UCR
Uppsala Clinical Research Center

CLINICAL TRIAL PROTOCOL

Improved treatment for patients with long-term opioid therapy for non-cancer pain in primary care

Opi-Prim

Trial Design
Pragmatic controlled before-and-after study

Trial No:	*Trial will be registered after feasibility study at clinicaltrials.gov*
UCR Project No:	

Sponsor:	*Region Uppsala, Primary Health Care (Nära vård och hälsa, NVH)*
Sponsor Representative:	*Louise Hamark, Director of Administration NVH*
Co-Sponsor:	*Uppsala University (UU), Department of Pharmacy*
Co-Sponsor Representative:	*Mats Karlsson, Head of Department of Pharmacy UU*
Coordinating Investigator:	*Anna Svensson, MD*
Principal Investigator(s):	*Magnus Peterson, MD, PhD (NVH)*

The following amendment(s) is/are accompanying the protocol:

1. Date: Contact Person *(initials)*:

2. Date: Contact Person *(initials)*:

Trial number:
Title of trial: Improved treatment for patients with long-term opioid therapy for non-cancer pain in primary care
Trial ID: Opi-Prim
Short background/Rationale/Aim: The evidence for prescribing opioids to patients suffering from chronic non-cancer pain is weak, and using opioids in these circumstances is questionable. Swedish primary health care is responsible for about one-third of all first-time opioid prescriptions and has the highest rate of prescription renewals for opioids. The decision for long-term opioid therapy (LTOT) should rest on an accurate pain analysis and should result in an individualized assessment where the risks of LTOT are set against the impact on quality of life that living with long-term pain entails. Multi-professional interventions and a person-centered approach are recommended for chronic non-cancer pain. Although pharmacists in primary health care have been established internationally with successful examples related to LTOT, their role in Swedish primary care and the management of chronic non-cancer pain remains to be studied. Currently, it is unclear which interventions are effective in reducing inappropriate LTOT and which alternative interventions are suitable for patients who are currently receiving LTOT. The involvement of a care manager in the patient´s care has shown promising results regarding quality of care for other long-term conditions, for example depresssion. In Region Uppsala, clinical pharmacists havte recently been employed in primary health care, but it is unclear what their tasks and responsibilities are and how to best make use of their competence. It is therefore relevant and justified to investigate a new person-centered team-based approach including care manager and pharmacist to optimize the management of pain in patients with chronic non-cancer pain in Swedish primary care. This project aims to reduce inappropriate LTOT and optimize pain management in patients with LTOT for chronic non-cancer pain in primary care through a new person-centered and team-based approach.
Primary objective: To investigate the effects of a new person-centred and team-based approach on pain interference in patients with LTOT for chronic non-cancer pain in primary care
Secondary objectives: To investigate the effects of a new person-centred and team-based approach in patients with LTOT for chronic non-cancer pain in primary care on secondary endpoints and to perform a process evaluation alongside the trial, including a feasibility study.
Primary endpoint: Pain interference measured after 3, 6, and 12 months
Secondary endpoints: Pain intensity, symptoms of depression, symptoms of anxiety, patient satisfaction, health-related quality of life, opioid use (morphine equivalents) and symptoms of withdrawal. All secondary endpoints will be measured after 3, 6, and 12 months.
Trial design and setting: This study is a controlled before-and-after study that has been designed, and will be reported, according to the CONSORT guidelines. Participation will be during 52 weeks (12 months). This study will be conducted at eight healthcare centres in Region Uppsala. At four of the healthcare centres, a new person-centred team-based treatment model including pharmacists (intervention) will be implemented. Prerequisites for these healthcare centres are the accessibility of at least one person of each healthcare profession: pharmacist, general practitioner (GP), psychologist (or social worker) and physiotherapist, where one of these (or a rehabilitation coordinator or a nurse) takes the role of care manager. Healthcare personnel will receive special training in managing patients with chronic pain before the study. In addition, four control healthcare centres without a pharmacist will be matched with the intervention healthcare centres according to geographic area (urban, suburban, rural), socioeconomical setting and the size of the centres (number of listed patients). No specific efforts of implementation will be made in these control centres. Prior to the full trial, a feasibility study will be conducted at one intervention centre and one control centre with 12 weeks follow-up per participant.

Trial population:

Eligible patients in the study are adult (>18 years) patients with their main healthcare contact at one of the healthcare centres included in the study, who have received long-term opioid therapy (> 90 days) for chronic pain prescribed by a GP during the recent 12 months, according to the primary healthcare quality indicator ”Lm12alla”.

Number of subjects:

Sample size calculations resulted in at least 55 participants per treatment group (110 in total) needed to measure a clinically relevant difference in the primary outcome. For the feasibility study, 5-10 participants per treatment group will be included.

Inclusion criteria:
Adult (>18 years) patient, main health care contact at one of the health care centres included in the study, received more than the equivalent of 90 days or more prescription of opioids for chronic pain made by GP during the recent 12 months, according to the primary healthcare quality indicator: ”Lm12alla”.

Exclusion criteria:
No current opioid use, been referred to a pain clinic or something similar during the last 6 months, is not able to speak Swedish, and is not able to provide informed consent.

Intervention:

Patients with pain > 3 months and treatment with opioids at the intervention healthcare centres who have agreed to participate will start their inclusion in the person-centred team-based treatment immediately at the index appointment. The intervention will be performed by healthcare personnel (GP, clinical pharmacist, physiotherapist and psychologist) who receive two half-days of training in person-centered care and managing patients diagnosed with chronic pain, before the study starts. The intervention will then consist of three phases.

Phase 1 (investigation and assessment, week 1-3):

- A medication review focusing on pain, sleep and depression/anxiety disorders according to the Swedish National Board of Social Affairs and Health HSLF-FS 2017:37 by a pharmacist.
- A thorough pain analysis by a GP according to existing guidelines including duration of pain, pain localization and pain mechanisms.
- A visit to a physiotherapist for evaluation and assessment of possible treatment regarding physical exercise/physical activities and related treatments.
- A visit to a psychologist for diagnostics and treatments regarding psychological and social factors.
- A visit to a care manager

Phase 2 (treatment plan, week 3-4):

- An appointment with all healthcare personnel involved in Phase 1 including the patient where an individualized rehabilitation plan is made based on the biopsychosocial model of pain and in accordance with the Swedish Medical Products Agency´s treatment recommendations.

Phase 3 (treatment and follow-up, week 4-24):

- Implementation of the individualized rehabilitation plan.
- Frequent follow-up contacts (1 per 1-3 weeks) by phone with an established contact person, i.e. care manager (pharmacist, physiotherapist, psychologist, rehabilitation coordinator or nurse).
  An appointment with all healthcare personnel involved in the rehabilitation plan, 3-4 months after the start of phase 2 to update the plan.

Control: Usual care at one of the control healthcare centres.

Ethical considerations: Ethical considerations have been made. All participants will provide written informed consent prior to trial participation. The feasibility study of this trial has received ethical approval from the Swedish Ethical Review Authority (registration number 2023-00313-01, date: 2023-04-23). Ethical approval will be sought for the final version of the trial protocol before the full trial can be conducted.
Trial period: Feasibility study: Q3 2023 – Q1 2024 Trial: Q2 2024 - Q4 2026

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2 LIST OF ABBREVIATIONS

List the abbreviations used in the protocol. At first appearance in the text, the abbreviated term should be spelled out and the abbreviation should be indicated in parentheses. Define the specialised or unusual terms used in the protocol.

AE	Adverse Event
ASR	Annual Safety Report *(replacing the previous DSUR)*
CRF	Case Report Form
CTR	EU Regulation 536/2014, also called CTR, Clinical Trials Regulation
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

3 PROJECT ORGANIZATION

This project is a collaboration between Region Uppsala, Primary Health Care (Nära vård och hälsa, NVH) and Uppsala University (UU) for which a collaborative agreement has been signed. The project organization is managed by a research group consisting of researchers and clinicians affiliated to either one of or both organizations, see below. A patient council for the study has been formed, consisting of patient representatives from three patient organizations. The patient council is regularly updated about the project plans and provides advice and proposals to the plans. The research group then needs to follow the patient council's advice or proposals, or explain why the advice/proposal are not being followed. The clinical trial or intervention study itself will be performed within NVH. UCR provides project planning and data management support and advice to the project organization. UCR is also planned to be involved in the statistical analysis (both planning and conducting).

Research group	Magnus Peterson, PI NVH Anna Svensson, Coordinating investigator NVH Sofia Kälvemark Sporrong, UU Thomas Kempen, UU Hanna Ljungvall, UU Lena Katila, UU Johanna Hellström, NVH
Patient Council	The Patient Council consists of members of the Fibromyalgia association in Uppland (part of the Swedish Fibromyalgia association; *Fibromyalgiföreningen*), Rheumatism district Uppsala län (part of the Swedish Rheumatism Federation; *Reumatikerförbundet*) and the Swedish Endometriosis association (*Endometriosföreningen)*. The representatives are: Elisabet Andersson Birgith Eklund Annika Gunnarsson Ewa Larsson Anna Röjmarker Marielle Sandstedt

4 BACKGROUND INFORMATION

Opioids are crucial for treatment of severe acute pain, during surgery, after trauma or when treating cancer related pain(1,2). However, the evidence for good pain relief for patients suffering from chronic non-cancer-pain is weak and using opioids during these circumstances is questionable(1,3,4). Although the opioid-prescription in Sweden is not anywhere near that in North America, there has in Sweden in recent years, been a shift from weak opioids (e.g. tramadol) to stronger opioids (e.g. oxycodone)(2,2,5). Furthermore, primary health care in Sweden is responsible for about one third of all first-time opioid prescriptions and has the highest rate of prescription renewals for opioids(2). There are indications of patients in primary health care, for which opioid prescriptions are renewed even though the indication for opioid treatment is doubtful, where a plan for the dose and duration of opioid prescription is missing and with multiple prescribers for their opioids.

The decision for long-term opioid therapy (LTOT) should rest on an accurate pain analysis based on the biopsychosocial model and should result in an individualized assessment where risks of LTOT are set against the impact on quality of life the living with long-term pain entails(3–11). Multi-professional and person-centred interventions are recommended for chronic non-cancer pain(7). However, opioid therapy may reduce patient motivation for such interventions(12–14). Currently, it is unclear which interventions are effective in reducing inappropriate LTOT and which alternative interventions are suitable for patients that are currently receiving LTOT(15). International research shows that active tapering of opioids with team-based interventions can be implemented successfully (8,12,16), but forms for implementing this in outpatient care in Sweden need to be developed and evaluated.

Clinical pharmacists in primary health care have been established internationally, for example in the UK, but are so far uncommon in the Swedish primary health care system(17). There are many international examples of successful collaboration with clinical pharmacists to reduce LTOT among patients suffering from chronic pain but their role in Swedish primary care and the management of chronic non-cancer pain remains to be studied(17). In Region Uppsala, clinical pharmacists have recently been employed in primary health care, but it is unclear what their tasks and responsibilities are and how to best make use of their competence. This provides an opportunity to investigate their potential role in reducing inappropriate LTOT in Swedish primary health care.

Primary healthcare providers in Region Uppsala are referred to the document “Pain-chronic pain, systematic investigation Primary health care” (18)which is based on national assessment and treatment guidelines.
How these guidelines are implemented in primary health care is unclear. Preparatory studies to this project show a lack of routines for person-centred and team-based work as well as lack of routines of opioid tapering, and suggests that patients treated with opioids appear to be excluded from multi-professional care. The GPs in our preparatory interview study signalled that patients treated with opioids would need

more extensive care to taper their medication. The pharmacists in the focus group interviews reported a desire to be more involved in the clinical work in general and opioid treatment in particular in patients with chronic pain. Other healthcare personnel at the healthcare centres requested more insight into each other´s work and improved teamwork. It is therefore relevant and justified to investigate a new person-centred team-based approach that includes pharmacist involvement to optimize the management of pain in patients with chronic non-cancer pain in Swedish primary care.

5 TRIAL OBJECTIVES

The overall aim of this project is to reduce inappropriate LTOT and to optimize pain management in patients with LTOT for chronic non-cancer pain in primary care through a new person-centred and team-based approach.

5.1 PRIMARY OBJECTIVES

The primary objective is to investigate the effects of a new person-centred and team-based approach on pain interference in patients with LTOT for chronic non-cancer pain in primary care.

5.2 SECONDARY OBJECTIVES

The secondary objective is to investigate the effects of a new person-centred and team-based approach in patients with LTOT for chronic non-cancer pain in primary care on secondary endpoints and to perform a process evaluation alongside the trial, including exploring the feasibility of the study design.

6 TRIAL DESIGN AND SETTING

6.1 TRIAL OUTLINE

The trial is a controlled before-and-after study that has been designed, and will be reported, according to the applicable CONSORT guidelines (19). No randomization or blinding will be involved. A feasibility study will be conducted prior to the full trial.

6.2 SETTING AND SITE SELECTION

This study will be conducted at eight healthcare centres in Region Uppsala, NVH. At four of the healthcare centres a new person-centred team-based treatment model including pharmacists (intervention) will be implemented. Basic conditions for these healthcare centres are the accessibility of at least one person of each healthcare profession: pharmacist, GP, psychologist and physiotherapist, where one of these (or a rehabilitation coordinator or a nurse) takes the role of care manager. Healthcare personnel will receive special training in person-centered care and managing patients diagnosed with chronic pain before the study. In addition, four control healthcare centres without a pharmacist will be matched with the intervention healthcare centres

according to according to geographic area (urban, suburban, or rural) and the size of the centres (number of listed patients). No specific efforts for implementation will be made in these control centres.

Patients being participants at the intervention health care centres will start their inclusion in the new person-centred team-based treatment immediately at the index appointment and up to 24 weeks. Participants at the control centres will receive usual care.

6.3 STAFF TRAINING AND IMPLEMENTATION

All personnel involved in the study (GPs, physiotherapists, psychologists (or social workers), pharmacists including the care manager) will participate in two half day-sessions of training. In addition to the two half-day sessions, the care managers (i.e. one in the team above, a rehabilitation coordinator or a nurse) will receive additionally two hours of training in providing person-centred and team-based care. The education focuses on optimized diagnostics and treatment of pain according to the biopsychosocial model including pharmacological aspects. The training includes interactive and case-based lectures on chronic pain, opioids, person-centred care and teamwork. The training will be held locally at each healthcare centre and be arranged by persons from the research group in collaboration with a psychologist and a physiotherapist from the Pain Clinic, Uppsala Academic Hospital. Further, the training will include information about the study. To ensure an adequate pain analysis the personnel involved will also receive instructions about how to document relevant findings in the patients´ electronic health recordings. To avoid duplication of work and overlaps at the various care visits, checklists will be created for each profession respectively, to result in coordinated documentation.

It is the responsibility of the investigators to ensure that all personnel involved in the trial are fully informed of all relevant aspects of the trial, including detailed knowledge of and training in all procedures to be followed.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 SUBJECT INCLUSION CRITERIA

Eligible patients in the study are adult (>18 years) patients with their main healthcare contact at one of the healthcare centres included in the study who have received the equivalent of 90 days or more prescription of opioids for chronic pain made by GP during the recent 12 months, according to the primary healthcare quality indicator ”Lm12alla” *(20)*, and provided written informed consent to participate.

7.2 SUBJECT EXCLUSION CRITERIA

Patients will be excluded if:

- They have been referred to a pain clinic (either at hospital or multimodal rehabilitation in primary care) within the last 6 months

- They have no current opioid use, severe cognitive dysfunction, e.g., suicidal ideation, psychotic symptoms, or dementia, that prevents informed consent.
- They use their opioids for cancer pain

7.3 WITHDRAWAL OF SUBJECTS

Subjects have the right to withdraw from the trial at any time without prejudice to future treatment. In addition, the subject may be withdrawn at the investigator's discretion at any time if it is in the subject's best interest. In the event that the subject drops out or withdraws from the trial, the reason for study discontinuation will be recorded in the CRF.
Reasonable efforts should be made to contact any subject lost to follow-up after end of treatment in order to complete assessments and retrieve any outstanding data.

Specific criteria for withdrawal are:
• Subject's decision
• Investigator's discretion
• Subject lost to follow-up/non-attendance
• Intercurrent illness

7.4 SCREENING AND RECRUITMENT OF SUBJECTS

Patients with prescription of opioids will be identified based upon a register of primary health care indicator: "Lm12alla"*(20)*. The list of possible subjects will be randomized and 10 at a time will be contacted, informed about the study and asked about participation via 1177 and a letter and, if no answer, by phone after a few days. Patients fulfilling the criterions of inclusion will be informed by phone and those who express interest in participating will be invited to a first visit at the health care center (index appointment).

The following information will be recorded in the participant's electronic health record (Cosmic): Trial name, date when signed informed consent was obtained, PI's contact information.

8 TREATMENT OF SUBJECTS

8.1 PHASE 1 (INVESTIGATION AND ASSESSMENT, WEEK 1-3):

- A medication review focusing on pain, sleep and depression/anxiety disorders according to the Swedish National Board of Social Affairs and Health HSLF-FS 2017:37 will be implemented by a pharmacist (21). This includes patient consultation to reconcile what medications the patient is using and has used before in relation to pain, sleep and depression/anxiety, and to identify potential drug-related problems (non-compliance, side effects, interactions, etc.).
- A thorough pain analysis is conducted by a GP according to existing guidelines including duration of pain, pain localization and pain mechanisms (4).

- A visit to a physiotherapist for evaluation and assessment of possible treatment regarding physical exercise/physical activities and related treatments.
- A visit to a psychologist for diagnostics and treatments regarding psychological and social factors.

- A person-centred approach is adopted in all patient consultations. In person-centred care the patient narrative is essential to invite the patient to a partnership including the person, not only the disease but how the disease affects the individuals' life as a whole. Decision on a rehabilitation plane should rest on a partnership between the person and health care, which includes sharing of information and a shared decision-making about treatment. To ensure a safe partnership, the patient´s narrative but also the responsibilities of both parties (patient and health care) as well as the rehabilitation plane is documented and transparent for all parts(22).

Phase 2 (treatment plan, vecka 3-4):

- An appointment with all healthcare personnel involved in Phase 1 including the patient where an individualized rehabilitation plan is set up based on the biopsychosocial model of pain and in accordance with treatment recommendations in the national clinical knowledge support, including aims, interventions and a follow-up plan (4,23). The rehabilitation plan will be based on the patient´s needs and conditions (e.g., a plan of opioid tapering including follow-up by the pharmacist) and documented in the participant´s electronic health record by the care manager. The rehabilitation plan will be available to the participant through the electronic health record or printed out, based on what is suitable for the participant.

8.2 PHASE 3 (TREATMENT AND FOLLOW-UP, WEEK 4-24):

- Implementation of the individualized rehabilitation plan.
- Frequent follow-up contacts (1 per 1-3 weeks) by phone with an established care manager, i.e. contact person (one of the team staff or a rehabilitation coordinator or a nurse) with a person-centred approach. The care manager´s responsibility will be to ensure that health services meet their commitments in the care plan and to serve as a main point of contact between participants and health care.
- An appointment with all health care personnel involved in the rehabilitation plan, 3-4 months after the start of phase 2 to update the plan.

8.3 CONTROL: USUAL CARE

Participants in the control healthcare centres will receive usual care. This may include appointments and treatment by a GP, nurse, physiotherapist and/or psychologist. No pharmacist will be working at the healthcare centre. However, NVH does provide centralized medication review services to all primary healthcare centres in Region Uppsala. Any healthcare professional may request a medication review by a pharmacist on a work-from-home basis as part of usual care.

9 ENDPOINTS AND OUTCOME MEASURE ASSESSMENT

9.1 PRIMARY ENDPOINT

Pain interference as measured with the Brief Pain Inventory – Short Form (BPI-SF)(24), question number 9 a-g. The primary outcome measure will be the difference in pain interference after 3, 6 and 12 months. A text message will be sent one week in advance to the digital link, and in case of missing data, a telephone call will be made as a reminder

9.2 SECONDARY ENDPOINTS

Secondary endpoints will be pain intensity (as measured with BPI-SF, question number 3-8), symptoms of depression (Patient Health Questionnaire-9; PHQ-9), symptoms of anxiety (General Anxiety disorder-7; GAD-7), patient satisfaction (Patients´ Global impression of Change; PGIC), quality of life (EQ-5D-5L), opioid use (morphine equivalents) and symptoms of withdrawal (Short Opioid Withdrawal *S*cale; SOWS). All outcomes in the intervention study are based on internationally recognized IMMPACT-guidelines(25). Secondary endpoints will be measured after 3, 6 and 12 months, including pain interference at these time points.

10 PROCESS EVALUATION

10.1 FEASIBILITY STUDY

The aim with the process evaluation unlike the feasibility is to explore the process and not only the feasibility. If the process is performed as planned, why the process works or not and in which context. What can improve to get a more optimized intervention. Factors related to the implementation of the intervention will be investigated. This will include individual interviews with all patients and one semi-structured follow-up focus groups with health care staff. Questions about the participants´ experience, success factors, barriers and suggestions for improvement are made by the researchers, which are then reported in text and tabular form. To examine the process during the intervention, semi-structured observations will be carried out for all care visits. Person-centred and team-based care are two factors to observe during the study. The result will be presented in text and tabular form. Patient recruitment data, completed intervention components data in term of fidelity, adaption, dose, reach and strength will be presented with descriptive statistics. The number and reasons for drop outs will be reported and analyzed descriptively. An expected duration of patient recruitment for the intervention
study will be calculated based on the feasibility. Based on the above results, the study protocol for the planned intervention study will be updated.

10.2 PROCESS EVALUATION DURING TRIAL

Similar to the feasibility study data collection and analysis above, a process evaluation according to the British Medical Research Council framework will be conducted to analyse implementation, protocol adherence and participants' experience and opinions(26,27) . The process evaluation includes evaluation of the training from the perspective of the healthcare staff in questionnaire and interview form. Furthermore, a continuous follow-up of the three phases of the intervention will be done, above all if and when they are carried out (protocol adherence) and how they work by performing observations. In addition, questionaries' and focus groups, or semi-structured interviews, will be held with the healthcare staff who carried out the intervention, as well as the operations manager at the participating healthcare centres. This is to identify success factors and areas for development. A heterogeneous sample of patients will be interviewed within one month of undergoing the intervention. These interviews deal with the patients' experiences of the intervention, as well as their suggestions for further development and implementation of the intervention. The process evaluation will be analysed descriptively and through qualitative content analysis as above. The process evaluation for the trial may come and change after the feasibility study.

11 TRIAL ASSESSMENTS AND PROCEDURES OVERVIEW

All trial assessments and procedures are viewed in Figure 1.

Time (months)	*Index (0)*	*1,5*	*3*	*6*	*12*
Inclusion:					
Screening in- and exclusion criteria	X				
Informed consent	X				
Interventions:					
Intervention: phase 1-3	♦—	—	—	—♦	
Control: usual care	♦—	—	—	—♦	
Data collection (intervention study):					
Baseline characteristics	X				
Pain interference (BPI-SF)	X		X	(X)*	(X)*
Pain intensity (BPI-SF)	X		X	(X)*	(X)*
Symptoms of depression (PHQ-9)	X		X	(X)*	(X)*
Symptoms of anxiety (GAD-7)	X		X	(X)*	(X)*
Patient satisfaction (PGIC)			X	(X)*	(X)*
Quality of life (EQ-5D-5L)	X		X	(X)*	(X)*

Self Efficacy(PSEQ-2)	X		X	(X)*	(X)*
Data collection (process evaluation):					
Process outcomes (intervention fidelity)		X	X	(X)*	(X)*
Interviews (patients)				X	
Focus group discussion (not all participants)				X	
Observation	◆———	———	———◆		

Figure 1. Schedule for inclusion, interventions and data collection according to the SPIRIT statement.

* Study participants in the feasibility study will possibly be asked to be part of the later intervention study where follow-up also takes place after 6, 9 and 12 months. This requires new informed consent from the study participant. BPI-SF = Brief Pain Inventory - Short form; EQ-5D-5L = EuroQol 5-dimension 5-level version; GAD-7 = General Anxiety Disorder-7; PGIC = Patients' Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; SOWS = Short Opiate Withdrawal Scale.

12 STATISTICS AND DATA MANAGEMENT

12.1 DATA MANAGEMENT

Data management will be handled as described in separate Data Management Plan

12.2 STATISTICAL ANALYSIS

Primarily, statistical analyses will be conducted based on intention-to-treat (ITT) principle. Patient characteristics will be presented descriptively per treatment group. The average value of pain interference and quality of life in accordance with BPI-SF will be calculated and analyzed separately per treatment group. The difference between the intervention group and the control group will be analysed through regression analysis including the ability to adjust for base line data and other covariates. ANOVA for repeated measurements will be used to analyse the average differences between the two groups until 12 months. The number of dropouts will be reported and analysed descriptively. All randomized study subjects completing the whole study period (complete cases) will be analyzed Per Protocol. For a specific analysis, study subjects with missing data on any of the variables in the model will be excluded from the analysis. Analyses of this population is seen as sensitivity analysis to investigate whether conclusions are sensitive to assumptions regarding the pattern of missing data. All analyses will be described in a prespecified statistical analysis plan (SAP). Significance tests will be two-tailed and a p-value less than 0.5 will be interpreted as significant. All statistical analyses are carried out in an SPSS, SAS or R. The process evaluation is analysed descriptively as well as through a qualitative thematic analysis.

12.2.1 ANALYSIS POPULATION

All eligible subjects will be included in the statistical analyses. Statistical analyses will be conducted based on intention-to-treat (ITT) principle.

12.3 DETERMINATION OF SAMPLE SIZE

The power calculation (and thus the sample size) is based on the assumption that the data are approximately normally distributed. We assume that the patient size in both treatment groups will be the same, 1:1. Based on previous studies and unpublished data from the U-PAIN cohort we assume that the baseline value (index visit) for the primary outcome is 6,0 in both treatment groups. We consider a difference in change of 1,0 between the groups at 12 months to be clinically relevant and assume that the standard deviation of the change is 1,43. To detect a difference of 1.0 in pain interference between the two groups with a power of 90% and a type-1 error of 5%, 46 participants in each treatment group is required. With regard to dropouts (20%) we aim for at least 55 participants per treatment group (110 in total). Based on the current patient count calculation (90% power and $\alpha = 0.05$ to detect a 1.0 difference in the primary outcome measure) based on previous studies (16) and data from the U-PAIN cohort (28), we aim in the intervention study for at least 55 study participants per treatment group (110 in total).

13 ETHICS

13.1 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions.

The risks of participating in the project are considered low. Treatment and assessment of the study participants in the feasibility as well as in the intervention study will deviate from current practice and may affect the participant´s physical and psychological health. A reduction in opioids may become relevant among some of the study participants which may affect them and lead to temporary symptoms of abstinence and increased pain. However, it is important to emphasize that treatment and assessment will follow current guidelines of chronic pain and current guidelines of opioid tapering.

The participants in the study will be in a position of dependence on the healthcare providers. However, this will not significantly deviate to the patient-staff relation in usual care. Furthermore, the study participants will be informed both verbally and in writing that they may withdraw their participation from the study whenever they want and that a withdrawal will not affect the usual care provided.

The project may lead to improved treatment of chronic pain in primary healthcare. An ethical problem may appear if the intervention is effective, but resources are too demanding, or that it displaces resources from other patient groups. As in many other situations, priorities of healthcare resources must then be made according to resources available.

13.2 SUBJECT INFORMATION AND INFORMED CONSENT

It is the responsibility of the Investigator to provide each subject with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the trial. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to decide whether or not to participate in the trial. The written subject information must not be changed without prior discussion with the Sponsor.

The subjects will be notified of their voluntary participation and of their freedom to withdraw from the trial at any time and without giving any particular reason. Subjects must also be informed that withdrawing from the trial will not affect their future medical care, treatment or benefits to which the subject is otherwise entitled.

The Investigator is responsible for obtaining written Informed Consent from all subjects (or their legally acceptable representatives and/or witnesses, where applicable) prior to enrolment in the trial.

The subjects will consent to:
- Participating in the trial.
- Sponsor representatives and regulatory authorities gaining full access to electronic health records, to verify the accuracy of the data collected in the trial.
- Recording, collection and processing of data and storing of data in a database.

It should be clearly stated that the data will not identify any subject taking part in the trial, in accordance with the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR).

A copy of the subject information and the Informed Consent form will be given to the subject. The Investigator (or the designated representative) who gave the verbal and written information to the subject will sign the Informed Consent form. The Investigator will file the signed Informed Consent forms in the Investigator's File for possible future audits and inspections.

13.3 ETHICAL REVIEW OF THE TRIAL

The feasibility study of this trial has received ethical approval from the Swedish Ethical Review Authority (registration number 2023-00313-01, date: 2023-04-23). The final version of the trial protocol and subject information must be approved by the Swedish Ethical Review Authority before the full trial can be conducted.

14 DATA HANDLING AND RECORD KEEPING

14.1 CASE REPORT FORMS

Case report forms will be completed for each included subject as detailed in the Data Management Plan (Appendix XX) The subject's identity must always remain confidential.

15 INSURANCE

The subjects are insured through the Swedish Social Insurance Agency (Försäkringskassan) and the Swedish Patient Insurance (Landstingens Ömsesidiga Försäkringsbolag) as part of standard health care.

16 TRIAL END OR TERMINATION

16.1 END OF TRIAL

The trial ends when the last subject has completed the last follow-up.

16.2 CRITERIA FOR TERMINATION OF THE TRIAL

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all CRFs must be completed as far as possible.

The trial can be prematurely discontinued in the following cases (examples):

- Trial protocol is difficult to cope with.
- Recruitment of eligible subjects is far too low.
- Unacceptable low Investigator, Sponsor or subject compliance.
- Critical change in personnel, administrative or scientific standards at the Sponsor or at the trial centre.
- No significant result will be obtained as anticipated.

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18 APPENDICES

Include the following optional appendices, if applicable: