BMJ Open U-PAIN cohort study among patients with chronic pain in specialised pain care: a feasibility study

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ABSTRACT

Objectives To examine acceptability of study participation and feasibility of (1) recruitment, (2) data collection and (3) outcome measures for the prospective U-PAIN cohort.

Design Internal feasibility study of a prospective cohort.

Participants and setting 64 patients, ≥18 years, with chronic pain at a multidisciplinary pain centre at a university hospital in Sweden.

Outcome measures Acceptability of study participation was measured with a study-specific 10-item Likert scale. A score <3 was considered feasible, for the two items that assessed respondent burden a higher score indicated lesser participant burden and a score >3 was feasible. Recruitment was assessed by participation rates at baseline and retention at the 1-year follow-up, with threshold values for feasibility at 75% and 80%, respectively. Data collection and outcome measures were examined by completions rates of study procedures (90% was considered feasible), sample scores, internal consistency (κ>0.70 was considered feasible), and agreement between self-reported data and data retrieved from medical records on opioid use (ICC or κ>0.60 was considered feasible).

Results Acceptability for study procedures was feasible, but participation rates were low: 25%. The retention rate at 1-year follow-up was 81% for those included in the feasibility study, that is, filling out computerised patient-reported outcome measures, and 65% for those using paper and pencil format. The completion rates for the different data collection methods ranged from 83% to 95%. Agreement between self-reported opioid use and prescribed dose and between opioid use disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and clinical International Classification of Diseases-10 (ICD-10) diagnoses for opioid dependence were almost perfect (κ=0.91 and κ=0.90, respectively).

Conclusions This feasibility study has helped to explore and improve methods for recruitment, data collection and use of outcome measures for the U-PAIN cohort. Low participation rate and high refusal rate at baseline is a challenge that needs to be further addressed.

BACKGROUND

This study concerns the acceptability and feasibility of the U-PAIN cohort, a prospective clinical cohort study with a target number of 1000 patients with chronic pain, that is, pain >3 months. For the planning of the U-PAIN cohort, it was important to investigate feasibility of the recruitment strategies, data collection methods and outcome measures, described in table 1.

The overall aim of the U-PAIN cohort is to identify predictors for risks and benefits associated with chronic opioid therapy (COT), here defined as regular use of opioids >3 months. The project includes a cross-sectional study of baseline characteristics of non-opioid users and opioid users, and a prospective, longitudinal cohort study over 5-years with endpoint measures every 12 months to prospectively identify patterns and trajectories of opioids use. This includes initiation and discontinuation of opioids, dose, duration, way of administration and type of opioid, to establish predictors of different courses of opioid use, including: (1) Non-adherent or aberrant opioid use, here defined as opioid use disorder (OUD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and (2) beneficial use, that is, increased ability to work, decreased pain disability, and improved health-related quality of life.

Harms and benefits of opioids for chronic pain remain unclear. Opioids may provide benefits in terms of pain relief and...
physical functioning, but the magnitude is likely to be small and decrease over time. Furthermore, COT is associated with dose dependent risk of adverse effects, for example, cognitive dysfunction, problematic opioid use and increased morbidity and mortality. 

There are methodological challenges in longitudinal studies of opioid use in patients with severe chronic pain. It remains unclear how to determine if a patient with chronic pain has a problematic opioid use, or what criteria should serve as gold standard in this context. This emphasises the importance of examining data collection and measures of problematic opioid use. Furthermore, patients may feel offended when asked about their opioid use, why both the methods chosen to assess opioid use, and the participant acceptability of these methods, needs to be evaluated. For the U-PAIN cohort study, OUD according to the DSM-5 criteria, described in figure 1, was chosen for defining problematic opioid use. However, interpreting function and opioid use in relation to pain severity remains complex, since loss of function can be related to both an increase in pain, as well as opioid-related problems, making it hard to distinguish if an individual meets the DSM-5 criteria for OUD or is using opioids appropriately for medical purposes.

Objectives
This study aimed to investigate the acceptability of study participation and feasibility of (1) recruitment, (2) data collection and (3) outcome measures of the U-PAIN cohort.

Research questions
► How do participants rate acceptability of study participation with regard to information about the study, access to computerised patient-reported outcome measures (PROMs), relevance of the research procedures, respondent burden and interactions with research staff?
► How feasible are the recruitment strategies with regard to recruitment rates and sample characteristics?
DSM-5 Opioid use disorder – Diagnostic criteria

1. Taking the opioid in larger amounts or for longer than you’re meant to.
2. Wanting to cut down or stop using opioids but not managing to.
3. Spending a lot of time getting, using, or recovering from use of opioids.
4. Cravings and urges to use opioids.
5. Not managing to do what you should at work, home, or school because of opioid use.
6. Continuing to use, even when it causes problems in relationships.
7. Giving up important social, occupational, or recreational activities because of opioid use.
8. Using opioids again and again, even when it puts you in danger.
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by opioids.
10. Needing more opioids to get the effect you want (tolerance). Do not apply under medical supervision.
11. Development of withdrawal symptoms, which can be relieved by taking more opioids. Do not apply under medical supervision.

Two or three symptoms indicate a mild substance use disorder; four or five symptoms indicate a moderate substance use disorder, and six or more symptoms indicate a severe substance use disorder. Items 10 and 11 are excluded if the drug is for medical use as prescribed.

ICD-10 Opioid dependence - Diagnostic guidelines

(a) a strong desire or sense of compulsion to take the substance;
(b) difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use;
(c) a physiological withdrawal state when opioid use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for opioids
(d) evidence of tolerance, such that increased doses of opioids are required in order to achieve effects originally produced by lower doses;
(e) progressive neglect of alternative pleasures or interests because of opioid use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
(f) persisting with opioid use despite clear evidence of overtly harmful consequences, such as, depressive mood states consequent to periods of heavy opioid use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

A definite diagnosis of dependence should usually be made only if three or more of the symptoms have been present together at some time during the previous year.

It is an essential characteristic of the dependence syndrome that either psychoactive substance taking or a desire to take a particular substance should be present; the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use.

This diagnostic requirement would exclude, for instance, surgical patients given opioid drugs for the relief of pain, who may show signs of an opioid withdrawal state when drugs are not given but who have no desire to continue taking drugs.

Figure 1  Opioid Use Disorder (OUD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and opioid dependence according to International Classification of Diseases, 10th Revision (ICD-10).

 ► How feasible are data collection methods with regard to completion rates?
 ► Are the outcome measures valid and reliable in this context and sample?

METHODS

Study design

This was an internal feasibility study of a prospective cohort, that is, the patients included in the feasibility study will also be included in the final U-PAIN cohort provided that no major changes are required regarding outcome measures and data collection. Baseline measures and end-point measures every 12 months during 5 years, for the U-PAIN cohort are described in table 1.

Participants and setting

The participants were recruited among individuals seeking treatment at a multidisciplinary pain centre at a university hospital in Sweden. The Pain Centre is a specialised secondary and tertiary care unit that accepts patients from all over Sweden, offering multidisciplinary inpatient and outpatient pain consultations and treatment.

Eligible participants were ≥18 years, competent in Swedish, with chronic pain, and able to provide informed consent.
considered feasible. Patients with ongoing, adjuvant or palliative cancer treatment were excluded.

The aim was to recruit 65 participants for this feasibility study. This was predicted to be adequate to investigate recruitment rates, ease of data collection and respondent burden, yet a large enough sample to assess feasibility for the full cohort study.

Patient and public involvement
No patient involved.

Procedures
Trained research staff screened for eligibility, recruited participants and collected data. Eligible individuals received written information about the study together with the invitation letter for the clinical consultation. The research staff phoned eligible individuals to inform them about the study. Individuals who expressed interest in participating were scheduled for a research visit in conjunction with their clinical consultation or inpatient stay at the Pain Centre. The research visit took between 90 min and 2 hours. Prior to the clinical consultation or inpatient programmes, patients filled out an online questionnaire comprising questions regarding demographic and 12 computerised PROMs, accessed through a secure personal log in on the Swedish Healthcare Guide’s digital platform. The PROMs were used for clinical purposes and as research data for those who consented study participation. Patients who did not use the Swedish Healthcare Guide’s digital platform were offered paper and pencil versions of the PROMs and were excluded from the feasibility study but still eligible for the cohort study. Items in the computerised PROMs were mandatory to fill out, with only a few exceptions described in the ‘Measures’ section. All participants provided written and informed consent before the research visit where they completed the structured interviews, physical performance tests, filled out six additional computerised study specific PROMs, and provided blood samples, as described in table 1.

Outcomes and measures
Acceptability
Acceptability of study participation was measured with a Likert scale constructed for the purpose of this study: The U-PAIN Acceptability Scale. The scale was developed in line with how measures of attitudes, burden and experience are proposed to be designed when assessing acceptability of healthcare interventions. It assessed adequacy of study information, ease of access to computerised PROMs, respondent burden, relevance of the study procedures and participant perception of interactions with research staff. A score of 1 indicated total agreement and a score of 5 indicated total disagreement. A score <3 was considered feasible. For the two items, item 7 and 8, that assessed respondent burden, a higher score indicated lower participant burden and here a score >3 was considered feasible.

Feasibility
Recruitment
To assess recruitment numbers of eligible participants, recruitment rates (>75% was considered feasible), retention rate at the 1-year follow-up (>80% was considered feasible) and sample demographics were recorded. Information on demographics was collected from the online questionnaire the participants filled out prior to the clinical consultations and research visit. Health data were retrieved from medical records. Chronic pain diagnoses according to the The International Association for the Study of Pain (IASP) classification of chronic pain for the International Classification of Diseases (ICD-11) were established retrospectively by the researchers, based on data retrieved from medical records.

Data collection
Data collection outcomes were completion rates of PROMs (>90% was considered feasible), if protocolised test and interviews were preformed or not preformed (>90% was considered feasible), and validation checks of collected data regarding self-reported opioid use.

To validate data collection methods for opioid use patterns, we examined agreement between:
1. Categories based on self-reported opioid use and categories based on prescribed opioid dose (κ=0.60 was considered feasible).
2. Self-reported opioid dose and prescribed opioid dose (ICC >0.60 was considered feasible).

The categories used to describe opioid use were defined accordingly:
1. No use.
2. Short-term or intermittent use.
   Criteria: short-term use defined as regular use of opioids for <3 months or intermittent use as dosing up to 10 days/months (independent of time frame).
3. Long-term use with low to moderate doses
   Criteria: use of opioids for >3 months, more than 10 days/month and mean daily dose <100 mg oral morphine milligram equivalents (MME).
4. Long-term use with high doses
   Criteria: use of opioids for >3 months, ≥100 MME.

Criteria for the categories were based on current evidence of dose-dependent risks, and dosing recommendations in clinical guidelines.

Self-reported opioid use, that is, type of opioid, dose, administration and number of days of opioid use last 30 days, was assessed with a structured ‘Time-line follow-back’ interview (TLFB). The TLFB was developed as a tool for eliciting retrospective information about drinking behaviour in persons with alcohol use, but it has been extended to assess the use of other substance types in different populations. It has been found fairly reliable for different kinds of substance use.

Before the administration of the TLFB, a trained interviewer showed the participant a list of opioid pharmaceuticals and asked if any of the drugs had been used during the last 4 weeks. To facilitate recollection, the interviewers
started with the most recent complete week, week 1 and worked backward one week at a time recording days of use for each opioid.

Duration, that is, more than 3 months, of opioid use was retrieved from medical records. The average dose of week 1 was used as baseline value with the assumption that it would be the most accurate, due to its proximity to baseline, and lesser risk of recall bias compared with weeks 2, 3 and 4. The additional 3 weeks reported in the TLFB were used to determine patterns of opioid use, that is, intermittent or regular use.

**Key and secondary cohort outcome measures**

The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommends six core outcome domains to be considered when designing chronic pain clinical trials, that is: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; and (6) participant disposition. Although this is not a clinical trial, we have chosen to adapt and address these outcome domains as appropriate. Key outcomes are risks of COT, defined as OUD according to the DSM-5 criteria described in figure 1, and benefits of COT, defined as self-reported work ability (work ability was not assessed for participants with retirement pension). Based on the recommended outcome measures by IMMPACT, the secondary variables were chosen as appropriate for the current study. Pain severity and pain interference is measured using...
Brief Pain Inventory (BPI) and rating of improvement with patient global impression of change.

The ICD-10 system is used for clinical diagnosis, and the ICD-10 opioid dependence criteria correspond to moderate-to-severe OUD, rather than any OUD. Therefore, to examine feasibility for using OUD according to DSM-5 as outcome measure we assessed:

1. Number of individuals meeting the OUD criteria according to DSM-5 (> individuals meeting clinical ICD-10 opioid dependence was considered feasible).

2. Agreement between moderate to severe OUD and clinical diagnoses for opioid dependence according to ICD-10, retrieved from medical records (κ>0.60 was considered feasible).

Opioid use disorder was assessed with a modified version of the substance use disorder (SUD) section (J) of the Swedish Mini-International Neuropsychiatric Interview (M.I.N.I.) for DSM-5. The M.I.N.I. is a structured diagnostic interview for the most common psychiatric disorders, designed for multicentre clinical trials and epidemiological studies, also used in non-research clinical settings.

The interview assesses eight categories of substances, including both prescribed medications and illicit substances: opioids (heroin and opium as a separate category), stimulants, cocaine, hallucinogens, inhalants, marijuana and sedatives. The SUD section was modified to assess current as well as life-time drug use, and medical as well as non-medical use. Before the interview, trained research staff showed participants a list of substances and read the following instructions: ‘I am going to show you and read to you a list of drugs. The list also includes some medicines. Please describe your use of the listed drugs and medicines, even if the medicine was prescribed to you by a doctor and used accordingly. I will ask you to describe life-time use, and your use during the past 12 months’.

To examine feasibility for measures of work ability, pain severity, pain interference and HRQoL we assessed:

1. Sample scores at baseline presented as means and medians.
2. Internal consistency of the PROMs assessing work ability, pain severity and pain interference (α>0.70 was considered feasible).

Work ability was measured with a computerised self-administered version of the Work Ability Index (WAI) and was part of the online questionnaire. The computerised WAI-form was optional, hence retired participants could skip filling out the form. WAI has been shown to have acceptable reliability and validity in different working populations, and predictive validity for long-term sick leave in the general population.

Pain severity and pain interference were assessed with the Brief Pain Inventory Short Form (BPI-SF), filled out online. The BPI-SF is a valid, reliable and commonly used scale which assess the localisation and severity of pain during the last 24 hours, and activity interference in individuals with pain.

Health-related quality of life was measured with a paper and pencil version of the EQ-5D-5L, developed by the EuroQoL Group. There is support for the validity and reliability of the EQ-5D’s descriptive system and the index values in many conditions and populations.

More thorough descriptions of the outcome measures are reported in online supplemental appendix 1. Description and results of other measures used in the U-PAIN cohort that are not key or secondary outcome measures are presented in the online supplemental table I–III.

Statistical analyses

The statistical analyses were carried out using the SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, V.26.0, IBM).

Independent two-tailed t-test and χ² test of independence were used for examining differences and proportions between participants and non-participants regarding age, sex and inpatient or outpatient care.

Intraclass correlation coefficient (ICC), single measures and absolute agreement, was used for assessing agreement between self-reported opioid dose week 1 and prescribed dose according to medical records. The ICC was considered poor if <0.40, fair 0.40–0.59, good 0.60–0.74 and excellent between 0.75–1.00.

Cohen’s kappa (κ) was used to examine agreement between categories based on current opioid use according to self-reported dose versus prescribed dose, and agreement between the structured interview establishing OUD according to DSM-5 and the clinical opioid dependence diagnosis according to ICD-10 derived from medical records. κ is a coefficient for rater agreement considering chance agreement. Values for κ range between −1 and +1, with +1 indicating total agreement between outcomes. Higher values of chance agreement result in lower κ values. As a low number of OUD diagnoses was expected in our sample an alternative calculation of κ was also conducted: The prevalence-adjusted bias-adjusted kappa (PABAK) that takes into account the categorisation by the interview and the prevalence of the clinical diagnosis.

Agreement was considered as poor <0, slight 0.00<κ<0.20, fair 0.21<κ<0.40, moderate 0.41<κ<0.60, substantial 0.61<κ<0.80 and almost perfect when κ>0.80.

Internal consistency was evaluated using Cronbach’s α. The α coefficient was considered acceptable above 0.70.

Statistical power for detecting an ICC of 0.85, assuming a power 80%, α=0.05 and acceptable ICC (q0) set to 0.70 is achieved, a sample of 53 participants would be sufficient.

The number of subjects required in a two-rater study to detect a statistically significant κ (p≤0.05), with 80% power, at a proportion 10% of positive diagnoses, assuming the null hypothesis value of κ to be 0.40, is 39, supporting that the sample size of 64 participants is sufficient.
The EQ-5D-5L Index Value Calculator developed by the EuroQol Group, using the U.K. value set, was used for calculations of EQ-5D-5L index scores.41

RESULT

Recruitment and sample characteristics

Baseline data were collected between February 2019 and June 2019 until 65 participants were consecutively recruited, and the first follow-up was completed approximately 12 months after the baseline visit. During the feasibility study, all patients seeking treatment at the Pain Centre were screened for eligibility by research staff, and 411 patients were assessed eligible for the cohort study and received written information about the study. The two main reasons for non-enrolment were declining participation or that no active enrollment strategies were applied, that is, no telephone calls prior to the clinical consultations. A higher proportion of those enrolled in the feasibility study (81%) completed the 1-year follow-up than those who did not use the computerised PROMs, and thus were only enrolled in the cohort study (65%), giving a total retention rate of 75%. The recruitment process and participant and refusal rates are described in figure 2.

There were no differences regarding age (mean age 50.3 vs 52 years) (t=0.93, p=0.35) or proportion of the sexes (42% men vs 31% men) (X²=2.78, p=0.10) between participants and non-participants. The proportion of individuals who participated was higher among patients who enrolled in in-patient care programmes (57%) compared with individuals seeking out-patient care (10%) (χ²=73.1, p<0.001).

All participants had at least one chronic pain diagnosis, that is, primary or secondary chronic pain,14 and 12 participants (19%) had both chronic primary and secondary pain diagnoses. Participant demographics and characteristics are described in table 2.

Acceptability of study participation

Overall acceptability of study participation according to the U-PAIN Acceptability Scale suggested that the study procedures were feasible. A majority of the participants reported that it was easy to find and fill out the online PROMs, that the research visit worked well in practice, and that the time required for the research procedures was reasonable. Data on acceptability and respondent burden of study participation are presented in table 3.

Data collection

The completion rates of the different study procedures ranged from 83% to 95%, as described in figure 2.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sample characteristics (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.3 (14.5)</td>
</tr>
<tr>
<td>Pain duration (years)</td>
<td>13.7 (14.1)</td>
</tr>
<tr>
<td>Women</td>
<td>36</td>
</tr>
<tr>
<td>Type of care</td>
<td></td>
</tr>
<tr>
<td>Inpatient pain rehabilitation</td>
<td>17</td>
</tr>
<tr>
<td>Inpatient multi modal pain assessment</td>
<td>33</td>
</tr>
<tr>
<td>Outpatient pain consultation</td>
<td>51.6</td>
</tr>
<tr>
<td>Nation of birth</td>
<td>57</td>
</tr>
<tr>
<td>Sweden</td>
<td>3</td>
</tr>
<tr>
<td>Other European country</td>
<td>4</td>
</tr>
<tr>
<td>Non-European country</td>
<td>6.2</td>
</tr>
<tr>
<td>Highest completed education</td>
<td>1</td>
</tr>
<tr>
<td>Not completed elementary school, junior secondary school or similar</td>
<td>15</td>
</tr>
<tr>
<td>Elementary school, junior secondary school or similar</td>
<td>16</td>
</tr>
<tr>
<td>2 years of high school education or vocational school</td>
<td>12</td>
</tr>
<tr>
<td>Three or 4 years of high school education</td>
<td>9</td>
</tr>
<tr>
<td>University or college education less than 3 years</td>
<td>11</td>
</tr>
<tr>
<td>University or college education three or more years</td>
<td>17.2</td>
</tr>
<tr>
<td>Occupation</td>
<td>15</td>
</tr>
<tr>
<td>Employed</td>
<td>1</td>
</tr>
<tr>
<td>Entrepreneur</td>
<td>1</td>
</tr>
<tr>
<td>Student</td>
<td>19</td>
</tr>
<tr>
<td>Retired (by age, disability or early retirement)</td>
<td>19</td>
</tr>
<tr>
<td>On long-term sick leave (more than 3 months)</td>
<td>5</td>
</tr>
<tr>
<td>Unemployed</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>6.3</td>
</tr>
<tr>
<td>Chronic pain diagnoses according to the The International Association for the Study of Pain (IASP) classification of chronic pain for the International Classification of Diseases-11</td>
<td>38</td>
</tr>
<tr>
<td>Chronic primary pain</td>
<td>1</td>
</tr>
<tr>
<td>Chronic cancer-related pain*</td>
<td>16</td>
</tr>
<tr>
<td>Chronic postsurgical or posttraumatic pain</td>
<td>7</td>
</tr>
<tr>
<td>Chronic neuropathic pain</td>
<td>2</td>
</tr>
<tr>
<td>Chronic secondary headache or orofacial pain</td>
<td>3</td>
</tr>
<tr>
<td>Chronic secondary visceral pain</td>
<td>14</td>
</tr>
</tbody>
</table>

*Postcancer pain.
Agreement between categories based on self-reported opioid use and categories based on prescribed dose and duration as measured with Cohen’s $\kappa$ was almost perfect ($\kappa = 0.91$).

Agreement measured with ICC, single measures, was excellent ($ICC = 0.95$) for self-reported average opioid dose week 1 and prescribed dose. Opioid use is described in Table 4.

Key and secondary cohort outcome measures

More than half of the sample reported any opioid use and 44% of the participants were prescribed COT. Thirty per cent of those prescribed opioids met the criteria for any OUD, and 8% of those prescribed opioids met the DSM-5 criteria for moderate or severe OUD. One-third of the participants was prescribed both opioids and benzodiazepines.

The number of identified OUD diagnoses according to DSM-5 exceeded the number of clinical opioid dependence diagnoses according to ICD-10 retrieved from medical records. Agreement between moderate to severe OUD according to DSM-5, and clinical ICD-10 diagnoses for opioid dependence was fair when measured with Cohen’s $\kappa$ ($\kappa = 0.38$), but almost perfect when using PABAK ($\kappa = 0.90$) for analyses.

### Table 3  Acceptability, depicted per item as frequencies and percentage, and median and IQR, (N=64)

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree n (%)</th>
<th>Agree n (%)</th>
<th>Partially agree n (%)</th>
<th>Disagree n (%)</th>
<th>Strongly disagree n (%)</th>
<th>Median (IQR) n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It was easy to find the online questionnaire</td>
<td>33 (25)</td>
<td>15 (23)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1 (1)</td>
<td>57</td>
</tr>
<tr>
<td>2. It was easy to fill out the online questionnaire</td>
<td>25 (39)</td>
<td>16 (25)</td>
<td>13 (20)</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>59</td>
</tr>
<tr>
<td>3. The questions in the online questionnaire were relevant to me</td>
<td>10 (16)</td>
<td>26 (41)</td>
<td>20 (31)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>60</td>
</tr>
<tr>
<td>4. The information about the research visit was clear and sufficient</td>
<td>31 (48)</td>
<td>21 (33)</td>
<td>7 (11)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>5. The research visit worked well in practice</td>
<td>36 (56)</td>
<td>18 (28)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>58</td>
</tr>
<tr>
<td>6. The time the research visit required was reasonable</td>
<td>34 (53)</td>
<td>15 (23)</td>
<td>7 (11)</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>59</td>
</tr>
<tr>
<td>7. The research visit was physically strenuous</td>
<td>2 (3)</td>
<td>6 (9)</td>
<td>13 (20)</td>
<td>12 (19)</td>
<td>24 (38)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>8. The research visit was psychologically strenuous</td>
<td>1 (2)</td>
<td>4 (6)</td>
<td>16 (25)</td>
<td>13 (20)</td>
<td>24 (38)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>9. The interaction with the research staff was good during the research visit</td>
<td>57 (89)</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>60</td>
</tr>
<tr>
<td>10. On the whole, I am satisfied with my participation in the research study</td>
<td>49 (77)</td>
<td>10 (16)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>60</td>
</tr>
</tbody>
</table>

A score of 1 indicated total agreement and a score of 5 indicated total disagreement. *High scores indicate less respondent burden.

### Table 4  Sample characteristics regarding opioid use and opioid use disorder (N=64)

<table>
<thead>
<tr>
<th>Opioid use</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed dose MME (n=64)</td>
<td>22.5 (59.8)</td>
<td>54.1 (97.6)</td>
<td></td>
</tr>
<tr>
<td>Self-reported dose MME (n=60)</td>
<td>7.2 (43.5)</td>
<td>49.9 (101.7)</td>
<td></td>
</tr>
<tr>
<td>Self-reported opioid use (n=60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>21</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Short-term or intermittent use (&lt;90 days, or &lt;10 days/months independent of time frame).</td>
<td>9</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Long-term use with low to moderate doses (&gt;90 days, &lt;100 mg MME)</td>
<td>21</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Long-term use with high doses (&gt;90 days, &gt;100 mg MME)</td>
<td>9</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Opioids+bensodiazepines (N=60)</td>
<td>21</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Opioid use disorder (OUD) (N=60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No OUD</td>
<td>49</td>
<td>81.7</td>
<td></td>
</tr>
<tr>
<td>Mild OUD</td>
<td>8</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Moderate OUD</td>
<td>1</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Severe OUD</td>
<td>2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Opioid dependence (ICD-10)* (N=64)</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical diagnosis retrieved from medical record. ICD-10, International Classification of Diseases, 11th Revision; MME, morphine milligram equivalent.
The participants reported poor self-reported work ability according to WAI, with no participant reporting good or excellent work ability. Results for WAI and additional cohort outcome measures are described in table 5.

**DISCUSSION**

In this feasibility study for the establishment of the procedures related to the U-PAIN cohort, study participants reported an overall satisfaction with study participation despite the rather demanding research protocol including a variety of methods for data collection. The 1-year retention rate suggests that the adherence to protocol was satisfying for those enrolled in the study, and that the methods for data collection were feasible for all formats but the paper pencil version of EQ-5D-5L and the WAI. However, the participation rate did not reach the feasibility threshold and the refusal rate was high compared with eligible patients during the period of data collection.

The overall good satisfaction with study participation is in line with previous research. It is nevertheless often difficult to implement research procedures in clinical settings because of staff resource availability and perceived respondent burden, which may have affected the participation rate in this study. Hence, our sample may not be representative for the study population, given that the most reported reasons for non-participation were lack of time, or lack of energy and too much pain. This may limit generalisability to patients with severe pain disability, or patients with low disability where lack of time because of full-time work limits participation. Even so, for prospective cohort studies there may be support for enrolling a subset of motivated participants who will engage in long-term follow-up rather than focusing on representativeness.

The high refusal rate increases the risk of systematic bias, thus, an important limitation to consider is the scarce exploration of demographic factors other than age, gender or care unit for those who did not consent to participate. For the future cohort study, a more thorough exploration of characteristics of non-participants and reasons for refusal will be required to enable strategies for adjustments of possible selection bias. For example, more than half of the participants in the study used opioids for pain management, and it is possible that individuals with opioid therapy were more interested to participate, thus over-represented, given the overall aim of the cohort study. However, the high prevalence of opioid use in our sample is similar to what has previously been described in patients treated in specialised pain care.

Using the TLFB interview for assessing opioid use seems feasible considering the almost perfect agreement between categories based on self-reported patterns of opioid use and categories based on data retrieved from medical records and self-reported dose versus prescribed dose. The TLFB made it possible to detect patterns of intermittent and regular use that could not have been retrieved from register data or medical records, supporting the use of self-reported data. During the feasibility study, we discovered that we did not assess self-reported duration of opioid use beyond the 30 days of the TLFB, leading to a change in the instructions for the TLFB, adding a question about duration of opioid use, that is, if the participant used opioids for more than 3 months. The rate of OUD reported by our sample is similar to what has been found in other populations with chronic pain and COT, although the proportion varies greatly depending on method for assessment and criteria for diagnoses, making comparison of results challenging. Our results suggest that the modified version of MINI (J) assesses OUD accurately in our sample. As expected, more individuals met the criteria for any OUD according to DSM-5, than the ICD-10 criteria for opioid dependence reported in medical records. This was further illustrated by the almost perfect agreement between moderate-to-severe OUD and clinical opioid dependence diagnoses according to ICD-10, after adjusting for prevalence bias. It seems, that with the minor revisions of the MINI (J), and training of research personnel,
some of the difficulties of applying the DSM-5 OUD criteria in a chronic pain context can be overcome, without losing the credibility and standardisation of DSM-5 criteria.

The paper and pencil version of the EQ-5D-5L did not reach the stipulated threshold for feasibility and had the lowest completion rate among the data collection methods. After the feasibility study was completed, an online version of the EQ-5D-5L has been made available on the Swedish Healthcare Guide’s digital platform, with permission obtained from the EuroQol Research Foundation, and is now used instead of the paper and pencil version to increase completion rates.

The use of computerised PROMs for collecting data for both clinical and research purposes was well accepted and reached the stipulated threshold for all measures but the WAI. Computerising the PROMs did not seem to affect their reliability and internal consistency, which is consistent with previous research, and our study supports the use of easily accessible online forms. However, it must be kept in mind that fully one-third of the enrolled participants during the time period for the feasibility study preferred paper and pencil versions of the PROMs, why both the online questionnaire and paper and pencil versions will continue to be offered, even though they did not reach the stipulated retention threshold. Participants who filled out the PROMs online were more inclined to participate in the 1-year follow-up, further supporting the use of online questionnaires over time. Efforts will be made to encourage the use of online forms rather than paper and pencil formats.

The decision to make the WAI optional in the online questionnaire raised difficulties in data collection, with lower completion rates across all participants. Therefore, to limit attrition, WAI will be mandatory for those in working age, with the possibility of a skip-out question for those with pension retirement. It can be noted that the WAI scores in this sample were poor, even lower than what have been previously reported in other pain population. Poor to moderate work ability according to the WAI has been shown predictive for functional outcomes in this population.53

CONCLUSIONS
This feasibility study has helped highlight and improve methods for recruitment, data collection and use of outcome measures for the U-PAIN cohort. Study participation was well accepted and the use of online PROMs for data collection and structured interviews to identify patterns of opioid use was feasible. However, low participation rate and high refusal rates at baseline is a challenge that needs to be further addressed, otherwise it may jeopardise reaching the target number of participants for the cohort, and limit the generalisability of future results.

Methodological limitations
Our study has some limitations that should be addressed. First, the planned follow-up for the definitive study is 5 years and the feasibility study only followed patients for 1 year, leaving the ability to predict the retention for the follow-up to 5 years uncertain. Second, the low participation rate and the small sample size leave uncertainties regarding the external and internal validity of the results and may not be extrapolated to the full cohort. Third, acceptability of study participation was assessed with a questionnaire that has not been systematically validated. However, the items are study specific, evaluating participants satisfaction, attitudes, perceptions and experiences of the study procedures in line with assessment of self-reported acceptability.13

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