Translation and validation of the COMM and ASI-SR – instruments for assessing substance use disorder development in a Swedish population of patients with long-term pain treated with opioids

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Study code: COMMISS

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1 Introduction

Long-term opioid therapy is one of the methods of treating long-term pain that in many cases leads to problematic use, development of addiction and complications.[1] Effective screening and risk assessment is important both before treatment begins, but also continuously during treatment. At the moment, there are no relevant or sufficiently sensitive questionnaires in Swedish for assessing risk development for opioid addiction in pain patients treated with opiods for long-term pain. Many instruments have been evaluated abroad and the ones with the greatest relevance are "Screener and Opioid Assessment for Patients with Pain" (SOAPP) [2] for assessment before starting treatment and "Current opioid misuse measure" (COMM) for control of ongoing treatment[2-5]. The Addiction Severity Index (ASI) is also a standardized assessment instrument, validated for assessment of general addiction problems. It contains a standardized semi-structured interview for the assessment of past and current problems in seven different areas; physical health, work/support, alcohol use, drug use, family/association, legal problems and mental health[6]. It is a time-consuming interview. A shorter version, the ASI-SR, has been validated for assessment in a Swedish population [7] and reflects more on ongoing problem. However, it is not specifically intended for, or validated, for pain patients with preferential iatrogenic use.

We therefore plan to translate the COMM form and validate it using the ASI-SR in a Swedish population of pain patients treated with opioids. At the same time, the prevalence of illicit substance use will be investigated in this population and compared with patients who are not treated with opioids. Inflammatory markers will be collected in Uppsala Biobank for future analyzes of neurobiological processes during the treatment of long-term pain. When this becomes relevant, a separate ethical application will be made.

2. Background

The use of opioids for long-term pain is related to an increased risk of developing addiction and complications, such as neuropsychological disturbances, depression, sleep disturbances, risk of overdose and even death. [1]

Long-term opioid therapy (LOB) for the treatment of long-term pain has not been shown to outweigh the risks and complications it may cause for most of the patients. The International Association for the study of Pain IASP stated in February 2018 that opioids should be reserved only for a group of specially selected patients, for a limited time and in a limited amount, and even then patients are at risk of developing these complications[8]. Thus, selection of a suitable patient as well as further strict controls of the treatment can be critical in reducing the risk of addiction development in these patients. Although pain patients in many cases meet criteria for substance dependence syndrome according to ICD 11 and DSM V classification, this dependence is not driven by the drug itself but by relief from pain [9].

Several methods for assessing the risk of opioid addiction have been evaluated, but none of them alone have shown sufficiently good results, which is why combinations of several methods are advocated. Medical, psychosocial and disease history from both patient and relatives has a central role. Young age (below 45 years) and male gender is a predisposing factor, but age and ethnic factors do not seem to be consistent in different studies [10, 11]. Urine drug testing is often cited as a gold standard for monitoring, but there is no evidence to support its accuracy, effectiveness in predicting, preventing, or reducing problematic behavior or fatal complications such as overdoses and death[10, 12-14]. Urine testing in pain clinics and health centers is problematic due to a lack of

appropriate facilities and embarrassment for the patients. Analysis by high-performance liquid chromatography and mass spectrometry of saliva samples has been compared with urine samples and shows a high detection rate and overall agreement regarding the results in 85%.[15, 16] Thus, saliva testing can be a suitable replacement for urine samples due to easier sampling and less impact on integrity. A weakness of saliva tests is cannabis analysis, as it can only be detected in saliva two days after use. One possibility to increase the detection window to 2-3 weeks is to analyze cannabinoids from capillary samples, Dry blood spot, with the same analysis methods[17]. Alcohol use is most suitable to be analyzed with Phosphatidylethanol sample in the blood (PETh)[18]. These laboratory methods would partly be good for validating questions related to the use of illicit substances in COMM, but also provide answers to the question what is the prevalence of substance use syndrome in the pain population treated with opioids. Today's high patient flow both in primary care and in hospitals makes long time-consuming interviews impossible, and clinics often have limited time for assessing the patients. Effective, digitalization-friendly instruments for risk assessment are therefore desirable.

There are some instruments in English, which were developed for risk assessment before LOB: Opioid risk tool (ORT)[19], Screener and Opioid Assessment for Patients with Pain (SOAPP) and its short version SOAPP-R (which is suitable for computerized collection of data)[20, 21], the Addiction Behavioral Checklist (ABC) [22] and the Physical Opioid Therapy Questionnaire (POTQ)[23].

Then there are others that are more suitable for ongoing treatment of LOB: Prescription Drug Use Questionnaire (PDUQ)[24, 25] or Prescription Drug Use Questionnaire-Patient version (PDUQ-p), Pain Medical Questionnaire (PMQ) or Modified Pain Medical Questionnaire (mPMQ), Prescription Opioid Misuse Index (POMI), Pain Assessment and

Documentation Tool (PADT), Prescribed Opioid Difficulties Scale (PODS) and Current Opioid Misuse Measure (COMM). Furthermore, there are other instruments for assessing all types of addiction that are not specific to opioids, such as DSM-IV, CAGE questionnaire, Addiction Severity Index, Michigan Alcohol Screening Test, Minnesota Multiphasic personality Inventory, Screening Instrument for Substance Abuse Potential [26, 27].

Many experts state that the evidence is insufficient for any of these instruments to have an effect in healthcare [13, 22, 28]. Many are too long and unrealistic to use in clinical practice [29]. Compilation of results for sensitivity and specificity of the various instruments both before and during ongoing LOB by Chou and colleagues can be found in Tables 1 and 2 below [10].

Table 1: Optimal balance between specificity and sensitivity of instruments before the start. Of COT:

Tool	*Sensitivity*	*Specificity*	*Study refferens*
SOAPP>7	*0.91 (95% CI, 0.78-0,98)*	*0,69 (95%,CI,0,54-0,81)*	*Butler 2004*
SOAPP>8	*0,68(95%, CI, 0,52-0,81)*	*0,38 (95% CI, 0,29-0,49)*	*Akbik 2006*
SOAPP-R score >18	*0,80 (95%CI, 0,70-0,89)*	*0,68 (95% CI, 0,60-0,75)*	*Butler 2008*
ORT>8	*Not applicable (not dichotomous)*	*Not applicable (not dichotomous)*	*Webster 2005*

Table 2: Optimal balance between specificity and sensitivity of instruments for detection of misuse during COT (Enligt Chou et al 2009)

Tool	*Sensitivity*	*Specificity*	*Study/quality*
COMM (17)>10	*0,74 (95%CI, 0,63-0,84)*	*0,73 (95% CI,0,65-0,80)*	*Butler 2008 …5/9*
ABC(20) 3 of20	*0,88*	*0,86*	*Wu 2006, 4/9*

PDUQ	*0,74 (95%, CI, 0.63-0.82)*	*0,57 (95% CI, 0,49-0,65)*	*Wasan 2007 6/9*

COMM was developed in the USA by Butler et al and shows promising results in the follow-up of pain patients with COT in primary care and the detection of patients at risk in acute care [30, 31].

A combination of the prescriber's assessment, SOAPP-R before the start of treatment and COMM during ongoing treatment and possibly random drug testing can predict SUD risk during opioid prescribing in the next 12 months [31].

The original article on COMM has identified 5 question areas (clusters) that the instrument assesses:

1. Symptoms and signs of drug abuse (question 1)
2. Emotional and psychiatric problems (questions 2,5,7,8,13)
3. Visitor characteristics/patterns (questions 3,12,17)
4. Evidence of untrue statement (doubt/lie/untruth) and drug use (questions 4,6,9,10,11)
5. Medication use and deviation from prescription (non-compliance) (questions 14,15,16). [4]

The short version of the ASI-SR has recently been translated into Swedish and validated for assessment of addiction problems and reflects 7 different areas of life: physical health, professional life, alcohol use, drug use, family and social life, criminality and mental health [7, 32] Thus, this instrument can be relevant as a reference for clinical assessment of dependence development in patients with LOB.

Our hypothesis is that COMM and ASI-SR are suitable forms for assessing the development of addiction among pain patients, which the patient can also fill out

digitally before the visit and will thus not burden the healthcare staff in terms of time. COMM is specifically developed for patients with pain and iatrogenic treatment with opioids in contrast to ASI-SR and may thus be more relevant. On the other hand, ASI-SR can better identify possible mental illness, criminality and be more sensitive to alcohol issues, which COMM does not clearly address.

The next aspect is whether a Swedish patient differs markedly from an American one, as the COMM was developed for the American population. It has now been translated into several languages and the first validations show good results ([33, 34]. Similar to the USA, many patients in our clinic have been introduced to opioids in primary and specialized care, but not via the pain clinic [35] . Prescription of strong opioids, especially oxycodone per capita is increasing dramatically, even though the total amount of opioids prescribed is decreasing. This trend seems to have been stable in Sweden for the last ten years [36]. On the other hand, Sweden has among the highest drug-related mortality per capita in Europe [37]. Although mortality related to prescription opioids in Sweden does not appear to be as dramatic as in the United States, the trend in the prescription of strong opioids is alarming and control mechanisms are needed to prevent a negative development in the future. Above all, an increased trend in oxycodone prescription and its correlation with oxycodone-related deaths in Sweden is alarming[38].

We plan to translate and validate the COMM as well as validate the ASI-SR for use within a Swedish population of patients with long-term pain and ongoing opioid treatment and examine internal validity in the Swedish population.

Furthermore, the correlation will also be examined against our external validity measures regarding pain, addiction, mental health, visitor characteristics, compliance with the treatment and secondary use of substances.

The survey also plans to answer the question regarding the prevalence of alcohol and other substance use is in patients with long-term pain and opioid treatment in Sweden. Opoids are considered to strongly affect the neuroinflammatory processes linked to the development of both different types of chronic pain and addiction. Blood samples are continuously being collected at the Uppsala pain center for the examination of biomarkers and DNA analysis within the U-Pain project. For example, studies of differences in biomarkers between patients with chronic pain with and without opioid therapy can provide important information about the underlying processes of many of the side effects we see from LOB. For any studies regarding biomarkers and genetic tests, separate ethical applications will be made. Therefore, the collection of blood is also planned for this purpose.

3. Aim

The primary aim is to translate COMM into Swedish and examine its reliability and validity against the ASI-SR in a Swedish population of pain patients with LOB.

The secondary aim is to investigate acceptability of the instrument in a Swedish population of pain patients with LOB.

The tertiary aim is to investigate the prevalence of alcohol and illicite substance use in a Swedish population of pain patients with LOB.

Samples will be collected to be able to study biomarkers and genetic analyzes at a later stage for a better understanding of mechanisms behind long-term pain. However, this is not part of this validation. These samples may be examined with the O-link neuroinflammatory panel and future genetic analyses, whereby a separate ethical application will be made.

4. Methods:

Phase 1:

Translation of the instrument takes place according to the "Patient-Reported Outcome (PRO) Consortium translation process guidelines" [39] and according to guidelines from the company MAPI Trust, which owns the rights to use the instrument. The process is described in the table below.

Step Name Description of the process Actor/responsibility

1. Preparations

   Request for rights for translation and validation of instruments for research and clinical use from COMM developers, company: Mapi research Trust.

   Contract with a Swedish professional translator (Accent Language Service Umeå). Lenka Katila applies.

   Granted by Birgitte Leroux, Mapi research Trust, 16.7.2020.

2. Translation into Swedish

   Translation into Swedish takes place with two translators; a professional translator and a researcher. Lenka Katila, researcher, 16.7.2020.

   Evalotta Boman, Accent Language Service.

3. Reconcilliation I

   Both translations are compiled, compared and the best Swedish version is produced. Lenka Katila and Evalotta Boman

4. Backward-translation into English

   Another professional translator back-translates the compiled Swedish version, without seeing the English original. David Ordoubadian, Accent Language Service.

5. Reconcilliation II of the compiled translation after comparison of the back translation

   Evaluation of back translation to achieve semantic equivalence and identify problems with the translation, compilation of versions and possibly make changes to the translation. Hanna Ljungvall, Rolf Karlsten, Pernilla Åsenlöf, Stephen Butler

6. Professional reading

   Two or more independent professional readers check translation, correct diacritical marks and grammar and a clinical expert in the field performs this step in parallel. Clinical expert: Expert and linguist: Annica Rhodin

   Language expert: Per Sellius

7. Cognitive interviews

   Conducted on five Swedish-speaking individuals, with different backgrounds, age and gender, and with long-term pain treated with opioids of various types. The interview will specifically examine whether all words are understood correctly, as well as that the respondents understand the question in the same way and that they perceive the answers as relevant and appropriately described.

   Lenka Katila, Hanna Ljungvall

   5.10.2022

8. Evaluation of cognitive interview

   The answers in the cognitive interviews are evaluated and compiled, feedback is presented to the translation team. Any revisions of the text are carried out and a

final revised version of the text is compiled. Rolf Karlsten, Lenka Katila, Hanna Ljungvall, Annicka Persson Rhodin, Pernilla Åsenlöv

9. Final revision and documentation (Proof reading).

   Review so that the proposed revision maintains conceptual equivalence and does not pose a risk to international harmonization of any future revisions, the proofreader's revised translation, or other relevant alternatives. Final professional reading and adaptation to the original graphic model (format/layout) as well as adaptation both for paper and screen, to avoid any problems with data collection. Rolf Karlsten, Lenka Katila, Hanna Ljungvall, Pernilla Åsenlöv , Alexander Rosendahl

10. Report

    Final report with documentation and description of all steps and decisions. Lenka Katila

12. Archiving Documentation that is archived:

- The qualifications and experience of the translation team
- Documentation of changes made during the translation process and reasons for changes
- Translation certificate
- Translation report including results of cognitive interviews Lenka Katila

Phase 2:

The next step is validation of COMM against ASI-SR in a Swedish population of patients with long-term pain according to the Cosmin guidelines [40] with the following steps:

1. Test of reliability for internal consistency, test-retest consistency and standard error of measure (SEM) and factor analysis with rotation in a Swedish population of patients with long-term pain and LOB.
2. Investigate COMM's validity regarding comprehensivity/scope and comprehensiveness/user-friendliness- and predictiveness/predictability in this population.
3. Investigate whether the instrument is acceptable in the population.
4. Investigate prevalence of illicit substance use parallel to LOB in pain patients and compare with opioid-free pain patients.

We plan to recruit 200 research subjects in the test group, both from primary care, specialized pain care, other specialized care (e.g. Endometriosis Center) and from addiction care (addiction medicine program for pain patients). In addition, it is planned to recruit 200 people from pain centers and primary care to the control group for prevalence measurement, patients who have long-term pain, but are not treated with opioids.

As we will have two groups of patients with long-term pain with and without opioid treatment, the participants will also be asked separately if they are willing to provide blood samples for the examination of biomarkers of pain (O-link panel) as well as genetic analysis for future research on effects of opioids and saving samples in the biobank.

5. Design:

Testing the COMM psychometric properties, validity and reliability study.

1) Selection

200 patients are planned to be recruited in the test group and 200 in the control group.

Recruitment is planned at:

- Pain Clinic, University Hospital Uppsala (recruitment manager Lenka Katila)
- Endometriosis Centre, Uppsala University Hospital (source Mats Olovsson, Christian Moberg, recruitment manager Lenka Katila)
- Primary care Uppsala Region (all primary care centers) (recruitment manager Magnus Petersson, Anna Svensson)
- LARO program for pain patients, University Hospital, Uppsala (recruitment manager Lenka Katila)

The inclusion criteria for the test group are patients with long-term, non-cancer-related pain (>3 months) at least 3 days a week, age 18-75 years, who have been treated with opioids for at least 1 month and who can speak, read and write in Swedish.

The inclusion criteria for the control group are patients with long-term, non-cancer-related pain (>3 months) at least 3 days a week, age 18-75 years, who are not treated with opioids (at inclusion and during the last 3 months) and who can speak, read and write in Swedish.

Exclusion criteria are other ongoing diseases or conditions that prevents the patient from completing to the study according to the doctor's assessment, or serious cognitive disorder that makes answering the questions impossible. Ongoing or treated cancer in the last 10 years. Insufficient knowledge of Swedish is also an exclusion criterion.

Process

a. Test group

All patients who have received prescriptions for opioids during the period 2021-2022 via the respective healthcare providers are identified via extracts from the Cosmic medical record system. Excerpts are carried out by the output unit at the IT department,

region Uppsala, at the request of the responsible researcher and responsible operations manager. The researcher responsible for recruitment identifies those who have long-term pain and LOB (criteria see above).

Identified patients are contacted by telephone, informed about the study and asked if they are interested in participating in the study. Those who respond will be contacted by the recruitment officer within 3 weeks. At the same time, the study is advertised at the respective receptions in the form of posters in the waiting rooms with the opportunity to contact researchers. The doctors working at the respective care facilities can also offer patients to participate in the study.

Those who choose to participate are invited to visit the research nurse or responsible researcher for information and to sign informed consent, take samples and submit answers digitally. For the part about biomarkers and DNA sampling, a special consent will be obtained, thus the patient can participate in the validation without having to provide a sample. If necessary, research staff will offer help to filli in the forms digitally on site. If possible, the visit is coordinated with any other planned visits to the establishment. Samples that will be taken will be:

1. Blood sample for analysis of PETh
2. Capillary blood from finger for DBS cannabis test
3. Saliva test for drug and drug screening.
4. Blood samples for biomarker research and genetic analyses. (if the research subject has given separate consent).

Within 2 weeks after the first visit, the first 100 research subjects may answer the COMM and P-GIC forms digitally again (test-retest).

The research subjects will also be asked in connection with the consent if they would like to be interviewed by a researcher. Among the first 30 research subjects who have accepted participation in the interviews, they will undergo a semi-structured interview (see section Qualitative review). If saturation is reached before 30 participants have been interviewed, the number may be lower.

i. Sample handling

i. PETh – At least 1ml of venous blood is taken into an EDTA tube with a purple stopper. The sample can be stored at room temperature for a maximum of 24 hours. The person must not drink alcohol 24 hours before the sample is taken. If transport to the laboratory cannot be arranged immediately, it is stored in a refrigerator. Samples are ordered in Cosmic with printing of a label used to mark the sample. The sample is sent at room temperature to the Academic Laboratory. From the Pain Center and Primary Care centers, research personnel personally deliver the sample to the laboratory. Analysis is performed by high-resolution liquid mass spectrometry (LC-HRMS), the sample is saved for two days and then discarded.

ii. DBS – Dry blood sample is a capillary blood sample, which is taken from the 3rd or 4th finger of the non-dominant hand and 2 drops are collected on a collection card. Collection cards are marked with a preprinted study-related barcode. It is transported to the Academic Laboratory together with other samples at room temperature. The laboratory freezes the sample to -70°C in its biobank and stores these for the analysis. DBS is placed in buffer solution and then analyzed with LC-HRMS for phosphatidylethanol and cannabinoids.

iii. Saliva sample – Saliva sample is collected with standartised sampling kit Quantisal. The sample is processed and saved in the biobank at the laboratory. Samples are taken

for batch analysis after pilot testing, at interim analysis and after collection of all samples.

iv. Blood samples for biomarker analysis for future studies of long-term pain and neuroinflammatory processes are handled as follows; Plasma, Tube: 1pc 7/6ml Vacuette K2EDTA tube with purple cork (456243) which after centrifugation and aliquoting is transported to Ishotellet and DNA analyzes (Tube: 2pc 4ml Vacuette K2EDTA tube with purple cork (454410), transported to Uppsala Biobank "Fryshotellet" .

b. Control group

Patients who are scheduled for a visit to the pain clinic, pain rehabilitation, neuromodulation or GP doctor's visit and are not on opioid treatment are recruited to the control group. Pre-screening of this is carried out by responsible recruitment personnel. People are contacted by phone by research staff and invited for sampling before their visit to the respective facility, and at the same time they are sent information about the study for patients. These people sign informed consent at the visit and only provide samples for blood, DBS, saliva tests, and possibly biobank samples for future analysis of biomarkers and DNA. Only demographic data is collected on these individuals, ie age, gender, status, education and employment and confirmation that they have a chronic pain condition and are not prescribed opioids. The sampling takes place in the same way as the test group. (see i. Sample handling)

c. Form and outcome measure (Answered only by the test group)

- COMM is based on 17 questions, all of which are answered on a 5-point Likert scale. [4]
- ASI-SR – (McLellan et al, 1992; Rosen et al ,2000, Ljungvall et al,) – is based on interview questions that are used for addiction monitoring by calculating "composite scores", mathematical score measures that are sensitive to change and that are used for

follow-up and research. The scoring measures are produced according to a standardized model from the National Board of Health and Welfare (2017). Each domain is calculated in point measures.

In addition to COMM and ASI-SR, the questionnaires BPI-SF, PGI-C, AUDIT and DUDIT will be completed electronically or at the first mailing. These correspond to scales for characteristics of selected patient groups regarding severity of pain, effect of treatment, alcohol and drug use.

- Brief Pain Inventory – short form (BPI-SF) - (Charles C. Cleeland, PhD, Pain research Group, Dept. of Neurology, University of Wisconsin Madison and Bengt Bergman: Lund division, Sahlgrenska University Hospital, Gothenburg) – measures ongoing intensity and impact of pain on different areas of life (eg activity, sleep, well-being). From there you can calculate the indexes "Pain Intensity" and "Pain Interference".
- Patient global impression of change – PGI-C (Geisser et al, 2010). The PGI-C is used to measure overall change in health status. The question is directed at whether the patient experiences an overall change in health status after starting treatment, in this case opioids.
- Alcohol Use Disorder Identification Test (AUDIT)[41] for alcohol use[41].
- Drug Use Disorder Identification Test (DUDIT)[42] for drug use.
- selected questions from the Pain Disability Index (PDI) which measure disability regarding work/study and social role/function.[43]
- Patient Health questionnaire (PHQ9)[44]
- Generalized anxiety disorder 7-item scale (GAD-7)[45]
- Form "Demographic data on research subject" (includes age, gender, education level, work status. requested in the survey).

- Demographic measures: age, sex, level of education, work status is requested in the survey, duration of treatment and pain condition and number of visits to healthcare in the last six months (specifically acute visits), diagnosis for which the preparation is prescribed, preparation and dose and actual amount prescribed in the last 6 months and any signs of overuse or problematic use are searched retrospectivly in the Cosmic record system by the responsible researcher.

Validation will be done against the results of drug and alcohol analysis from saliva tests and blood.

As the original COMM instrument has identified 5 categories of questions, each area will be assessed against the following instruments:

1. Symptoms and signs of drug abuse (question 1) – AUDIT, DUDIT, ASI-SR, drug and alcohol test

2. Emotional and psychiatric problems (questions 2,5,7,8,13) – ASI-SR, GAD-7, PHQ9

3. Visitor characteristics/patterns (questions 3,12,17) - medical record data

4. Occurrence of untrue statement (doubt/lie/untruth) and drug use (questions 4,6,9,10,11) - medical record data, drug and alcohol tests

5. Medication use and deviation from prescription (non-compliance) (questions 14,15,16). – medical record data, occurrence of overprescription.

Pain-related questions will be assessed with the BPI-SF.

d. Qualitative review

The research subjects will also be asked in connection with the consent if they would like to be interviewed by a researcher. Thirty of the first research subjects who answer yes will undergo a semi-structured interview where ease of use is examined using the

"think aloud" method, i.e. questions about what the subjects think about the forms. Main issues are understanding of the questions, choice of language and possible associations that can be perceived negatively. The interview is then reviewed with qualitative content analysis.

e. Expert assessment

In addition, further evaluation will be carried out where 10 experts in this field in Sweden (Pain doctors, addiction medicine doctors, psychologists, behavioral scientists, etc.) will be asked to answer questions regarding the assessment of content validity and their estimation will be the basis for calculating the Content validity index (CVI).

6. Sample size

Bonett's formula has been used to calculate the sample size at a minimum Crohnbach alpha index of 0.7 and p= 0.05 and a desired power of at least 80%. The desired number for this analysis is 66 people.

For confirmatory factor analysis with rotation, 170 people are necessary (minimum 10 per free parameter, n=17) and this was adjusted due to the risk of study dropouts to 200 people[46]. The final number of people desired to be recruited to achieve relevant strength is estimated to be 200.

For prevalence measurement, the number of positive responses for at least one substance is expected to be 10% in the test group and 1% in the control group. To achieve alpha 0.05 and beta 0.85, n=114 need to be recruited for an expected result of 10%, (beta 0.95 n=225, Beta=0.9 n=183). With a calculated risk of 5% drop-out, we will include all 200 patients in the test group and 200 in the control group. After collection of 100 patients, an interim analysis will be carried out to estimate results and if any group size needs to be adjusted.

For test-retest, the first 100 of these patients will be selected from the test group.
For the qualitative part, an interview with a maximum of 30 patients is planned, consecutively among the first to accept participation in this part. If sufficient information emerges earlier from the interviews (saturation), the number may be smaller.

7. Statistical analysis

The entire study and the statistical plan are designed in collaboration with statistician Anders Berglund from Clinical Neuroscience at KI and Statistics Academy.
Health data from medical records and data from respective forms as well as laboratory responses are compiled in a study database and transferred to the statistics program for analysis. Internal consistency and reliability are examined with Cronbach's alpha, which is expected to be higher than 0.70 with $p \leq 0.05$[47]. For analysis of agreement between the two test occasions of COMM, intraclass correlation (ICC) will be used. The results measured are the total sum of points in COMM. ICC coefficient is judged to be low below 0.40, satisfactory between 0.40-0.59, good between 0.60-0.70 and excellent between 0.75-1.00 [48].

Correlation of results of COMM and ASI-SR is assessed with Pearsson and Spearman correlation coefficient for the respective clusters of questions. The different clusters/dimensions of questions in the form that can be identified to correlate together are examined with confirmatory factor analysis with rotation. Discriminant validity of ASI-SR composite scores and external validity measures will be calculated with intercorrelation matrix between COMM groups of questions, ASI-SR composite scores and external validation measures. The limit requirement for charges is >0.40.

SPSS, SAP and Amos programs are used for statistical processing. The qualitative part is not covered by the statistical plan.

In prevalence estimation, both groups will be described with descriptive statistics. Occurrence of addictive drugs and drugs as well as measures of alcohol use (PETh) during the last 3 weeks in both the test group and the control group will be compared with a chi2 test. Odds analysis of secondary use of illegal substances, parallel dependence on other substances and drugs and alcohol during LOB is carried out. Correlation analysis of PETh results from standard blood tests and DBS is carried out.

8. Timetable

Recruitment will start in the december of 2023. Collection of data and samples is estimated to last for at least one year until the required number of research subjects is recruited, estimated to take 24 months, but a maximum of 36 months. Processing of data and compiling results and script is estimated to begin in 2025. Completion of study is estimated to 31.12. 2025, but may be extended depending on the pace of recruitment. Publication is planned for 2026-7.

9. Relevance to the society

Treatment with opioids for long-term non-cancer-related pain should only take place in carefully selected patients, where the risk of addiction development is low and even then, the treatment must be monitored. Identification of the risk of addiction before starting treatment is important, as well as follow-up with the identification of early signs of addiction. Currently, there is no validated Swedish instrument that identifies addiction problems in patients with pain and ongoing opioid treatment. COMM is

developed specifically for this group and thus has the potential to facilitate assessment and follow-up of patients. The ASI-SR is validated for the addiction population, but not for pain patients. Routine urine drug screening is a problem for most healthcare facilities in Sweden. Introduction of new analytical methods with high specificity and sensitivity but at the same time low costs and easy handling is important in securing patients' health. Knowledge of the prevalence of substance use in Sweden is important both in the national health economic considerations, when introducing and designing clinical routines and assessment of the individual care recipient.

10. Ethical aspects

The subject's data will be pseudonymized and saved with a special study code, which only the study doctor has access to on the Pain Centre's research database. Results will be presented at group level and no data on patient identity will be presented in publications. The sampling does not deviate from usual clinical sampling. Test results from PETh will be able to be used in clinical assessment, which is still part of usual clinical consideration. Answers to drug samples will not be available in clinical practice, moreover, samples are analyzed long after the clinical visit. The patient need not fear that the result will affect the doctor's assessment and treatment. Samples are destroyed if the patient requests this or after the study is completed, except for the samples for analyzes of neurobiological markers in opioid use, which will be saved in the biobank for 15 years.

In conclusion, the benefit of the information, which may contribute to improved care of this patient population, exceeds the potential risks to which the research subject may be exposed.

11. Data processing

All data will be handled confidentially in accordance with the Data Protection Regulation (GDPR) Article 6 and stored in an encrypted folder on the Pain Clinic's server in the manner and for the time required by the regulations. Data is processed using statistical software by professional statistician. Data undergoing statistical processing is coded. Study data will be stored for 15 years.

12. Funding:

The Pain Centre Uppsala University Hospital is the main financier (partly clinical funds but also Research and development funds of Region) with contributions from Kamprad Family Research Grant, Uppsala University, Department of Surgical Sciences, Department of Neurosciences, Department of Public Health and Care Sciences, General Medicine and Preventive Medicine, Primary Care, Region Uppsala and the Academic Laboratory in the form of salary to participating researchers. The academic laboratory is responsible for the costs for storage of samples at the laboratory and analyzes of DBS samples. Projects have so far been granted SEK 3,640,000 from R&D funds.

13. Distribution of responsibilities

Rolf Karlsten, senior consultant, associate professor and section manager for the Pain Center is the Principal Investigator for the implementation of the entire project, responsible for financing and oversees all parts of the project.

Lenka Katila, consultant in pain medoicine and PhD student in the project. Lenka has clinical links to the Pain Centre, the Addiction Clinic and the Endometriosis Centre. She

is coordinating researcher and is responsible for translation and the validation process, EPN application, recruitment within specialist care at Academic hospital, statistical analysis, coordinator of the qualitative part and coordination of publications and dissemination of the results to the public and professions.

Hanna Ljungvall is a sociologist and doctor of medicine. She is participating in discussion about project design, translation, responsible for qualitative interviews and its qualitative analysis.

Pernilla Åsenlöf is a physiotherapist at the pain center and professor in physiotherapy. She has an advisory function and review regarding the translation and validation process. Her great knowledge in qualitative research is of great importance in the parts where qualitative methods and analysis are carried out. Important role in the preparation of manuscripts and in the publication process.

Annica Rhodin, doctor and doctor of medicine, is an expert researcher in drug addiction and participation in the translation and is an advisor in the entire process.

Anna Svensson, general practitioner and PhD student is responsible for the recruitment process in primary care and participation in qualitative interviews.

Magnus Peterson is a general practitioner, pain consultant participating in the discussion about project design with overall responsibility for recruitment in primary care.

Anders Berglund, Doctor of Philosophy, is participating in the discussion about the design of the project and is responsible for the statistical plan and analysis.

Torbjörn Åkerfeldt, is a senior physician and medical management manager at the Academic Laboratory with long-term experience in drug and drug analysis and a doctoral student at the Department of Medical Research. Participates both in planning and practical implementation of study as well as evaluation of results.

Kim Kultima is associate professor in the Department of Medical Science and biomedical analyst with expertise in applied biomedical analyses. Responsible for carrying out analyses, checking results and their interpretation.

Rezvan Kiani Dehkordi – research nurse at the Pain Centre, responsible for documentation, sample handling procedures and GCRP

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