4 484 in the trial. Also, recurring web-based meeting opportunities will be provided, where IPRP team
5 485 members will be encouraged to discuss experienced or perceived difficulties, and a
6 486 questionnaire will be sent out after the study period with the aim of assessing treatment fidelity
7 487 (treatment integrity and treatment differentiation) by gathering data on how treatment was
8 488 delivered (manner *versus* treatment manual, intervention's alignment to intended theoretical
9 489 base). This will allow results to be interpreted and will facilitate practical implementation.^{71 72}
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491 **Statistical methods**

492 A statistical analysis plan (SAP) will expand on statistical principles, statistical analyses, the
493 planned handling of missing data, possible additional analyses (subgroups etc.) and interim
494 analyses. In both the pilot study and the R-RCT, descriptive statistical analyses will be
495 performed to provide transparent reporting of characteristics of both participants and
496 participating IPRP units. In addition, IPRP units will be prompted to register the number of
497 patients they ask to participate, those excluded based on eligibility criteria, and those who
498 decline participation. Analyses of pilot data (ratings of key feasibility outcomes) made by IPRP
499 teams on a four-point Likert scale (i.e. 1= strongly disagree, 2= disagree, 3= agree, 4= strongly
500 agree) will be calculated as proportions in four categories for each item. Ratings ≥ 3 will be
501 considered as acceptable feasibility. Analyses of primary and secondary outcomes in main trial
502 will be performed based on PATRON data and registry data. The clinical effectiveness of eVIS
503 will be analyzed for each outcome using multivariate statistical and repeated measures analyses
504 as a preliminary plan. Both the intention-to-treat and the per-protocol sample will be analyzed,
505 but the intention-to-treat analysis will be considered as the primary analysis. All p-values will
506 be presented. If a p-value is ≤ 0.05 , the null hypothesis will be rejected and eVIS will be
507 considered effective according to the outlined hypothesis. To perform cost-effectiveness
508 calculations, data on health-related quality of life measured by EQ-5D will be retrieved from
509 SQRP. EQ-5D is the standard instrument used to evaluate health costs and cost effectiveness.
510 Calculations of quality-adjusted life-years (QALYs) will be performed by multiplying health-
511 state utility (measured using the EQ-5D Index score) by time spent in this specific health state.⁷³
512 ⁷⁴ In addition, calculations of the incremental cost effectiveness ratio (ICER) will be made as
513 the difference in the cost of two interventions divided by their affect.⁷⁵
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515 **Data monitoring**

516 Trial data will be monitored and regularly assessed for integrity and errors. All data monitoring
517 will be performed completely independently from sponsors and competing interests. An
518 independent data monitoring committee (DMC) will be appointed to critically review data
519 safety in the trial. Veronica Sjöberg (VS) will be responsible for the monitoring of all data
520 collected in the pilot study. A data management plan (DMP) will be outlined by the first author
521 (VS) and implemented by the principal investigator (LV) to ensure sound data structure (folder
522 structure, file naming, organization), and data storing.

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DISCUSSION

526 This article describes a protocol for a R-RCT trial of a novel e-Health intervention. The trial
527 will contribute to establish evidence for the effectiveness of individualized physical activity and
528 exercise among patients living with chronic pain and participating in IPRP. The methodology
529 and feasibility of the trial will be evaluated in an early phase by a pilot study, which will
530 contribute to optimized robustness of the subsequent R-RCT-trial and enable further refinement
531 of the intervention. Despite many efforts have been taken to develop health promoting
532 interventions for this patient group, it is rare that such interventions are systematically
533 developed and includes both objective and patient reported outcomes. The potential
534 measurement errors of self-reported constructs of physical activity are well known and this trial
535 contributes to introducing objective measurement methods in a clinical context. The eVIS-
536 intervention is developed according to MRC's framework for development and evaluation of
537 complex interventions.²⁹ It consists of both objectively measured physical activity level
538 (steps/day), and patients own reports on pain intensity, interference on daily activities and
539 individual daily activity goal, all joint in the web application named PATRON. This enables
540 known facilitating mechanisms for behavior change (e.g., as self-monitoring etc.)³² whilst
541 including several core outcome domains.^{34 76} The agile development process has enabled
542 continuous evaluation and improvement of the intervention based on data provided from
543 patients, clinicians, and researchers in different fields. Objectively measured constructs of
544 physical activity by Fitbit devices have been criticized due to lack of accuracy of measurements
545 of time spent in moderate to vigorous physical activity (MVPA) where various devices
546 overestimate the measurement⁷⁷. Preceding this study, our research group performed an

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3 547 evaluation of Fitbit Versa's criterion validity of measuring energy expenditure, heart rate and
4 548 step count among patients living with chronic pain. Results confirmed previous study results in
5 549 adjacent patient groups reporting that Fitbit Versa systematically overestimated energy
6 550 expenditure, however, measurements of step count both in laboratory and in free-living setting
7 551 were valid.³³

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12 552 In this trial participants will be recruited at IPRP units nationally distributed. All units adopt to
13 553 core IPRP content regarding modalities, but it is well-known that both duration and intensity
14 554 greatly vary which may limit generalization of the results.²⁵ To achieve maximum external
15 555 validity, we will collect data on the specific characteristics of all participating units and include
16 556 this in the final analyses. Unknown engagement in other out-patient treatments under study
17 557 period, may be a potential source of bias, though data on in-patient engagement will be known
18 558 through registry data from the National Patient register. Non-adherence to daily self-report in
19 559 PATRON can be expected and may differ between intervention- and control group (differential
20 560 missing). Measures will be taken to optimize adherence in both groups such as regular auditing
21 561 of registrations in PATRON followed by personal emails with encouragement to follow
22 562 protocol. To minimize the risk of contamination between groups, and to ensure that the study
23 563 will be carried out in compliance with the study protocol, all participating staff at the IPRP units
24 564 will participate in a study-specific course prior entering the trial. Results generated from the
25 565 pilot study and the subsequent effectiveness trial will inform pain management field with new
26 566 knowledge on eVIS's potential to increase pain rehabilitation program's effectiveness by
27 567 individualized physical activity levels among patients living with chronic pain.

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42 43 569 **Harms and adverse events**

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45 570 Participating patients and healthcare staff at the participating IPRP units will be encouraged to
46 571 report any adverse events such as unexpected side effects or symptom deterioration,⁷⁸ which
47 572 will also be reported to the Swedish Ethical Board Review.

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52 53 574 **Ethics and dissemination**

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55 575 The trial is prospectively registered in ClinicalTrials.gov (trial registration number
56 576 NCT05009459) and was approved by the Swedish Ethics Review Board in May 2021 (Dnr
57 577 2021/02109). The trial will be conducted in compliance to the Helsinki Declaration.⁷⁹ Important

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3 578 protocol modifications will be communicated to the Swedish Ethics Review Board as well as
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5 579 to all participating IPRP units and participants. To protect confidentiality, all data will be coded
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7 580 by an individual code, and the encryption key will be stored separately. Data will be stored at
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9 581 an intended project server at Dalarna University, which is secured by regular backups. No
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11 582 unauthorized persons will have access to data, e.g., data will only be accessible by researchers
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13 583 in the trial after approval from the principal investigator. Results of the pilot study and the main
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15 584 trial will be submitted for publication in peer-reviewed journals and communicated in national
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17 585 and international research networks, as well as in relevant clinical settings, including patient
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19 586 associations.

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23 **Author contribution statement**

24 589 LV and BÄ are responsible for the conception of the trial. LV is the principal investigator and
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26 590 is involved in all methodological decisions. VS, ET, AM, JW, RLM, BÄ, MH, MB, and LV all
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28 591 contributed to study design and were all involved in the development processes (the evaluation
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30 592 of criterion validity of the wrist-worn activity tracker and the evaluations of the content validity
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32 593 and clinical feasibility) of the intervention. RLM performed the preliminary power and sample
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34 594 size calculations and was involved in all associated decisions. VS wrote the first draft of the
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36 595 manuscript, was responsible for revising the manuscript's intellectual content based on all co-
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38 596 authors conscientious input and conducted manuscript revisions according to peer-reviewer's
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40 597 comments. All authors read and approved the final version of the manuscript. For this article,
41
42 598 no ghost authors, guest authors, or professional writers have or will be used. Author eligibility
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44 599 is and will be based upon the ICMJE Recommendations for the Conduct, Reporting, Editing,
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46 600 and Publication of Scholarly work in Medical Journals.

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50 **Trial status**

51 602 Recruitment of participants was initiated late October 2021 and the trial is planned to be
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53 603 completed on 31 December 2024.

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57 **Funding**

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3 607 This trial is funded by the Swedish Research Council for Health, Working Life and Welfare
4 608 (2017-00491), the Research Council (2018-02455), the Swedish Association for Survivors of
5 609 Polio, Accident, and Injury (2020-03), and research funding from Dalarna University (No grant
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7
8 610 number). The funders had no role in study design and will have no role in any part of the
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10 611 implementation of the study or the reporting of its results.
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613 **Competing interests**

614 None declared.

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616 **Access to data**

617 This is a protocol describing a trial design. All authors will have access to the final trial
618 dataset.

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620 **Supplementary files:**

- 621 - Completed SPIRIT 2013 Checklist
- 622 - Patient consent form (in Swedish)

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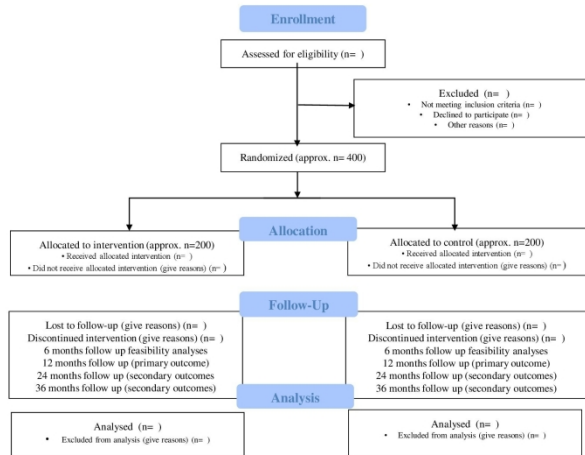


Figure 1. CONSORT 2010 Flow diagram chart of study design and enrollment.

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Figure 2. Schematic illustration of the eVIS-intervention's three elements: i) the data collection element of physical activity level (steps/day), patient-report of pain interference on daily activities, pain intensity and pharmacological consumption, ii) the visualisation element of collected data in different graphs and compilations of data, and iii) the communication element.

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

Section/ item	Item No	Description	Page number in Main document (clean copy)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 21
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	22 (not contact info)
	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	22
	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)	19
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	16-17
Objectives	7	Specific objectives or hypotheses	5-6, 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)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11 a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11 b	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)	18-19
	11 c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	18-19
	11 d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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	9-16 Table 1 Table 2

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)	Table 1 Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 18-19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			15
Sequence generation	16 a	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	17-18
Allocation concealment mechanism	16 b	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	17
Implementation	16 c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	17 a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17 b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18 a	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	Table 1 9-16
	18 b	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	18-19
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	20
Statistical methods	20 a	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	19
	20 b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20 c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring	21 a	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	20
	21 b	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	19
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	21

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
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)	21-22
Consent or assent	26 a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26 b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	20
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	No
Dissemination policy	31 a	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	21-22
	31 b	Authorship eligibility guidelines and any intended use of professional writers	22
	31 c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary files [In Swedish]
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	NA

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