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Study Protocol

Conditioned Open-Label Placebos to Facilitate Opioid Reduction in Patients with Chronic Noncancer Pain: Study Protocol of a Randomized Controlled Trial

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Abstract

Introduction

Chronic non-cancer pain (CNCP) presents a global health problem, with a significant increase in opioid prescriptions over recent decades. However, opioid therapy poses risks of adverse events, overdose, and non-medical use. As a result, many patients seek to discontinue or reduce their opioid intake. Strategies for opioid tapering often lack efficacy, prompting the investigation of novel approaches like open-label placebo (OLP), i.e., the administration of a placebo with full disclosure that it is a placebo. OLP has shown efficacy in CNCP syndromes and has been suggested as a promising candidate for medication tapering. This study aims to assess whether OLPs can enhance the reduction of daily morphine equivalent dose (MED) in CNCP patients and examines its potential in mitigating opioid withdrawal symptoms.

Methods and analysis

This study is designed as a randomized, controlled, single-center trial. Participants will be randomized into either an OLP group or a control group. The study duration will span 6–9 weeks, during which all participants will aim to reduce their opioid intake. Both groups will monitor their opioid intake daily using a diary app and will receive feedback on their progress of reducing opioids. Additionally, participants in the OLP group will receive OLP tablets for the entire study period. During the first week, the OLP group will undergo a one-week learning phase (=acquisition phase) using a classical conditioning paradigm, where each opioid intake is paired with a placebo. In the subsequent five weeks, the OLP group will enter a dose-extension phase in which only the first opioid intake of the day is paired with a placebo and additional placebos can be taken as desired. At the end of the study, qualitative interviews will be conducted with the first 15 participants in the OLP group. The primary outcome measure is daily opioid intake. Secondary outcomes include opioid withdrawal symptoms, pain severity, disability, anxiety, depression, opioid beliefs, intervention expectancy, and qualitative data. Statistical analyses will include ANCOVA and regression models.

Ethics and dissemination

The Ethics Committee of the Canton of Zurich, Switzerland, approved the study (SNCTP-nr.: SNCTP000005853 / BASEC-nr.: 2023-02327).
Participants will be compensated with CHF 100 for their full participation in the study. Participants who will take part in the qualitative interview at visit 6 will be compensated with additional CHF 15.

Registration details

This study is registered at clinicaltrials.gov: NCT06350786.

Key words

Open-label placebo; chronic noncancer pain; opioid reduction; opioid tapering; randomized controlled trial

Strengths and limitations of this study

- This study introduces an OLP intervention for opioid tapering in chronic non-cancer pain, harnessing the mechanisms of the placebo-effect, such as classical conditioning and expectations.
- Benefits of participants receiving the OLP intervention include a potentially reduced need for opioid medication and, potentially the experience of fewer side effects.
- The OLP tablet intake investigated in this study does not expose participants to known or expected risks exceeding the risks of the standard care encompassing opioid reduction.
- OLP and the control group are designed to ensure structural equivalence. Both groups feature electronic monitoring a of opioid intake and the same number of interactions with a member of the study team.

Introduction

Background and Rationale

Chronic non-cancer pain (CNCP) is a major global health issue, affecting nearly 20% of adults in Europe alone [1]. This has led to a substantial increase in opioid prescriptions for CNCP management, both in the United States and Europe over the past two decades [2–6]. Despite this, there is no consistent international treatment standard for the long-term therapeutic use of opioids in CNCP management, according to the guidelines provided by the Association of Scientific Medical Societies in Germany [7]. Additionally, opioid therapy is associated with various adverse events and risks, including abuse, overdose, and opioid-induced hyperalgesia [8–10].

Since risks often outweigh benefits [11], many patients receiving opioid therapy report the desire to stop or cut down their opioid use [12,13]. Current strategies for tapering include dose reduction protocols, pharmacological opioid replacements, and non-pharmacological therapies. However, systematic reviews concluded that there is only very low-quality evidence available that opioid tapering interventions may be effective [9,14,15]. The feasibility of nonpharmacological adjunctive therapies is limited in primary care settings as they are typically time-consuming, difficult to access, costly, and managed outside the direct patient-physician interaction [16]. Pharmacological approaches, on the other hand, lack patient empowerment [17]. These challenges prompt the need for developing other types of tapering protocols.

Notably, the endogenous opioid system plays a role in mediating the placebo response, with placebo effects being particularly pronounced in opioid trials [18,19]. This is particularly important for CNCP, where patients show substantial and clinically relevant placebo responses [20–22]. However, the administration of deceptive placebos violates patients' right to autonomy [23,24]. Administering placebo without deception could harness the placebo effect successfully and ethically [25–28].

The administration of an open-label placebo (OLP) intervention, i.e., the placebo administration with full disclosure of being a placebo, is promising. OLPs have proven effective in managing CNCP syndromes, such as chronic low back pain [29,30] and irritable bowel syndrome [21,31]. Several (network) meta-analyses have demonstrated that patients receiving OLPs experience significantly greater pain relief compared to those in control groups [32,33]. Moreover, and of relevance when it comes to the need to reduce opioid medication, OLPs have been shown to be a promising candidate for medication tapering [34]. This effect can be understood through a conditioning paradigm, where the process of tapering works by pairing the medication (the unconditioned stimulus) with the neutral stimulus of an OLP during a learning phase. Subsequently, in the evocation phase, the OLP alone acts as a conditioned stimulus, eliciting a response similar to that of the medication [35–38]. Recent findings suggest that OLP analgesia, similar to deceptive placebo analgesia, is mediated by endogenous opioid systems [39]. One pilot study with 20 spinal

cord injury and polytrauma patients has employed this approach and showed that OLPs are effective [28]. In a different study using a single-group design, that examined OLPs as an adjunctive intervention for opioid reduction in acute pain, pain relief scores for placebos and opioids did not differ significantly [27]. Furthermore, conditioned OLP has been shown to reduce daily opioid consumption and postsurgical pain among patients recovering from spine surgery: Patients in the conditioned OLP group used approximately 30% less daily morphine milligram equivalents compared to those in the treatment-as-usual group [40].

These findings are in line with studies spanning two decades, revealing that it is possible to condition the opioidergic system [41–44].

Despite these promising findings, there is a lack of trials that examine OLP as an adjunctive intervention for the reduction of opioid medication in the CNCP population. This is noteworthy, given that therapeutic opioid doses are associated with side effects, along with clinically relevant responses to OLPs. The OLP intervention offers a promising approach to tapering long-acting opioids within a structured reduction regimen, potentially leveraging placebo analgesic effects in CNCP patients without compromising pain relief efficacy.

Our study addresses this gap by specifically examining the use of OLPs for opioid tapering in the CNCP population. While prior research has demonstrated the analgesic efficacy of OLPs in chronic pain conditions and their potential in reducing opioid consumption in surgical or acute pain, these findings have not yet been extended to patients with CNCP undergoing structured opioid tapering. Additionally, our study explores the feasibility and acceptability of integrating OLPs into primary care opioid tapering protocols, areas that remain underexplored in the existing literature.

Aims and Objectives

The primary aim of the present study is to evaluate whether the daily morphine equivalent dose (MED) of opioid medication in patients with CNCP can be reduced with an OLP adjunctive intervention compared to a control group. Our secondary aim is to evaluate whether the OLP intervention can reduce opioid withdrawal symptoms in comparison to the control group.

Methods and Analysis

Study Design

This study is a randomized, controlled, single-center trial with two parallel groups. The study duration will span 6-9 weeks, from pre-screening to study conclusion. The primary endpoint is the change in opioid consumption between the first 7 days with start of the acquisition phase and last 7 days of the dose-extension phase. It is calculated as mean daily use of opioid medication (i.e., the daily morphine equivalent dose, MED) over each 7-day period. Participants will be assigned to the OLP and control

groups. Randomization will be conducted using a three-level stratified block randomization based on their baseline MED as follows: low (< 40 mg), moderate (40 mg–100 mg), and high (> 100 mg). Participants in both groups will record their daily opioid intake, and the OLP group will additionally record their placebo intake, with the SEMA3 [45] smartphone application. The data collected in SEMA3 will comprise the name of the opioid, the type of opioid (e.g., tablet), daily intake quantities (dosage) as well as time and date of intake. These details will then be used for electronic monitoring (EM) feedback, which will be delivered during three visits (7, 21 and 42 days after baseline) and will take approximately 30 minutes. EM feedback will be similar for both groups and will be based on a graph representing daily opioid medication intake, as entered by the participants into SEMA3. During the EM feedback, the study member will discuss with the study participant the adherence to their medication intake in an empathic and non-judgmental manner.

Self-reported outcome measures will be collected via surveys on an online platform, Research Electronic Data Capture (REDCap) [46], during four visits for both study groups (14 days prior to baseline, at baseline, and 7 and 42 days after baseline). Both groups will receive the interventions from the project manager and study team members. All members of the team have been trained in delivering the intervention and have completed the Good Clinical Practice course at the University Hospital Zurich. Due to the transparent nature of the OLP intervention, participants and investigators will not be blinded to group assignments.

Eligibility Criteria

Inclusion criteria assessed during the pre-screening procedure include age 18 or older, proficiency in German, chronic non-cancer pain for at least six months, chronic opioid medication use for more than three months, oral intake of opioids, self-reported motivation for opioid reduction, a primary treating physician overseeing the opioid reduction process, and access to a computer or tablet with an email account.

Exclusion criteria include psychotic symptoms, suicidality, cognitive impairment, planned surgery within the next two months, self-reported illicit drug, harmful alcohol use, intolerance to placebo ingredients (e.g., lactose, sucrose, corn-starch), serious health issues preventing study participation, and concurrent involvement in other CNCP studies. Participants may continue to use their regular medication (i.e., other than opioid medication).

Recruitment

Participants will be recruited primarily via flyers and posters at the University Hospital of Zurich pain outpatient department and related clinics. Additionally, recruitment will occur at outpatient pain clinics, pain centers, general practitioners' practices, pain community centers, addiction associations,

and pharmacies throughout Switzerland, with a focus on the canton of Zürich. Online recruitment will also be conducted. All study processes will take place at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the University Hospital of Zurich to maintain a single-center approach.

Study Procedures at Each Visit

For each participant, the study will include a total of six study visits over the course of 6 to 9 weeks. Please refer to Figure 1 for a detailed overview of the study design and study flow. Each phase is described below.

Pre-screening via telephone call and informed consent (visit 1, timepoint t-2, -21 days prior to baseline)

During an initial telephone contact at timepoint t-2, a pre-screening will take place to verify potential eligibility for participation in the study. Potential study participants will receive detailed study information and the informed consent form by mail.

Screening (visit 2, timepoint t-1, -14 days prior to baseline)

Once informed consent is signed by participants, they will complete an online screening questionnaire via REDCap to further evaluate their eligibility. This screening includes more detailed assessments of clinical and demographic criteria compared to the broader criteria evaluated during pre-screening. If eligibility criteria are met, participants will be scheduled for the baseline visit on-site. Additionally, the primary treating physician will be informed about the study participation and will receive a link to a questionnaire in REDCap to assess their expectations regarding whether their patient will reduce the amount of opioids during the study, along with a second questionnaire to evaluate the physician's acceptability of the OLP approach.

Baseline assessment at study site or via telephone call (visit 3, timepoint t0, 0 days)

Participants will be informed of their group assignment (i.e., OLP or control) and will receive a group-specific rationale from a study member. Both treatment rationales will explain the potential benefits of EM feedback in supporting patients during voluntary prescription opioid tapering. The treatment rationale for the OLP group is based on the discussion points, adapted from Bernstein [27], including the following statements:

1. Opioids work by telling your body that you are experiencing less pain.
2. Placebos should be taken every time an opioid is taken, supporting the reduction of opioid medication (as shown by previous studies).

3. By pairing the tablets together, your brain will learn to release chemicals like endorphins that cause pain relief in response to the placebo, just as it does in response to the opioid.
4. At a certain point, placebos might provide adequate pain relief, and you may need fewer opioids.

The OLP group will additionally receive placebo tablets for six weeks (150 placebo tablets = three blister packs).

The treatment rationale for the control group will solely explain the potential benefits of EM feedback, without any discussion points, as this group will not receive any placebos.

Subsequently, self-reported baseline surveys will be assessed by both groups online in REDCap. After completing the online surveys, daily monitoring of opioid and placebo tablet intake via the SEMA3 app will be explained to the participants.

After the baseline visit, participants in the OLP group will undergo a one-week acquisition phase, where they will pair each opioid intake with an OLP tablet to initiate a learning process via classical conditioning.

Interim visit via telephone call (visit 4, timepoint t1, 7 days after baseline)

Seven days after the baseline, a meeting via telephone call will take place between the study participant and a study team member. Participants in both groups will receive a brief repetition of the group-specific rationale. Subsequently, EM feedback will be provided to both study groups. EM feedback will be based on a graph representing daily opioid and placebo (for the OLP group) intake, as entered by the participants into SEMA3. The study member conducting the intervention will discuss the adherence to the participant's medication intake in an empathetic and non-judgmental manner. The EM feedback will be similar in both groups. Thereafter, the link for the online questionnaires in REDCap will be sent to participants of both groups for the assessment of the secondary outcomes. The same questionnaire as at timepoint t0 will be used.

After the interim visit, the dose-extension phase will start and will continue until the study concludes. In this phase, participants will only pair the first opioid intake of the day with a placebo. For the OLP group, additional placebo tablets may be taken throughout the day as needed, and all additional placebo intake will be recorded in the SEMA3 app.

Booster visit via telephone call (visit 5, timepoint t2, 21 days after baseline)

In both groups, a booster meeting via telephone call will take place between the study participant and a study team member to ensure that the intervention has been understood as agreed upon in the last meeting, including a brief repetition of the group-specific rationale. EM feedback will be provided to

participants in both groups in the same way as during Visit 4. For the OLP group, the dose-extension phase will continue unchanged until the end of the study.

Post visit at study site or via telephone call (visit 6, timepoint t3, 42 days after baseline)

At the end of the sixth week, the study intervention will end for both groups, and participants will take part in the last intervention at the study site or via telephone call. EM feedback will be provided to participants in both groups in the same way as during visits 4 and 5. Subsequently, participants will complete an online questionnaire in REDCap with the secondary outcomes and evaluation outcomes. Furthermore, the first 15 participants of the OLP group will take part in a semi-structured interview. The choice of number was made to gather insights as fast as possible about the chances and hurdles of the OLP approach, also for upcoming trials planned while the current RCT is still ongoing. The qualitative interview will aim to gather in-depth experiences of participants and will cover the following topics (the interview guide can be found in the eAppendix 1):

- Experiences of the OLP intervention within the study
- Acceptability of the OLP intervention
- Prerequisites, ideas, and concerns regarding practical OLP implementation

Participants will be compensated for their participation with 100 CHF, with an additional reimbursement of 15 CHF for those participating in the interviews. Study results will be provided to participants on request.

Patient Involvement

A patient partner was contacted prior to the study start and was involved in detailing the study design and procedures. In a later phase, the patient reviewed the study protocol to ensure clarity and relevance from the patient's perspective. Additionally, the patient played an active role in simulating the first intervention (t0) and the treatment rationale for the control group, providing feedback regarding the plausibility of the intervention, which helped refine the study approach.

Study Outcomes

Please refer to Table 1 for a detailed overview of study outcomes and measurement time points.

Primary Outcome: Daily Opioid Consumption

The primary study outcome will be assessed based on the daily dose (i.e., total amount) of opioid medication consumption. Given that participants will potentially be prescribed a range of opioid medications, daily morphine equivalent dose (MED) will be standardized using the morphine milligram equivalent (MME) conversion factor with the following formula: MED = daily dose of single opioid *

MME conversion factor [47]. The total morphine equivalents are subsequently summed to assess the total amount of opioid medication taken per day (i.e., sum of the different opioids with regard to their daily dose). Each opioid is assigned its own conversion factor in relation to morphine, which can be obtained from conversion tables [47].

Although the data of the daily intake of the opioid medication will be recorded daily, the two main time points of interest for the primary outcome will be t0 and t3. The change between these two time points will be examined. The average (mean) consumption of opioid medication (MED) during the first seven days (starting with the acquisition phase) and the last seven days of the dose-extension phase will be calculated for each participant in MED.

Secondary Outcomes

- Main Secondary Outcome: Subjective opioid withdrawal symptoms will be collected via a survey in REDCap at t0, t1, and t3, respectively. The two main time points of interest are t0 and t3. The change between these two time points will be examined. The Subjective Opiate Withdrawal Scale (SOWS) measures gastrointestinal, autonomic, musculoskeletal and psychiatric symptoms that typically occur during opioid withdrawal [48]. Sufficient sensitivity and moderate test-retest reliability could be shown for SOWS, as well as high validity and internal consistency [48]. In our study, we use the German translation, which was supplemented by four additional questions in the questionnaire [49]. The intensity of the withdrawal symptoms is rated by patients on a scale between 0 (= not at all) and 4 (= extremely), the scores for individual symptoms are added to a total sum score, which can range from 0 to 64. The SOWS was validated in a study on inpatient opioid withdrawal with CNCP patients of a German sample [49].
- Other Secondary Outcomes: Other secondary outcomes will be collected via a survey in REDCap. All of these data are collected from the study participants at t0, t1, and t3, respectively, except the intervention expectancy outcome, which will be examined at the study start only (t0). The two main time points of interest are t0 and t3. The change between these two time points will be examined.
    - *Pain Severity*: Pain severity is assessed using the ICD-11 specifiers or 'extension codes' [50]. The index combines patient-assessed ratings of pain intensity, pain-related distress and pain-related interference. Each of these ratings is assessed on an 11-point NRS ("*Numeric Rating Scale*"), and these are mapped into the following categories depending on the NRS score: none = NRS 0, mild = NRS 1 - 3, moderate = NRS 4 - 6 and severe = NRS 7 - 10. The preliminary German translation was provided by a member of the IASP task force ICD Initiative.
    - *Pain Disability:* The Pain Disability Index (PDI) measures the subjective degree of self-reported impairment caused by the pain problem in everyday life. Seven domains

of life are assessed: (1) family and domestic responsibilities, (2) recreation, (3) social activities, (4) occupation, (5) sexual life, (6) self-care, and (7) essential activities. The internal consistency is Cronbach's α = 0.83 - 0.90. Findings demonstrate one-dimensionality, criterion-related and construct validity (e.g., Oswestry Low Back Pain Disability Questionnaire: r = 0.76, pain intensity: r = 0.23 - 0.62, BDI: r = 0.26 - 0.52, CES-D: r = 0.55). Criterion-related validity is also supported by findings on inpatients with pain who were assigned three stages of chronification based on the Mainz staging concept of chronic pain. Percentile ranks are available [51].

- *Anxiety*: The German version of the Generalized Anxiety Disorder – 7 (GAD-7) is a brief instrument for assessing self-reported generalized anxiety disorder (GAD) symptoms [52]. The internal consistency is Cronbach's α = 0.89 and the German version has been validated on a representative sample of the German population. The seven items of the GAD-7 ask about the main diagnostic criteria of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnoses (DSM-IV) and ICD-10 criteria, including worrying, trouble relaxing, and feeling nervous.
- *Depression*: The Patient Health Questionnaire – 9 (PHQ-9) measures the severity of depression in self-report [53]. The module consists of nine items and is part of the Patient Health Questionnaire (PHQ-D). The German version of the PHQ was derived from the 'Prime MD Patient Health Questionnaire' and is based on the depression criteria of the DSM-IV [53]. The internal consistency for the depression module is Cronbach's α = 0.88 and was validated on a representative patient sample as well as on a representative sample of the general German population [54].
- *Beliefs regarding opioid use*: The Pain Opioid Analgesics Beliefs – Cancer (POABS-CA) measures pain opioid beliefs based on two components (i.e. negative effect beliefs and pain endurance beliefs) with 10 items and a 5-point Likert scale ranging from 0 ("strongly disagree") to 4 ("strongly agree") [55]. The higher the score, the more negative the opinion about the use of opioid analgesics for cancer pain, and the stronger the belief that pain should be endured. From a study with patients with cancer in a Taiwan population, a Cronbach's alpha of 0.84 for the total scale, 0.74 for the negative affect belief scale, and 0.80 for the pain endurance beliefs scale has been reported [56]. For our study, we use the version translated into German which applied the questionnaire to a primarily non-cancer population [57].
- *Intervention Expectancy:* At the study start (t0), participants' intervention expectations will be measured in analogy to our most relevant outcomes. For this, the following item will be used: "How confident are you that you can reduce/discontinue

your opioid medication?" Second, to measure the expected withdrawal symptoms at the end of the study, we will use the items from the Subjective Opiate Withdrawal Scale (SOWS) [53]. The introduction of this questionnaire will be adjusted so that the questions of the questionnaire are related to the participants' expectancy regarding their opioid withdrawal symptoms at the end of the study, rather than their current opioid withdrawal symptoms.

Evaluation Outcomes:

- *Rationale Credibility*: The rationale credibility of the OLP intervention will be assessed in the OLP group at study end (t3). The following questions will be asked: "During the study, did you believe that these were placebo tablets that did not contain a pharmacologic agent?", "Did you find the explanation of why the placebo intervention may work helpful?", "How helpful did you find the explanation of why placebo intervention can work?". Answers will be rated on a Likert scale ranging from 0 = Not at all to 4 = Extremely.
- *Placebo Understanding:* The Placebo Understanding Questionnaire will be administered to both study groups at the study end (t3), assessing participants' understanding of placebo and their attitudes toward non-specific therapies. The first three items of this questionnaire specifically evaluate placebo understanding and will be used for this study [58].
- *Patient-Provider Connection:* The Patient Provider Connection is a subscale of the German version of the Healing Encounters and Attitudes List (HEAL) which can be used independently from the six subscales [59]. The seven items are rated on a five-point Likert scale ranging from "not at all" to "very strong" assessing participants' attitudes towards patient-provider connection as a non-specific intervention effect. The German version of the HEAL has been validated on a representative sample of subjects (N = 165) who received healthcare treatments within the past year. The questionnaire will be assessed at study end (t3).
- *Non-Opioid Medication Intake:* Participants' non-opioid medication intake will be assessed at t0 and t3 by asking the participants about the medication's name, dosage, and reason for intake. In contrast to opioid medication, non-opioid medication will be assessed via REDCap.
- *Intervention implementation:* To examine the influence of the individual administering the study intervention, we record at t0, t1, t2 and t3 which study member implemented the intervention in the respective study groups.

Treating Physicians' Outcomes

- *Primary Treating Physicians' Intervention Expectancies:* At t0, the primary treating physicians' expectations will be measured in analogy to our most relevant outcomes. First, we will ask the physician how satisfied they think that the patient is with the opioid medication and whether they are optimistic that the patient will reduce the amount of opioids. Motivation will be assessed on a satisfaction ruler ranging from 0 % to 100 % [60]. Second, to measure their expectation regarding their patients' withdrawal symptoms at the end of the study, we will use selected items from the SOWS questionnaire [53]. The introduction of this questionnaire will be adjusted to ensure that its questions relate to the primary treating physicians' expectations regarding their patients' opioid withdrawal symptoms at the conclusion of the study.
- *Primary treating physicians' acceptability of the OLP approach*: At t0, the primary treating physicians will be asked about their acceptability of the OLP approach. For this, we ask them to imagine a scenario where a physician uses OLPs to help a patient reduce opioids. We will use two key items "Is it acceptable for the physician to try a placebo intervention?" and "Would you, as a patient, be willing to take this intervention?" Both questions use a five-point Likert scale, ranging from "No, not at all," "No," "Yes and no," "Yes," and "Yes, totally" [61]. Further variables include the perceived competence of the physician, along with patient satisfaction and worry regarding the treatment from the patient's perspective [12]. Competence will be answered on a seven-point Likert scale, ("Highly incompetent", "Incompetent", "Somewhat incompetent", "Neither incompetent nor competent", "Somewhat competent", "Competent", "Highly competent"). Satisfaction item can be answered on a seven-point Likert scale ("Very dissatisfied", "Dissatisfied", "Somewhat dissatisfied", "Neither dissatisfied nor satisfied", "Somewhat satisfied", "Satisfied", "Very satisfied"). Worry will be displayed on a seven-point Likert scale, ("Much more worried", "Moderately more worried", "Somewhat more worried", "Neither more nor less worried", "Somewhat less worried", "Moderately less worried", "Much less worried"). Finally, four additional items will be asked to assess interpersonal trust in the patient-physician relationship and the doctor ´s warmth to be answered on five-point Likert scale ("Strongly disagree" "Disagree" "Neither disagree nor agree "Agree" and "Strongly agree") [62].

EM-related Outcomes:

- *Placebo tablet count:* The intake of placebo tablets in the OLP group will be electronically monitored using SEMA3 from t0 to t3, serving as the primary way for assessing placebo intake. Additionally, a tablet count of the returned placebo blisters at t3 will be conducted, and the number of remaining tablets will be documented. A ratio

can be calculated from the tablet count recorded in SEMA3 and the count of tablets from the returned blisters, which can then be used for statistical analysis. For the statistical analysis the overall placebo intake between t0 and t3 is of interest.

- *Opioid use*: Participants in both groups will record their daily intake of opioid medication (including on-demand opioid medication) from t0 to t3 using SEMA3. The data collected this way will be used for EM feedback at t1, t2, and t3.

Qualitative Outcomes:

- The qualitative interview will be audio recorded. The study team will create transcripts of the audio recordings using the MAXQDA VERBI software [63] which will be examined subsequently with the method of thematic analysis using the same software.

Safety Outcomes:

During the EM feedback at t1, t2, and t3, participants will be asked if they have experienced any symptoms since the last visit. A study member will document these symptoms and discuss with the Project Manager or Sponsor Investigator whether they are related to study participation. If so, they will be recorded as an Adverse Event in REDCap and will be reported to the Ethics Committee and Swissmedic.

Data Management

All data and documents will be maintained in one of the following data management systems: TMF (Trial Master File), eTMF (electronic Trial Master File), REDCap, and SEMA3. TMF/eTMF, monitored by the Project Manager and Study Investigator, ensure restricted access for authorized team members. Person-identifying data of participants will be collected in a pCRF (paper Case Report Forms). Study data of each participant and study data for study procedure will be collected and recorded by electronic Case Report Forms (eCRFs) in REDCap. The eCRFs in REDCap will be set up by the Clinical Trials Center of the University Hospital Zurich.

Determination of Sample Size

A similar study on opioid dose reduction was conducted in CNCP patients, comparing an OLP with a TAU group [28]. With the data extracted from that study an SD value of 1.03 could be calculated for the between-group difference [63]. This effect size is notably high compared to other OLP studies, with recent meta-analyses reporting overall effects of SMD 0.72 [33] and SMD 0.88 [64]. Given the high variability and exceptional effect size, a conservative effect size of d = 0.60 was used for our sample size calculation. Using ANCOVA with the allocation group (OLP/control) as an independent

between-subject variable, and accounting for a 20% dropout rate, the final sample size is 86 (43 per group).

Statistical Analyses

Primary Analysis

For the analysis of the primary endpoint the baseline consumption of opioid medication will be calculated as the average (mean) of the first seven days of the study (from t0). For the analysis the differences in the consumption of opioid medication across the two groups of this study will be assessed. The primary aim will be analysed by a linear model in an analysis of covariance (ANCOVA), with the consumption at baseline as covariate and the randomized allocation (OLP vs. control group) as explanatory variable. The normality assumption will be graphically assessed. Log-transformation will be considered in case of violation. The dependent variable will be the average consumption of the opioid medication over the last seven days at t3.

Main Secondary Analysis

For the analysis of the main secondary endpoint the differences in the withdrawal symptom scores (SOWS) across the two groups will be assessed. The secondary endpoint will be analysed by a linear model with the withdrawal symptom scores at baseline as covariate and the randomized allocation (OLP vs. control group) as explanatory factor (ANCOVA). The normality assumption will be graphically assessed. Log-transformation will be considered in case of violation. The dependent variable will be the withdrawal symptom scores at t3.

Other Secondary Analyses

For the analysis of further secondary endpoints the differences across the two groups of various other scores assessed during our study will be examined. Each of these endpoints will be analysed by a linear model with their scores at baseline as covariate and the randomized treatment (OLP vs. control group) as explanatory factor (ANCOVA). The dependent variable will the corresponding scores at t3. These secondary endpoints are the following: Pain severity degree (ICD-11 specifiers), Pain disability degree (PDI); Anxiety (GAD-7); Depression (PHQ-9); Pain Opioid Beliefs (POABS-CA); Treatment Expectancy.

Analyses for Evaluation Outcomes

A t-test will be employed to compare the evaluation outcomes between the two groups. In the case that there is no normal distribution for the data, non-parametric procedures such as Wilcoxon / Mann-Whitney will alternatively be used for the statistical tests.

Qualitative Analyses

We will analyze the qualitative data by means of thematic analysis, taking a hybrid approach of inductive and deductive coding and theme development [65]. In this approach, core themes will be first elicited inductively from the collected data [66]. Subsequently, the core themes will be examined deductively with respect to theoretical assumptions about the OLP treatment rationale [67].

Monitoring

The investigator's site will collaborate with the Clinical Trials Center of the University Hospital Zurich to ensure monitoring. Monitoring activities are defined in a study-specific Monitoring Plan according to the Clinical Trials Center Monitoring.

Ethics and Dissemination

After obtaining ethical approval, the present study was preregistered at clinicaltrials.gov (Registration-Number: NCT06350786) (WHO, 2022) and at the Swiss Federal Database SNCTP (via BASEC) at kofam.ch (SNCTP-nr.: SNCTP000005853 / BASEC-nr.: 2023-02327).

This study involves placebo tablets ('P-Tabletten blau', Zentiva), which will be administered. The placebo tablets are an inert substance without any specific pharmacological effects, containing the following ingredients: lactose monohydrate, potato starch, pregelatinized starch (maize), magnesium stearate, povidone K 25, talc, and Patent Blue V.

Participants receive an information sheet and consent form providing sufficient details to make an informed decision about participation. Formal consent is obtained before any procedures, and participants retain a signed copy of the consent form.

On request patients will be informed about the findings of our study. The findings from the primary and secondary analyses will be submitted for publication in peer-reviewed journals.

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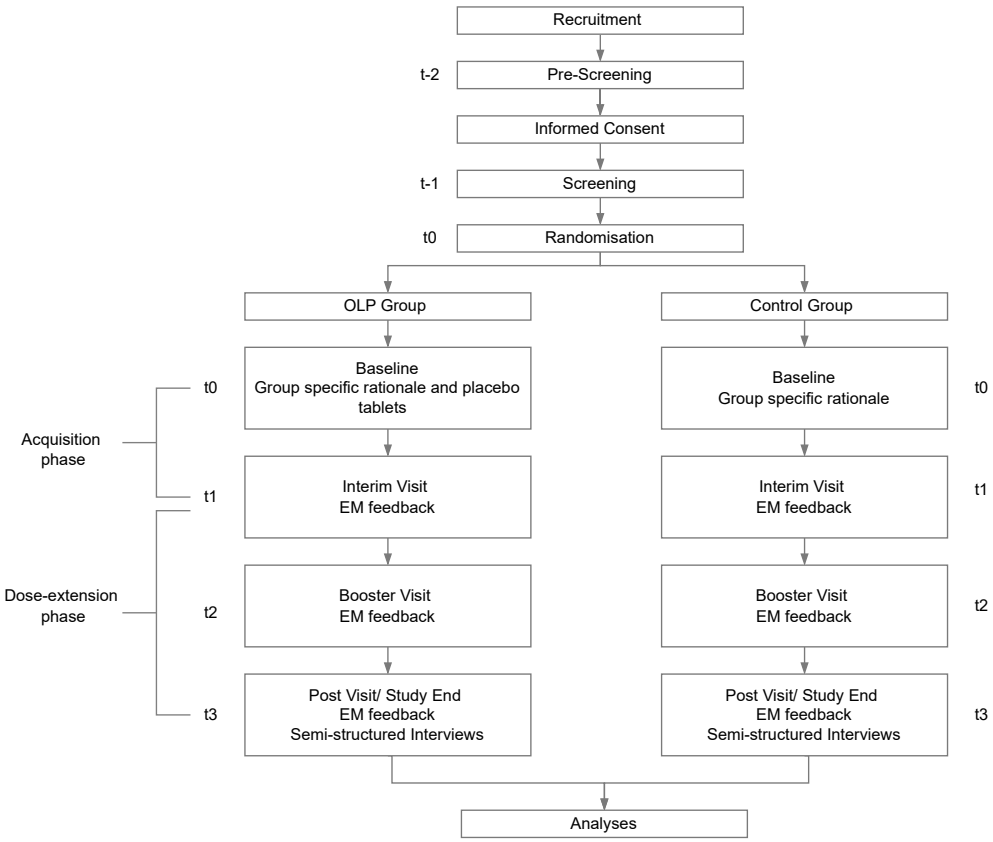
Table 1. Study Outcomes and Measuring Points

Study Schedule								
			Screening		**Intervention**			**On-going intake**
			Pre-Screening	Screening	Acquisition phase	Dose-extension phase	Dose-extension phase	Dose-extension phase	
		Visit	1	2	3	4	5	6	
		Timepoint	t-2	t-1	t0	t1	t2	t3	
		Days	-21	-14	0	7	21	42	
		Location	Phone	Online	On-Site/ Phone	Phone	Phone	On-Site/ Phone	Daily monitoring with App SEMA3
		Assessments			Baseline	Interim	Booster	Post	
Group specific intervention	Treatment rationale				x	x			
	EM feedback					x	x	x	
Screening	Study information		x						
	Informed Consent		x						
	Screening			x					
Contact Physician	Physicians' treatment expectancies			x					
	Physicians' acceptability of OLP			x					
Randomisation	Randomisation				x				
Primary Outcome	Opioid medication capture				x				
	Opioid medication intake								x

Secondary Outcomes	Subjective opioid withdrawal (SOWS)				x	x		x	
	Pain severity (ICD-11)				x	x		x	
	Pain disability (PDI)				x	x		x	
	Anxiety (GAD-7)				x	x		x	
	Depression (PHQ-9)				x	x		x	
	Pain Opioid Analgesics Beliefs (POABS-CA)				x				
	Intervention Expectancy				x				
Evaluation Outcomes	Rationale credibility (OLP group only)							x	
	Placebo understanding							x	
	Patient Provider Connection (HEAL)							x	
	Non-Opioid Medication intake				x			x	
	Intervention Implementation				x	x	x	x	
EM-related Outcomes	Placebo medication intake								x
	Opioid adherence								x
Qualitative Outcomes	Qualitative interview							x	
Safety Outcomes	Safety Outcomes					x	x	x	

Figure 1: *Study Design and Flow of Participants*



SUPPLEMENTARY MATERIALS

Conditioned Open-Label Placebos to Facilitate Opioid Reduction in Patients with Chronic Noncancer Pain: Study Protocol of a Randomized Controlled Trial

Table of Contents

eAppendix 1. Qualitative Interview

Note: The following qualitative interview is a translation from the original German document.

Experiences with the OLP Intervention

1. *Please think back to the time during the Mind-Body Management intervention. How did you experience this phase? Please share your experiences.*

2. *When you think of specific moments during the Open-Label Placebo or Mind-Body intervention, what situations or aspects stand out positively? What helped you or was particularly useful?*

3. *Were there any moments or experiences during the intervention that you found challenging? What was difficult to implement or hard to cope with?*

Acceptance of the OLP Approach

4. *At the beginning of the intervention, you were given an explanation (rationale) of how and why Open-Label Placebos work. When you think back to that explanation, what aspects did you particularly understand well? What thoughts did you have about it?*

5. *Now that you have experienced the intervention: Can you imagine using Open-Label Placebos again in the future? Under what circumstances would this be conceivable for you? Please share your thoughts.*

6. *Think about people in your social environment: Would you share your experiences with placebos with them or recommend that they try it? How do you imagine such conversations would go?*

Prerequisites, Ideas, and Concerns Regarding the Practical Implementation of OLP

7. *When you think about your daily routine: How could a Mind-Body intervention personally fit into your everyday life? Please describe how this could look in practice.*

8. *Imagine you are in a clinic where other patients are also undergoing a Mind-Body intervention. How do you think they would respond to this intervention? Please tell us what you imagine.*

9. *If doctors prescribe Open-Label Placebos to patients: What do you think they should particularly pay attention to? What would be important to ensure the intervention is well accepted?*

BMJ Open

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Complementary medicine
Keywords:	Pain management < ANAESTHETICS, PUBLIC HEALTH, Chronic Pain

Study Protocol

Conditioned Open-Label Placebos to Facilitate Opioid Reduction in Patients with Chronic Non-cancer Pain: Study Protocol of a Randomized Controlled Trial

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Contributors: **Katja Carratta**: conceptualization, methodology, writing – review & editing. **Kiara Bodonyi**: conceptualization, methodology, writing – original draft preparation, writing – review & editing. **Antje Frey Nascimento**: methodology, writing – review & editing. **Daniel Friis**: methodology, writing – review & editing. **Roland von Känel**: methodology, writing – review & editing. **Lukas Bircher**: methodology, writing – review & editing. **Helen Koechlin**: methodology, writing – review &

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Conflict of interest: None.

Data Availability Statement: The anonymised datasets generated during the current study will be made available in a public data repository [i.e., OSF] upon publication.

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Version: 2

Abstract

Introduction

Chronic non-cancer pain presents a global health problem, with a significant increase in opioid prescriptions over recent decades. However, opioid therapy poses risks of adverse events, overdose, and non-medical use. As a result, many patients seek to discontinue or reduce their opioid intake. Strategies for opioid tapering often lack efficacy, prompting the investigation of novel approaches like open-label placebo (OLP), i.e., the administration of a placebo with full disclosure that it is a placebo. OLP has shown efficacy in chronic non-cancer pain syndromes and has been suggested as a promising candidate for medication tapering. This study aims to assess whether OLPs can enhance the reduction of daily morphine equivalent dose (MED) in chronic non-cancer pain patients and examines its potential in mitigating opioid withdrawal symptoms.

Methods and analysis

This study is designed as a randomized, controlled, single-center trial. Participants will be randomized into either an OLP group or a control group. The study duration will span 6–9 weeks, during which all participants will aim to reduce their opioid intake. Both groups will monitor their opioid intake daily using a diary app and will receive feedback on their progress of reducing opioids. Additionally, participants in the OLP group will receive OLP tablets for the entire study period. During the first week, the OLP group will undergo a one-week learning phase using a classical conditioning paradigm, where each opioid intake is paired with a placebo. In the subsequent five weeks, the OLP group will enter a dose-extension phase in which only the first opioid intake of the day is paired with a placebo and additional placebos can be taken as desired. At the end of the study, qualitative interviews will be conducted with the first 15 participants in the OLP group. The primary outcome measure is daily opioid intake. Secondary outcomes include opioid withdrawal symptoms, pain severity, disability, anxiety, depression, opioid beliefs, intervention expectancy, and qualitative data. Statistical analyses will include ANCOVA and regression models.

Ethics and dissemination

The Ethics Committee of the Canton of Zurich, Switzerland, approved the study (SNCTP-nr.: SNCTP000005853 / BASEC-nr.: 2023-02327).

Participants will be compensated with 100 Swiss Francs for their full participation in the study. Participants who will take part in the qualitative interview will be compensated with additional 15 Swiss Francs.

Registration details: This study is registered at clinicaltrials.gov: NCT06350786.

Key words

Open-label placebo; chronic non-cancer pain; opioid reduction; opioid tapering; randomized controlled trial

Strengths and limitations of this study

- This is the first study to assess the effectiveness of an OLP intervention for opioid tapering in patients with chronic non-cancer pain using a randomized controlled trial design.
- Based on behavioral learning theory, the study utilizes a conditioning-based learning paradigm to pair opioid intake with placebo intake, potentially inducing the placebo effect.
- OLP and the control group are designed to ensure structural equivalence, with both groups featuring electronic monitoring of opioid intake and the same number of interactions with a member of the study team.
- A qualitative assessment is included to explore participants' experiences with the OLP intervention, providing insights into feasibility and acceptability.
- The study is conducted at a single center, which may limit the generalizability of findings to broader clinical settings.

Introduction

Background and Rationale

Chronic non-cancer pain is a major global health issue, affecting nearly 20% of adults in Europe alone [1]. This has led to a substantial increase in opioid prescriptions for chronic non-cancer pain management, both in the United States and Europe over the past two decades [2–6]. Despite this, there is no consistent international treatment standard for the long-term therapeutic use of opioids in chronic non-cancer pain management, according to the guidelines provided by the Association of Scientific Medical Societies in Germany [7]. Additionally, opioid therapy is associated with various adverse events and risks, including abuse, overdose, and opioid-induced hyperalgesia [8–10].

Since risks often outweigh benefits [11], many patients receiving opioid therapy report the desire to stop or cut down their opioid use [12,13]. Current strategies for tapering include dose reduction protocols, pharmacological opioid replacements, and non-pharmacological therapies. However, systematic reviews concluded that only low-quality evidence supports the effectiveness of opioid tapering interventions [9,14,15], while the results show only limited effects [16]. The feasibility of nonpharmacological adjunctive therapies is limited in primary care settings as they are typically time-consuming, difficult to access, costly, and managed outside the direct patient-physician interaction [17]. Pharmacological approaches, on the other hand, lack patient empowerment [18]. These challenges prompt the need for developing other types of tapering protocols.

Notably, the endogenous opioid system plays a role in mediating the placebo response, with placebo effects being particularly pronounced in opioid trials [19,20]. This is particularly important for chronic non-cancer pain, where patients show substantial and clinically relevant placebo responses [21–23]. However, the administration of deceptive placebos violates patients' right to autonomy [24,25]. Administering placebo without deception could harness the placebo effect successfully and ethically [26–29].

The administration of an open-label placebo (OLP) intervention, i.e., the placebo administration with full disclosure of being a placebo, is promising. OLPs have proven effective in managing chronic non-cancer pain syndromes, such as chronic low back pain [30,31] and irritable bowel syndrome [22,32]. Several (network) meta-analyses have demonstrated that patients receiving OLPs experience significantly greater pain relief compared to those in control groups [33,34]. Moreover, and of relevance when it comes to the need to reduce opioid medication, OLPs have been shown to be a promising candidate for medication tapering [35]. According to principles of behavioral learning theory, this effect can be understood through a conditioning paradigm, in which the process of

medication tapering is facilitated by repeatedly pairing the active medication (unconditioned stimulus) with an OLP (neutral stimulus) during an initial learning phase. Through this repeated association, the body begins to link the intake of the OLP with the effects of the medication. Over time, as medication doses are gradually reduced, the OLP alone takes on the role of a conditioned stimulus, triggering a response similar to that of the medication [36–39]. One pilot study with 20 spinal cord injury and polytrauma patients has employed this approach and showed that OLPs are effective [29]. In a different study using a single-group design, that examined OLPs as an adjunctive intervention for opioid reduction in acute pain, pain relief scores for placebos and opioids did not differ significantly [28]. Furthermore, conditioned OLP has been shown to reduce daily opioid consumption and postsurgical pain among patients recovering from spine surgery: Patients in the conditioned OLP group used approximately 30% less daily morphine milligram equivalents compared to those in the treatment-as-usual group [36]. These findings are in line with studies spanning two decades, revealing that it is possible to condition the body's opioid system [37–40].

Despite these promising findings, there is a lack of trials that examine OLP as an adjunctive intervention for the reduction of opioid medication in the chronic non-cancer pain population. This is noteworthy, given that therapeutic opioid doses are associated with side effects, along with clinically relevant responses to OLPs. The OLP intervention offers a promising approach to tapering long-acting opioids within a structured reduction regimen by using a conditioning paradigm that pairs opioid intake with OLP administration. This approach aims to gradually transfer the learned response from the active medication to the OLP.

Our study addresses this gap by specifically examining the use of OLPs for opioid tapering in the chronic non-cancer pain population. While prior research has demonstrated the analgesic efficacy of OLPs in chronic pain conditions and their potential in reducing opioid consumption in surgical or acute pain, these findings have not yet been extended to patients with chronic non-cancer pain undergoing structured opioid tapering. We decided to include a control group attempting opioid reduction without the use of OLPs in order to maintain structural equivalence between groups. Additionally, our study explores the feasibility and acceptability of integrating OLPs into primary care opioid tapering protocols, areas that remain underexplored in the existing literature.

Aims and Objectives

The primary aim of the present study is to evaluate whether the daily morphine equivalent dose (MED) of opioid medication in patients with chronic non-cancer pain can be reduced with an OLP

adjunctive intervention compared to a control group. Our secondary aim is to evaluate whether the OLP intervention can reduce opioid withdrawal symptoms in comparison to the control group.

Methods and Analysis

Study Design

This randomized, controlled, single-center trial with two parallel groups began in March 2024 and is expected to conclude in early 2026. The study duration will span six to nine weeks, from pre-screening to study conclusion. The primary endpoint is the change in average opioid consumption between the first seven days of the learning phase and the last seven days of the dose-extension phase. It is calculated as mean daily use of opioid medication (i.e., the daily morphine equivalent dose, MED) over each seven-day period. Participants will be assigned to the OLP and control groups. For randomization, a three-level stratification factor will be determined for the randomisation so that participants will be equally assigned to OLP and control group, respectively, based on their baseline MED as follows: low (< 40 mg), moderate (40 mg–100 mg), and high (> 100 mg). Participants in both groups will record their daily opioid intake, and the OLP group will additionally record their placebo intake, with the SEMA3 [41] smartphone application. The placebo tablets used in this study ("P-Tabletten blau", Zentiva) are round, blue, and contain no active pharmacological ingredients. They have been successfully used in previous open-label placebo studies [42,43]. The blue color was chosen based on research indicating that blue is generally perceived as calming and relaxing, which is particularly relevant in the context of pain [44].

The data collected in SEMA3 will comprise the name of the opioid, the type of opioid (e.g., tablet), daily intake quantities (dosage) as well as time and date of intake. These details will then be used for electronic monitoring feedback, which will be delivered during three visits (seven, 21 and 42 days after baseline). Electronic monitoring feedback will be similar for both groups and will be based on a graph representing daily opioid medication intake, as entered by the participants into SEMA3. During the electronic monitoring feedback, the study member will discuss with the study participant the adherence to their medication intake in an empathic and non-judgmental manner.

Self-reported outcome measures will be collected via surveys on an online platform, Research Electronic Data Capture (REDCap) [45], during four visits for both study groups (14 days prior to baseline, at baseline, and seven and 42 days after baseline). Both groups will receive the interventions from the project manager and study team members. All members of the team have been trained in delivering the intervention and have completed the Good Clinical Practice course at the University Hospital Zurich. Due to the transparent nature of the OLP intervention, participants and investigators will not be blinded to group assignments.

Eligibility Criteria

Inclusion criteria assessed during the pre-screening procedure include age 18 or older, proficiency in German, chronic non-cancer pain for at least six months, chronic opioid medication use for more than three months, oral intake of opioids, self-reported motivation for opioid reduction, a primary treating physician overseeing the opioid reduction process, and access to a computer or tablet with an email account.

Exclusion criteria include psychotic symptoms, suicidality, cognitive impairment, planned surgery within the next two months, self-reported illicit drug use, harmful alcohol use, intolerance to placebo ingredients (e.g., lactose, sucrose, corn-starch), serious health issues preventing study participation, and concurrent involvement in other chronic non-cancer pain studies. Participants may continue to use their regular medication (i.e., other than opioid medication).

Recruitment

Participants will be recruited primarily via flyers and posters at the University Hospital of Zurich pain outpatient department and related clinics. Additionally, recruitment will occur at outpatient pain clinics, pain centers, general practitioners' practices, pain community centers, addiction associations, and pharmacies throughout Switzerland, with a focus on the canton of Zürich. Online recruitment will also be conducted. All study processes will take place at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the University Hospital of Zurich to maintain a single-center approach.

Study Procedures at Each Visit

For each participant, the study will include a total of six study visits over the course of six to nine weeks. Please refer to Figure 1 for a detailed overview of the study design and study flow. Each phase is described below.

Pre-screening via telephone call and informed consent (visit 1, timepoint t-2, -21 days prior to baseline)

During an initial telephone contact at timepoint t-2, a pre-screening will take place to verify potential eligibility for participation in the study. Potential study participants will receive detailed study information and the informed consent form by mail.

The original informed consent form can be found in German in the supplemental material A, as well as an English translation in the supplemental material B.

Screening (visit 2, timepoint t-1, -14 days prior to baseline)

Once informed consent is signed by participants, they will complete an online screening questionnaire via REDCap to further evaluate their eligibility. This screening includes more detailed assessments of clinical and demographic criteria compared to the broader criteria evaluated during pre-screening. If eligibility criteria are met, participants will be scheduled for the baseline visit. Additionally, the primary treating physician will be informed about the study participation and will receive a link to a questionnaire in REDCap to assess their expectations regarding whether their patient will reduce the amount of opioids during the study, along with a second questionnaire to evaluate the physician's acceptability of the OLP approach.

Baseline assessment at study site or via telephone call (visit 3, timepoint t0, 0 days)

Participants will be informed of their group assignment (i.e., OLP or control) and will receive a group-specific rationale from a study member. Both treatment rationales will explain the potential benefits of electronic monitoring feedback in supporting patients during voluntary prescription opioid tapering. The treatment rationale for the OLP group is additionally based on the discussion points, adapted from Bernstein [27], including the following statements:

1. Opioids work by telling your body that you are experiencing less pain.
2. Placebos should be taken every time an opioid is taken, supporting the reduction of opioid medication (as shown by previous studies).
3. By pairing the tablets together, your brain will learn to release chemicals like endorphins that cause pain relief in response to the placebo, just as it does in response to the opioid.
4. At a certain point, placebos might provide adequate pain relief, and you may need fewer opioids.

The OLP group will additionally receive placebo tablets for six weeks (150 placebo tablets = three blister packs).

The treatment rationale for the control group will solely explain the potential benefits of electronic monitoring feedback, without any discussion points, as this group will not receive any placebos.

Subsequently, self-reported baseline surveys will be assessed by both groups online in REDCap. After completing the online surveys, daily monitoring of opioid and placebo tablet (for the OLP-group) intake via the SEMA3 app will be explained to the participants.

After the baseline visit, participants in the OLP group will undergo a one-week learning phase, where they will pair each opioid intake with an OLP tablet to initiate a learning process via classical conditioning.

Interim visit via telephone call (visit 4, timepoint t1, seven days after baseline)

Seven days after the baseline, a meeting via telephone call will take place between the study participant and a study team member. Participants in both groups will receive a brief repetition of the group-specific rationale. Subsequently, electronic monitoring feedback will be provided to both study groups. Thereafter, the link for the online questionnaires in REDCap will be sent to participants of both groups for the assessment of the secondary outcomes. The same questionnaire as at timepoint t0 will be used.

After the interim visit, the dose-extension phase will start and will continue until the study concludes. In this phase, participants of the OLP group will only pair the first opioid intake of the day with a placebo, regardless of whether it is a long- or short acting opioid. Pairing the first opioid intake with a placebo helps maintain the conditioned response, in line with the conditioning paradigm. This approach is based on evidence that intermittent reinforcement - continued pairing of placebo with the active drug - enhances resistance to extinction of the conditioned response [46]. For the OLP group, additional placebo tablets may be taken throughout the day as needed, and all additional placebo intake will be recorded in the SEMA3 app.

Booster visit via telephone call (visit 5, timepoint t2, 21 days after baseline)

In both groups, a booster meeting via telephone call will take place between the study participant and a study team member to ensure that the intervention has been understood as agreed upon in the last meeting, including a brief repetition of the group-specific rationale. Electronic monitoring feedback will be provided to participants in both groups in the same way as during Visit 4. For the OLP group, the dose-extension phase will continue unchanged until the end of the study.

Post visit at study site or via telephone call (visit 6, timepoint t3, 42 days after baseline)

At the end of the sixth week, the study intervention will end for both groups, and participants will take part in the last intervention at the study site or via telephone call. Electronic monitoring feedback will be provided to participants in both groups in the same way as during visits 4 and 5. Subsequently, participants will complete an online questionnaire in REDCap with the secondary outcomes and evaluation outcomes.

Furthermore, the first 15 participants of the OLP group will take part in a semi-structured interview. The choice of number was made to gather insights as fast as possible about the chances and hurdles of the OLP approach, also for upcoming trials planned while the current RCT is still ongoing. The qualitative interview will aim to gather in-depth experiences of participants and will cover the following topics (the interview guide can be found in the supplemental material C):

- Experiences of the OLP intervention within the study
- Acceptability of the OLP intervention
- Prerequisites, ideas, and concerns regarding practical OLP implementation

Patient and Public Involvement statement

A patient partner was contacted prior to the study start and was involved in detailing the study design and procedures. In a later phase, the patient reviewed the study protocol to ensure clarity and relevance from the patient's perspective. The patient partner provided valuable input on recruitment strategies, including how to effectively communicate the study to potential participants and make participation more accessible. The patient partner's involvement also extended to discussions on the structure and feasibility of participation. Additionally, the patient played an active role in simulating the first intervention (t0) and the treatment rationale for the control group, providing feedback regarding the plausibility of the intervention, which helped refine the study approach. The patient partner himself experiences chronic pain and is currently taking opioids, which he aims to reduce. He therefore represents our study population.

Study Outcomes

Please refer to Table 1 (see supplemental material D) for a detailed overview of study outcomes and measurement time points.

Primary Outcome: Daily Opioid Consumption

The primary study outcome will be assessed based on the daily dose of opioid medication consumption. Given that participants will potentially be prescribed a range of opioid medications, daily morphine equivalent dose (MED) will be standardized using the morphine milligram equivalent (MME) conversion factor with the following formula: MED = daily dose of single opioid * MME conversion factor [47]. The total morphine equivalents are subsequently summed to assess the total amount of opioid medication taken per day (i.e., sum of the different opioids with regard to their daily dose). Each

opioid is assigned its own conversion factor in relation to morphine, which can be obtained from conversion tables [47,48].

Although the data of the daily intake of the opioid medication will be recorded daily, the two main time points of interest for the primary outcome will be t0 and t3. The change between these two time points will be examined. The average (mean) consumption of opioid medication (MED) during the first seven days (starting with the learning phase) and the last seven days of the dose-extension phase will be calculated for each participant in MED.

- Opioid medication capture: All opioid medication intake will be recorded via a survey in REDCap at t0. This will document the exact amount, opioid name, form of administration (e.g., tablet, drops), dosage per unit (e.g., mg per mL for liquid opioids), frequency of intake, and duration of opioid use (i.e., how long participants have been taking the medication).

Secondary Outcomes

Main Secondary Outcome

- *Subjective opioid withdrawal symptom:* Subjective opioid withdrawal symptoms will be collected via a survey in REDCap at t0, t1, and t3, respectively. The two main time points of interest are t0 and t3. The change between these two time points will be examined. The Subjective Opiate Withdrawal Scale (SOWS) measures gastrointestinal, autonomic, musculoskeletal and psychiatric symptoms that typically occur during opioid withdrawal [49]. In our study, we use the German translation, which was supplemented by four additional questions in the questionnaire [50]. The intensity of the withdrawal symptoms is rated by patients on a scale between 0 (= not at all) and 4 (= extremely).

Other Secondary Outcomes: Other secondary outcomes will be collected via a survey in REDCap. All of these data are collected from the study participants at t0, t1, and t3, respectively, except the intervention expectancy outcome, which will be examined at the study start only (t0). The two main time points of interest are t0 and t3. The change between these two time points will be examined.

- *Pain Severity*: Pain severity is assessed using the validated German translation of the International Classification of Diseases, 11th Revision (ICD-11) specifiers, also referred to as "extension codes" [51]. The index combines patient-assessed ratings of pain intensity, pain-related distress and pain-related interference. Each of these dimensions is measured on an 11-point Numeric Rating Scale ranging from 0 (none) to 10 (severe).
- *Pain Disability:* The validated German version of the Pain Disability Index (PDI) measures the

subjective degree of self-reported impairment caused by the pain problem in everyday life. Seven domains of life are assessed: (1) family and domestic responsibilities, (2) recreation, (3) social activities, (4) occupation, (5) sexual life, (6) self-care, and (7) essential activities [52].

- *Anxiety*: The validated German version of the Generalized Anxiety Disorder – 7 (GAD-7) is a brief instrument for assessing self-reported generalized anxiety disorder symptoms [53]. The seven items of the questionnaire assess the main diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnoses (DSM-IV) and criteria, including worrying, trouble relaxing, and feeling nervous.
- *Depression*: The Patient Health Questionnaire – 9 (PHQ-9) measures the severity of depression in self-report [54]. The module consists of nine items and is part of the Patient Health Questionnaire (PHQ-D). The German version was derived from the 'Prime MD Patient Health Questionnaire' and is based on the depression criteria of the DSM-IV [54].
- *Beliefs regarding opioid use*: The Pain Opioid Analgesics Beliefs – Cancer (POABS-CA) measures pain opioid beliefs based on two components (i.e. negative effect beliefs and pain endurance beliefs) with 10 items and a 5-point Likert scale ranging from 0 ("strongly disagree") to 4 ("strongly agree") [55]. For our study, we use the validated German translation, which has been applied to a primarily non-cancer population [56].
- *Intervention Expectancy:* At the study start (t0), participants' intervention expectations will be measured in analogy to our most relevant outcomes. For this, the following item will be used: "How confident are you that you can reduce/discontinue your opioid medication?" Second, to measure the expected withdrawal symptoms at the end of the study, we will use the items from the Subjective Opiate Withdrawal Scale (SOWS) [49]. The introduction of this questionnaire will be adjusted so that the questions of the questionnaire are related to the participants' expectancy regarding their opioid withdrawal symptoms at the end of the study, rather than their current opioid withdrawal symptoms.

Outcomes Related to Electronic Monitoring:

- *Placebo tablet count:* The intake of placebo tablets in the OLP group will be electronically monitored using the SEMA3 app from t0 to t3, serving as the primary way for assessing placebo intake. Additionally, a tablet count of the returned placebo blisters at t3 will be conducted, and the number of remaining tablets will be documented. A ratio can be calculated from the tablet count recorded in the SEMA3 app and the count of tablets from the returned blisters, which can

then be used for statistical analysis. For the statistical analysis the overall placebo intake between t0 and t3 is of interest.

- *Opioid adherence*: Participants in both groups will record their daily intake of opioid medication (including on-demand opioid medication) from t0 to t3 the SEMA3 app. The data collected this way will be used for electronic monitoring feedback at t1, t2, and t3.

Evaluation Outcomes:

- *Rationale Credibility*: The rationale credibility of the OLP intervention will be assessed in the OLP group at study end (t3). The following questions will be asked: "During the study, did you believe that these were placebo tablets that did not contain a pharmacologic agent?", "Did you find the explanation of why the placebo intervention may work helpful?", "How helpful did you find the explanation of why placebo intervention can work?". Answers will be rated on a Likert scale ranging from 0 = Not at all to 4 = Extremely.
- *Placebo Understanding:* The Placebo Understanding Questionnaire will be administered to both study groups at the study end (t3), assessing participants' understanding of placebo and their attitudes toward non-specific therapies. The first three items of this questionnaire specifically evaluate placebo understanding and will be used for this study [57].
- *Patient-Provider Connection:* The Patient Provider Connection is a subscale of the validated German version of the Healing Encounters and Attitudes List (HEAL) which can be used independently from the six subscales [58]. The seven items are rated on a five-point Likert scale ranging from "not at all" to "very strong" assessing participants' attitudes towards patient-provider connection as a non-specific intervention effect. The questionnaire will be assessed at study end (t3).
- *Non-Opioid Medication Intake:* Participants' non-opioid medication intake will be assessed via REDCap at t0 and t3 by asking the participants about the medication's name, dosage, and reason for intake.
- *Intervention implementation:* To examine the influence of the individual administering the study intervention, we record at t0, t1, t2 and t3 which study member implemented the intervention in the respective study groups.

Treating Physicians' Outcomes

- *Primary treating physicians' acceptability of the OLP approach*: At t0, the primary treating

physicians will be asked about their acceptability of the OLP approach. For this, we ask them to imagine a scenario where a physician uses OLPs to help a patient reduce opioids. We will use two key items "Is it acceptable for the physician to try a placebo intervention?" and "Would you, as a patient, be willing to take this intervention?" Both questions use a five-point Likert scale ranging from "No, not at all," to "Yes, totally" [59]. Further variables include the perceived competence of the physician, along with patient satisfaction and worry regarding the treatment from the patient's perspective [12]. Competence will be answered on a seven-point Likert scale ranging from "Incompetent" to "Highly competent". Satisfaction item can be answered on a seven-point Likert scale ranging from "Very dissatisfied" to "Very satisfied". Worry will be displayed on a seven-point Likert scale ranging from "Much more worried" to "Much less worried". Finally, four additional items will be asked to assess interpersonal trust in the patient-physician relationship and the doctor´s warmth to be answered on five-point Likert scale ranging from "Strongly disagree" to "Strongly agree"[60].

- *Primary Treating Physicians' Intervention Expectancies:* At t0, the primary treating physicians' expectations will be measured in analogy to our most relevant outcomes. First, we will ask the physician how satisfied they think that the patient is with the opioid medication and whether they are optimistic that the patient will reduce the amount of opioids. Motivation will be assessed on a satisfaction ruler ranging from 0 % to 100 % [61]. Second, to measure their expectation regarding their patients' withdrawal symptoms at the end of the study, we will use selected items from the Subjective Opiate Withdrawal Scale (SOWS) questionnaire [49]. The introduction of this questionnaire will be adjusted to ensure that its questions relate to the primary treating physicians' expectations regarding their patients' opioid withdrawal symptoms at the conclusion of the study.

Qualitative Outcomes:

- The qualitative interview will be audio recorded. The study team will create transcripts of the audio recordings using the MAXQDA VERBI software [62], which will be examined subsequently with the method of thematic analysis using the same software.

Additional Symptoms:

- Participants answer three questions regarding additional symptoms that might have occurred since the last visit at the study site. These will be measured two times: on day seven after the first intervention visit (baseline) and on day 42. The questions are the following:
  - "How have you been since the last visit?" (open answer format)

- "Did you have certain symptoms?" (yes/no)
- If the participant answered yes in question 2, a follow up question will be displayed: "Please describe the symptoms you had in detail." (open answer format)

Safety Outcomes:

During the electronic monitoring feedback at t1, t2, and t3, participants will be asked if they have experienced any symptoms since the last visit. A study member will document these symptoms and discuss with the Project Manager or Sponsor Investigator whether they are related to study participation. If so, they will be recorded as an Adverse Event in REDCap. Although serious adverse events are not expected due to the nature of the study, potential serious adverse events related to opioid analgesics and their tapering - such as suicidal ideation - may occur. In such cases, the investigator delivering the study intervention will contact the participant's primary treating physician. If it cannot be excluded that the serious adverse event is attributable to the intervention under investigation, the Investigator will report it to the Ethics Committee within 15 days. Any urgent safety or protective measures taken during the study will also be promptly reported to the Ethics Committee, as required

Data Management

All data and documents will be maintained in one of the following data management systems:-Trial Master File,-electronic Trial Master File, REDCap, and SEMA3. Trial Master File, electronic Trial Master File, monitored by the Project Manager and Study Investigator, ensure restricted access for authorized team members. Person-identifying data of participants will be collected using paper Case Report Forms. Study data of each participant and study data for study procedure will be collected and recorded by electronic Case Report Forms in REDCap. These will be set up by the Clinical Trials Center of the University Hospital Zurich.

Determination of Sample Size

A similar study on opioid dose reduction was conducted in chronic non-cancer pain patients, comparing an OLP with a treatment-as-usual group [29]. With the data extracted from that study, standard deviation value of 1.03 could be calculated for the between-group difference [63]. This effect size is notably high compared to other OLP studies, with recent meta-analyses reporting overall effects of standardized mean differences 0.72 [34] and 0.88 [64]. Given the high variability and exceptional effect size, a conservative effect size of d = 0.60 was used for our sample size calculation.

The calculation was based on a power of 80% and a significance level (alpha) of 0.05. Using ANCOVA with the allocation group (OLP/control) as an independent between-subject variable, and accounting for a 20% dropout rate, the final sample size is 86 (43 per group).

Statistical Analyses

Primary Analysis

For the analysis of the primary endpoint the baseline consumption of opioid medication will be calculated as the average (mean) of the first seven days of the study (from t0). For the analysis the differences in the consumption of opioid medication across the two groups of this study will be assessed. The primary aim will be analysed by a linear model in an analysis of covariance (ANCOVA), with the consumption at baseline as covariate and the randomized allocation (OLP vs. control group) as explanatory variable. The normality assumption will be graphically assessed. Log-transformation will be considered in case of violation. The dependent variable will be the average consumption of the opioid medication over the last seven days at t3. Intention to treat (ITT) analyses will be carried out.

Main Secondary Analysis

For the analysis of the main secondary endpoint the differences in the withdrawal symptom scores (SOWS) across the two groups will be assessed. The secondary endpoint will be analysed by a linear model with the withdrawal symptom scores at baseline as covariate and the randomized allocation (OLP vs. control group) as explanatory factor (ANCOVA). The normality assumption will be graphically assessed. Log-transformation will be considered in case of violation. The dependent variable will be the withdrawal symptom scores at t3.

Other Secondary Analyses

For the analysis of further secondary endpoints the differences across the two groups of various other scores assessed during our study will be examined. Each of these endpoints will be analysed by a linear model with their scores at baseline as covariate and the randomized treatment (OLP vs. control group) as explanatory factor (ANCOVA). The dependent variable will the corresponding scores at t3. These secondary endpoints are the following: Pain severity degree (ICD-11 specifiers), Pain disability degree (PDI); Anxiety (GAD-7); Depression (PHQ-9); Pain Opioid Beliefs (POABS-CA); Treatment

Expectancy. Additionally, exploratory sensitivity analyses are planned to examine possible moderators (e.g., opioid dosage) of treatment outcomes [65].

Analyses for Evaluation Outcomes

A t-test will be employed to compare the evaluation outcomes between the two groups. In the case that there is no normal distribution for the data, non-parametric procedures such as Wilcoxon / Mann-Whitney will alternatively be used for the statistical tests.

Qualitative Analyses

We will analyze the qualitative data by means of thematic analysis, taking a hybrid approach of inductive and deductive coding and theme development [66]. In this approach, core themes will be first elicited inductively from the collected data [67]. Subsequently, the core themes will be examined deductively with respect to theoretical assumptions about the OLP treatment rationale [68].

Monitoring

The investigator's site will collaborate with the Clinical Trials Center of the University Hospital Zurich to ensure monitoring. Monitoring activities are defined in a study-specific Monitoring Plan according to the Clinical Trials Center Monitoring.

Ethics and Dissemination

The study has received approval from the Ethics Committee of the Canton of Zurich (BASEC-Nr. 2023-02327 / SNCTP-Nr.: SNCTP000005853). All participants will provide written informed consent prior to enrollment. Study data will be handled in accordance with national data protection regulations. The results will be submitted for publication in peer-reviewed journals and presented at national and international conferences. Participants may request a summary of the study findings upon completion. The trial is registered at ClinicalTrials.gov (NCT06350786).

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Figure Legends

Figure 1: *Study Design and Flow of Participants*

Supplemental Material

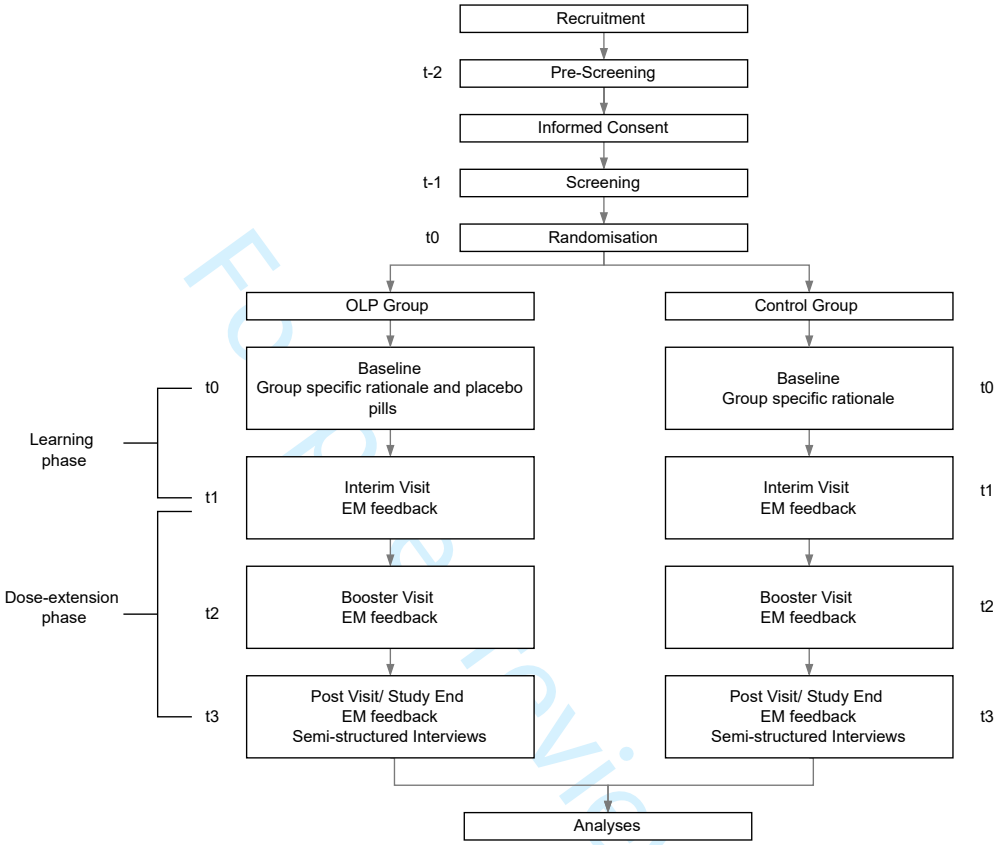
Supplemental Material A: Informed Consent – original German file.

Supplemental Material B: Informed Consent – English translation.

Supplemental Material C: Qualitative Interview

Supplemental Material D: Table 1

Figure 1: *Study Design and Flow of Participants*



Note. EM feedback = Electronic Monitoring Feedback

Supplemental Material

Conditioned Open-Label Placebos to Facilitate Opioid Reduction in Patients with Chronic Non-cancer Pain: Study Protocol of a Randomized Controlled Trial

Supplemental Material A: Informed Consent – original German file.

Note: This is the form that has been accepted by the ethics committee.

Supplemental Material B: Informed Consent – English translation.

Supplemental Material C: Qualitative Interview

Note: The following qualitative interview is a translation from the original German document.

Supplemental Material D: Table 1

Supplemental Material A: Informed Consent (original German file)

Universitätsspital Zürich
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Anfrage zur Teilnahme an der Studie

*Studientitel: Konditionierte offene Placebos zur Unterstützung der Reduktion opioider Schmerzmittel bei Patient*innen mit chronischen nicht krebsbedingten Schmerzen: Eine randomisierte kontrollierte Studie*

Laienverständlicher Titel: Mind-Body Management: Ein Ansatz, der Sie bei der Reduktion von Opioiden unterstützt

Sehr geehrte Dame, sehr geehrter Herr

Hiermit möchten wir Sie über unser Forschungsvorhaben informieren und Sie anfragen, ob Sie daran teilnehmen möchten. Bevor eine neue Interventionsmethode angewendet werden darf, muss erforscht werden, wie diese Interventionsmethode wirkt.

Eine solche Forschung nennen wir eine klinische Studie. In unserer Studie wollen wir herausfinden, ob sogenannte Open-Label Placebos (OLP) im Zusammenhang mit einer Mind-Body-Management Intervention als Begleitmassnahme zur Reduktion von opioiden Schmerzmitteln unterstützend wirken. Die Bezeichnung OLP bedeutet, dass bei der Placebo-Anwendung eine offene Aufklärung und Information über die Wirkstofffreiheit des Placebopräparats stattfindet: Das heisst, die Einnahme von Placebos erfolgt im Wissen, dass diese keine pharmakologisch aktiven Wirkstoffe enthalten.

Sie leiden an chronischen nicht krebsbedingten Schmerzen und nehmen opioide Schmerzmittel ein. Sie sind motiviert, die opioiden Schmerzmittel zu reduzieren. Sie sind bereits in Behandlung bei einem primär behandelnden Arzt oder einer primär behandelnden Ärztin, mit welchem / welcher Sie die Reduktion durchführen werden. Deshalb fragen wir Sie an, ob Sie an dieser Studie teilnehmen möchten.

Ihre Teilnahme ist freiwillig. Die folgende Patienteninformation soll Ihnen bei der Entscheidung helfen. Alle Fragen zur Studienteilnahme können Sie im Gespräch mit der Prüfperson stellen. So nennen wir die Forscher*innen, die für eine Studie verantwortlich sind und die Sie im Rahmen dieser Studie betreuen. Wenn Sie teilnehmen wollen, unterzeichnen Sie bitte am Ende die Einwilligungserklärung. Mit Ihrer Unterschrift bestätigen Sie, dass Sie

die Patienteninformation gelesen und verstanden haben. Wenn Sie etwas nicht verstehen, fragen Sie bitte die Prüfperson.

Die Patienteninformation und Einwilligungserklärung bestehen aus vier Teilen:

Teil 1 Das Wichtigste in Kürze
Teil 2 Darum geht es im Detail: Informationen zur Studie
Teil 3 Datenschutz und Versicherungsschutz
Teil 4 Einwilligungserklärung

Wenn Sie **Teil 1** lesen, dann erhalten Sie einen Überblick über die Studie. In **Teil 2** erklären wir Ihnen den ganzen Ablauf und Hintergrund der Studie im Detail. **Teil 3** enthält die Informationen zum Daten- und Versicherungsschutz. Mit Ihrer Unterschrift am Ende des Dokuments, **Teil 4**, bestätigen Sie, dass Sie alles verstanden haben und mit der Teilnahme einverstanden sind.

Diese Studie wird vom schweizerischen Nationalfonds finanziert. PD Dr. phil. Cosima Locher verantwortet und leitet die Studie.

Im Rahmen dieser Studie ist für Sie zuständig:

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Teil 1:
Das Wichtigste in Kürze

1. Warum führen wir diese Studie durch?

Bei chronischen nicht krebsbedingten Schmerzen ist es zentral, die Reduktion von opioiden Schmerzmitteln zu begleiten, damit unerwünschte Nebeneffekte verringert / vermieden werden können.

In dieser Studie untersuchen wir, ob eine Mind-Body Management Intervention im Zusammenhang mit der Einnahme von Placebos als Begleitmassnahme zur Reduktion von opioiden Schmerzmitteln unterstützend wirken und dadurch unerwünschte Nebenwirkungen verringern kann. Bei der Mind-Body Management Intervention wird davon ausgegangen, dass sich Körper und Geist gegenseitig beeinflussen. In Kapitel 4 erfahren Sie mehr zum wissenschaftlichen Hintergrund dieser Studie.

2. Was müssen Sie tun, wenn Sie teilnehmen?

Die Teilnahme an dieser Studie dauert für Sie insgesamt maximal 9 Wochen. Die Studie teilt sich in eine Voruntersuchungsphase und eine Interventionsphase auf. Die Voruntersuchungsphase dauert maximal 3 Wochen und die Interventionsphase 6 Wochen. Während der Gesamtdauer von maximal 9 Wochen werden wir Sie zu 6 Terminen einladen. Zwei dieser Termine werden gegebenenfalls vor Ort stattfinden. Die anderen Termine werden online durchgeführt.

<u>Voruntersuchungsphase</u>:

- Telefonischer Erstkontakt und Studieninformation sowie erste Abklärungen zur Studienteilnahme (Dauer ca. 30 Minuten)
- Voruntersuchung über Online-Fragebogen (Dauer ca. 30 Minuten)

<u>Interventionsphase</u>:

- Erster Interventionstermin per Telefon beziehungsweise Videokonferenz oder vor Ort mit gruppenspezifischer Intervention sowie Ausfüllen eines Online-Fragebogens (Dauer ca. 90 Minuten)
- Zweiter Termin per Telefon oder Videokonferenz mit gruppenspezifischer Intervention sowie Ausfüllen eines Online-Fragebogens (Dauer ca. 75 Minuten)
- Dritter Termin per Telefon oder Videokonferenz, kurze gruppenspezifische Intervention sowie Ausfüllen eines Online-Fragebogens (Dauer ca. 75 Minuten)
- Abschlusstermin per Telefon beziehungsweise Videokonferenz oder vor Ort und Ausfüllen eines Online-Fragebogens (Dauer ca. 90 Minuten)

- Am Ende des letzten Termins wird ein kleiner Anteil der Studienteilnehmer*innen zusätzlich an einem abschliessenden Interview teilnehmen (Dauer ca. 30 Minuten). Das Interview wird per Audio aufgenommen.

Die Anzahl der Termine können Sie der Tabelle in Kapitel 5 entnehmen.

Wenn Sie sich entscheiden teilzunehmen, werden Sie zufällig einer von zwei Gruppen zugeteilt. Sie gehören entweder zur OLP-Gruppe oder zur Kontrollgruppe. In beiden Gruppen erhalten Sie eine gruppenspezifische Intervention. Während Sie in der OLP-Gruppe zusätzlich zu Ihren opioiden Schmerzmitteln Placebos erhalten, ist das in der Kontrollgruppe nicht der Fall. Zudem werden Sie unabhängig davon, welcher Gruppe Sie angehören, die Einnahme Ihrer opioiden Schmerzmittel während der Gesamtdauer der Studie elektronisch erfassen (elektronisches Monitoring). In der OLP-Gruppe wird die Einnahme der Placebos ebenfalls während der Gesamtdauer der Studie erfasst.

In Kapitel 5 erfahren Sie mehr zum Ablauf und Vorgehen der Studie.

Bei einer vollständigen Teilnahme an der Studie werden Sie mit einem Geldbetrag in der Höhe von CHF 100 (zusätzlich CHF 15 für die Teilnahme am Interview) entschädigt.

Ihre primär behandelnde Ärztin / Ihr primär behandelnder Arzt wird über Ihre Teilnahme an der Studie informiert. Unabhängig von der Studienintervention wird sie / er mit Ihnen die Reduktion Ihrer Schmerzmittel und Ihre Behandlung durch- und weiterführen.

3. Welcher Nutzen und welches Risiko sind mit der Teilnahme verbunden?

Nutzen

- Die Teilnahme an dieser Studie kann Ihnen Unterstützung bei der Reduktion Ihrer opioiden Schmerzmitteln bringen und zu einer Minderung der durch die Reduktion verursachten Nebenwirkungen führen.
- Sie können von der fortlaufenden, elektronischen Aufzeichnung der Einnahme Ihrer opioiden Schmerzmittel profitieren, indem Sie Rückmeldungen zum Einnahmemuster Ihrer Medikamente erhalten.
- Sie helfen mit Ihrer Teilnahme ein besseres Verständnis im Umgang mit der Reduktion von opioiden Schmerzmitteln bei chronischen nicht krebsbedingten Schmerzen zu erhalten.
- Die Ergebnisse dieser Studie können in der Zukunft für andere Personen mit chronischen Schmerzen, die opioide Schmerzmittel erhalten, wichtig sein.

Risiko

- Es sind keine studienspezifischen Risiken zu erwarten, da es sich um Placebos ohne pharmakologische Wirkung und eine fortlaufende, elektronische Aufzeichnung (elektronisches Monitoring) handelt.

- Während der Reduktion Ihrer opioiden Schmerzmittel und der Teilnahme an den Interventionen der Studie kann es sein, dass Sie sich vermehrt mit Ihren chronischen nicht krebsbedingten Schmerzen auseinandersetzen. Das kann möglicherweise zu einer verstärkten Wahrnehmung der Symptome, jedoch auch zu einem besseren Symptommanagement und somit wiederum zur Verbesserung der chronischen nicht krebsbedingten Schmerzen führen.

In Kapitel 6 finden Sie weitere Informationen zu Risiken und Belastungen.

Teil 2:
Darum geht es im Detail: Informationen zur Studie

4. Der wissenschaftliche Hintergrund der Studie

4.1 Hintergrund: Warum führen wir diese Studie durch?

In unserer vom Schweizerischen Nationalfonds (SNF) geförderten Studie untersuchen wir eine Mind-Body Management Intervention zur Unterstützung der Reduktion von opioiden Schmerzmitteln bei chronischen nicht krebsbedingten Schmerzen. Im Rahmen der Mind-Body Management Intervention werden den Teilnehmenden unterstützende Mechanismen und Wege vermittelt, die auf zwei Ebenen wirken: Auf den Körper und den Geist. Dazu werden Placebos als Prüfsubstanz verwendet. In bisherigen Studien konnten diese zur Unterstützung der Reduktion opioider Schmerzmittel bei akuten Schmerzen erfolgreich eingesetzt werden. Nur Teilnehmende der Untersuchungsgruppe erhalten Placebos. Sowohl in der OLP-Gruppe als auch in der Kontrollgruppe erfolgt eine fortlaufende elektronische Aufzeichnung der Einnahme der Medikamente. Dieses sogenannte elektronische Monitoring ermöglicht eine Rückmeldung über die Einnahme der opioiden Schmerzmittel und der Placebos. Dadurch kann eine positive Einstellung zur Reduktion der opioiden Schmerzmittel unterstützt werden.

Für unsere Studie suchen wir Personen, die länger als sechs Monate chronische nicht krebsbedingte Schmerzen haben, seit mindestens drei Monaten opioide Schmerzmittel einnehmen und den Wunsch haben, diese zu reduzieren. Daher fragen wir Sie für die Teilnahme an unserer Studie an.

Wir folgen in unserer Studie dem Konzept der Gesundheitsförderung. Ein zentrales Element ist dabei die Förderung der Fähigkeit für ein selbstbestimmtes Handeln (*Empowerment*). Weiter wird angenommen, dass Körper und Geist miteinander verbunden sind und sich gegenseitig beeinflussen. Diese Wechselwirkungen geschehen weitgehend unbewusst und können auch einen Einfluss auf die Schmerzwahrnehmung haben.

4.2 Aufbau der Studie: Wie gehen wir vor?

In unserer Studie werden die Teilnehmenden zufällig in zwei Gruppen eingeteilt. Dies ist wichtig, um verlässliche Ergebnisse der Studie zu erhalten. Man nennt diesen Vorgang Randomisierung. Jede Gruppe bekommt eine andere Behandlung. In unserer Studie gibt es zwei Gruppen:

- Gruppe 1 (OLP-Gruppe) erhält eine Mind-Body Management Intervention zusammen mit Placebos. Das verwendete Placebopräparat hat keine pharmakologische Wirkung und ist in der Schweiz zugelassen. Es heisst «*P-Tabletten blau*» von Zentiva und

enthält Milchzucker, Haushaltszucker und Traubenzucker. Neben der Verabreichung von Placebos wird deren Einnahme und die Einnahme der opioiden Schmerzmittel elektronisch aufgezeichnet (elektronisches Monitoring).

- Gruppe 2 (Kontrollgruppe) erhält keine Placebos. Es erfolgt alleine eine fortlaufende elektronische Aufzeichnung (elektronisches Monitoring) der täglich eingenommenen opioiden Schmerzmittel.

Jede Einnahme der Schmerzmittel und gegebenenfalls der Placebos wird von Ihnen täglich mit der App SEMA3 erfasst. Darauf basierend werden wir bei Ihren Studienbesuchen mit Ihnen Ihr Einnahmeverhalten besprechen.

In verschiedenen Studien konnte gezeigt werden, dass offene Placebos bei der Reduktion von opioiden Schmerzmitteln unterstützend sind. Wir wissen aber noch wenig darüber, ob dies auch bei chronischen nicht krebsbedingten Schmerzen der Fall ist. Daher möchten wir in unserer Studie herausfinden, ob offene Placebos die Reduktion von opioiden Schmerzmitteln begünstigt. Bei unserer Studie werden Sie offen darüber informiert, dass Sie Placebos einnehmen und diese keine pharmakologische Wirkung haben.

Sowohl in der OLP-Gruppe als auch in der Kontrollgruppe obliegt die Verschreibung der opioiden Schmerzmittel, die Erstellung des Reduktionsplans dieser Medikamente sowie dessen Durchführung vollständig bei Ihrer primär behandelnden Ärztin / Ihrem primär behandelnden Arzt. Das Studienteam wird die von Ihrer Ärztin / Ihrem Arzt vorgegebene medizinische Behandlung zur Reduktion der Medikamente nicht beeinflussen.

4.3 Regelungen zur wissenschaftlichen Forschung mit Menschen

Wir machen diese Studie so, wie es die Gesetze in der Schweiz vorschreiben (Humanforschungsgesetz, Datenschutzgesetze). Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige Ethikkommission hat die Studie geprüft und bewilligt.

Unsere Studie ist eine nationale Studie. Das heisst, es gibt 86 Teilnehmende in der Schweiz. Eine Beschreibung dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit: www.kofam.ch (SNCTP-Nr.: SNCTP000005853 / BASEC-Nr.: 2023-02327).

5. Ablauf der Studie

5.1 Was müssen Sie tun, wenn Sie an der Studie teilnehmen?

Die Teilnahme an der Studie ist freiwillig und dauert maximal 9 Wochen. Sie müssen sich an den Ablaufplan halten (→ Kapitel 5.2) und auch an alle Vorgaben, die Ihre Prüfperson macht. Dies beinhaltet das Einhalten von vereinbarten Terminen, das Ausfüllen der Fragebögen und die tägliche Erfassung Ihrer opioiden Schmerzmittel.

Sie müssen Ihre Prüfperson informieren,

- wenn sich Ihr Gesundheitszustand ändert, z. B. wenn es Ihnen schlechter geht oder wenn Sie neue Beschwerden haben; dies gilt auch, wenn Sie die Studie vorzeitig abbrechen (→ Kapitel 5.3 und 5.4);
- über die Einnahme und Dosisänderung von Medikamenten – auch im Verlauf der Studie;
- über die gleichzeitige Behandlung und Therapie bei anderen Ärzt*innen.

5.2 Was passiert bei den Terminen?

Im Verlauf Ihrer Teilnahme finden sechs Studienkontakte statt. Zwei von diesen Terminen gehören zur Voruntersuchung. Die anderen vier Termine gehören zur eigentlichen Studienintervention. Für die Studienintervention kommen Sie zwei Mal zu uns vor Ort und zwei Mal treffen wir uns per Telefon beziehungsweise Videokonferenz oder alle Termine finden per Telefon beziehungsweise Videokonferenz statt. Die Dauer der Termine ist unterschiedlich und liegt zwischen 15 und 90 Minuten. Die Abfolge der Termine ist in der Abbildung weiter unten angegeben.

Voruntersuchungsphase (maximal 3 Wochen):

- Während des telefonischen Erstkontakts informieren wir Sie über die Studie und machen erste Abklärungen zur Studienteilnahme. Das Telefongespräch dauert etwa 30 Minuten.
- Bei der Voruntersuchung ca. eine Woche nach unserem ersten Kontakt werden Sie online einen Fragebogen ausfüllen. Mit diesem Fragebogen klären wir ab, ob Sie an der Studie teilnehmen können. Das Ausfüllen des Fragebogens dauert etwa 30 Minuten.

Interventionsphase (6 Wochen):

- Wenn Sie an der Studie teilnehmen können, findet der erste Besuch entweder bei uns an der Haldenbachstrasse 16 / 18 in Zürich statt oder der Interventionstermin findet per Telefon beziehngsweise Videokonferenz statt. Dieser Termin dauert insgesamt etwa 90 Minuten. Wir teilen Ihnen mit, welcher Studiengruppe Sie zugeteilt werden und beginnen mit der Studienintervention. Als Teil davon besprechen wir mit Ihnen unser Vorgehen in Ihrer Gruppe (etwa 15 Minuten). Falls Sie zur OLP-Gruppe gehören, bekommen Sie im Anschluss an den Termin auch die Placebos. Danach füllen Sie einen Fragebogen aus. Das Ausfüllen des Fragebogens dauert ungefähr 60 Minuten. Schliesslich erklären wir Ihnen, wie Sie die tägliche Einnahme Ihrer opioiden Schmerzmittel mittels der App SEMA3 eingeben können.
- Das nächste Treffen findet eine Woche nach diesem ersten Interventionstermin per Telefon oder Videokonferenz statt. Die Studienintervention wird fortgeführt und richtet sich danach, welcher Gruppe Sie angehören. Zusätzlich bekommen Sie von uns Rückmeldung zur Einnahme Ihrer opioiden Schmerzmittel. Das Telefonat beziehungsweise die Videokonferenz dauert etwa 30 Minuten. Im Anschluss an diesen Termin werden Sie wiederum einen online Fragebogen ausfüllen (Dauer etwa 20 Minuten). Insgesamt dauert dieser Termin ungefähr 50 Minuten.

- Nach zwei weiteren Wochen findet ein weiterer Termin per Telefon oder Videokonferenz statt. Bei diesem Termin besprechen wir Ihre Fragen und geben Ihnen Rückmeldung zur Einnahme Ihrer opioiden Schmerzmittel seit Ihrem letzten Treffen mit uns. Insgesamt dauert dieser Termin ungefähr 30 Minuten.
- Der letzte Besuch findet wiederum bei uns an der Haldenbachstrasse 16 / 18 in Zürich oder per Telefon beziehungsweise Videokonferenz statt. Während dieses Termins beenden wir die Studienteilnahme mit einem Abschlussgespräch, und die Studienentschädigung in der Höhe von CHF 100 wird Ihnen ausbezahlt. Auch beim letzten Termin füllen Sie einen Fragebogen aus. Das Ausfüllen des Fragebogens dauert wiederum etwa 20 Minuten. Insgesamt dauert dieser Besuch also ungefähr 90 Minuten.
- Zusätzlich zum letzten Studienbesuch bei uns wird ein kleiner Anteil der Studienteilnehmenden an einem Interview teilnehmen (Dauer etwa 30 Minuten). Ob Sie für dieses abschliessende Interview ausgewählt wurden, teilen wir Ihnen bei Ihrem ersten Termin mit. Eine Audioaufzeichnung dieses Interviews wird erstellt. Für die Teilnahme am Interview werden Sie mit zusätzlichen CHF 15 entschädigt.

Durch diese Untersuchungen sehen wir, wie gut die OLP-Intervention im Vergleich zur Intervention der Kontrollgruppe wirkt in Bezug auf die Opioid-Reduktion.

Der Ablaufplan auf der nächsten Seite zeigt alle Termine. Während die blau hinterlegten Spalten die Termine der Voruntersuchung darstellen, sind die Spalten der Termine und Studienbesuche der eigentlichen Studienintervention grün hinterlegt. Die Häklein ✓ kennzeichnen die Aktivitäten der einzelnen Termine.

Ablaufplan

Termin / Studien-besuch	**1**	**2**	**3**	**4**	**5**	**6**
Phase	**Voruntersuchung**		**Studienintervention**			
Datum	max. 3 Wochen vorher	max. 2 Wochen vorher	Studienstart	1 Woche nachher	3 Wochen nachher	6 Wochen nachher
Dauer	30 Min.	30 Min.	90 Min.	50 Min.	30 Min.	90 Min.
Wo	Telefon	Online	Vor Ort/Online	Online	Online	Vor Ort/Online
Studien-Information	✓					
Fragebogen		✓	✓	✓		✓
Gruppen-spezifische Intervention			✓	✓	✓	✓
Interview						(✓)

Wir vereinbaren die Termine gemeinsam mit Ihnen. Sie erhalten einen genauen Überblick über die Termine. Wir sind darauf angewiesen, dass die Termine eingehalten werden. Wir bitten Sie, uns frühzeitig zu informieren, falls Sie einen Termin aus wichtigen Gründen verschieben müssen.

5.3 Wann endet die Teilnahme an der Studie?

Für Sie dauert die Teilnahme maximal 9 Wochen. Sie können Ihre Teilnahme jederzeit auch früher abbrechen (→ Kapitel 5.4). Sie müssen nicht erklären, warum Sie nicht mehr teilnehmen möchten. Wenn Sie selbst Ihre Teilnahme früher beenden möchten, sprechen Sie bitte mit Ihrer Prüfperson.

Auch wenn Sie Ihre Teilnahme vorzeitig beenden, werden Sie weiter von Ihrer primär behandelnden Ärztin / Ihrem primär behandelnden Arzt medizinisch behandelt und betreut. Bitte bringen Sie dann alle Prüfpräparate und Prüfmaterialen (Placebos und leere Placebo-verpackungen und Blister), die wir Ihnen gegeben haben, zu uns zurück.

Wenn Ihre Teilnahme vorzeitig endet, werden wir die bis dahin erhobenen Daten (z.B. Monitoringdaten der opioiden Schmerzmittel und Placebos, Fragebögen) noch für die Studie auswerten.

In seltenen Fällen kann es vorkommen, dass wir jemanden von der Studie vorzeitig ausschliessen müssen. Das ist zum Beispiel der Fall, wenn sich Ihr gesundheitlicher Zustand unerwartet und schwerwiegend verschlechtern würde. In diesem Fall werden wir gemeinsam mit Ihrem behandelnden Arzt / Ihrer behandelnden Ärztin das weitere Vorgehen besprechen.

5.4 Was passiert, wenn Sie nicht teilnehmen wollen?

Wenn Sie nicht an der Studie teilnehmen möchten, existieren erprobte Angebote für die Hilfestellung zur Reduktion von opioiden Schmerzmitteln bei chronischen nicht krebsbedingten Schmerzen, über die Sie Ihre primär behandelnde Ärztin oder Ihr primär behandelnder Arzt aufklären und beraten kann.

5.5 Schwangerschaft

Sollten Sie während der Studie schwanger werden, müssen Sie Ihre Prüfperson umgehend informieren. In diesem Fall werden Sie gebeten, ebenfalls Ihre primär behandelnde Ärztin / Ihren primär behandelnden Arzt zu informieren. Die Prüfperson wird mit Ihnen das weitere Vorgehen besprechen.

6. Risiken, Belastungen und Nebenwirkungen

6.1 Welche Risiken und Belastungen können auftreten?

Es sind keine studienspezifischen Risiken zu erwarten, da es sich um eine offene Vergabe von Placebos ohne pharmakologische Wirkung und die fortlaufende Aufzeichnung opioider Schmerzmittel handelt. Die Auseinandersetzung mit Ihren chronischen nicht krebsbedingten Schmerzen können möglicherweise zu einer verstärkten Wahrnehmung der Symptome, jedoch auch zu einem besseren Symptommanagement und somit wiederum zur Verbesserung der chronischen Schmerzen führen. Wir werden Sie dazu befragen.

7. Finanzierung und Entschädigung

Diese Studie wird von der Sponsorin PD Dr. phil. Cosima Locher veranlasst und vom Schweizerischen Nationalfonds vollständig finanziert.

Die beteiligten Forschenden haben keinen unmittelbaren finanziellen Vorteil an der Durchführung dieser Studie.

Wenn Sie bei dieser Studie mitmachen, erhalten Sie dafür bei vollständiger Teilnahme folgende Entschädigung: 100 CHF. Die Auslagen wie Reisespesen, die durch die Teilnahme bedingt sind, sind bereits in der Entschädigung enthalten. Die Teilnehmenden des Interviews am letzten Termin werden zusätzlich mit 15 CHF entschädigt. Es entstehen keine Kosten durch die Teilnahme an dieser Studie für Sie oder Ihre Krankenkasse.

8. Ergebnisse aus der Studie

Es gibt Ergebnisse, die Sie selbst betreffen. Diese Ergebnisse teilt Ihnen Ihre Prüfperson mit. Es gibt auch Zufallsbefunde. Zufallsbefunde sind „Begleit-Ergebnisse“, die nicht beabsichtigt sind. Dies kann ein Risiko für eine Erkrankung (z.B. Depression) sein. Es würde sich aber lediglich um ein Risiko für eine Störung handeln, die weiter durch Fachpersonen abgeklärt werden sollte. Das Studienteam stellt keine Diagnosen. Wenn Sie darüber nicht informiert werden wollen, sprechen Sie bitte vor Studienbeginn mit Ihrer Prüfperson.

Es gibt auch die Gesamtergebnisse der Studie, die aus den Daten von allen Teilnehmenden kommen. Dazu gehört zum Beispiel, dass wir mehr über die Anwendung von Open-Label Placebos im Zusammenhang mit chronischen nicht krebsbedingten Schmerzen wissen (→ Kapitel 4.1). Diese Ergebnisse betreffen Sie und Ihre Gesundheit nicht direkt. Ihre Prüfperson kann Ihnen am Ende der Studie eine Zusammenfassung der Gesamtergebnisse zukommen lassen.

Teil 3:
Datenschutz und Versicherungsschutz

9. Schutz von Daten und Proben

Wir schützen Ihre Daten (z.B. Angaben zur Medikamenteneinnahme aus Ihrer Krankengeschichte). Zum Schutz von Daten und Proben gibt es in der Schweiz strenge gesetzliche Regelungen.

9.1 Verschlüsselung von Daten

Bei jeder Studie entstehen Daten aus den Untersuchungen (z.B. Fragebögen, elektronisches Monitoring). Diese Daten werden dokumentiert. Das passiert meist elektronisch in grossen Tabellen, den sogenannten «Datenerhebungsbögen». Alle Daten werden verschlüsselt dokumentiert. «Verschlüsselt» heisst, dass persönliche Informationen getrennt von den Untersuchungsergebnissen aufbewahrt werden. Dazu gibt es eine Liste, die jede Person mit einem eindeutigen Code identifiziert. So stehen z.B. Ihr Name, Ihr Geburtsdatum oder Ihr Wohnort nicht direkt im Datenerhebungsbogen. Diese Liste bleibt für die Dauer von 10 Jahren an der Klinik für Konsiliarpsychiatrie und Psychosomatik des Universitätsspitals Zürich. Niemand sonst bekommt diese Liste.

Am Ende der Studie werden Ihre Daten vollständig anonymisiert, frühestens am Ende der gesetzlich vorgegebenen Aufbewahrungsdauer. Das bedeutet, dass es nicht mehr möglich sein wird, Sie ohne unverhältnismässigen Aufwand zu identifizieren. Zur Anonymisierung werden verschiedene Massnahmen eingesetzt, u.a. die Vernichtung des Codes und der Liste.

Die Server der App SEMA3, die für das elektronische Erfassen der Opioid- und Placebo-Einnahme verwendet wird, sind an der Universität Melbourne, Australien, angesiedelt. Persönliche Angaben von Ihnen (wie Name, Telefonnummer, Emailadresse) werden nicht auf der Plattform der App gespeichert. Sie können von den Mitgliedern des Studienteams nur durch einen Code identifiziert werden, der mit Ihrer verschlüsselten Emailadresse verbunden ist. Der Code wird verwendet, um zu kontrollieren, ob Sie bereits ein SEMA3 Benutzerkonto haben. Das Datenschutzrecht in Australien ist weniger streng als in der Schweiz. Die Universität Melbourne sichert in ihrer Privacy Policy die Einhaltung der EU-Datenschutzvorgaben zu, die zum Schweizer Recht gleichwertig sind [https://sema3.com/privacy.html]. Das Universitätsspital Zürich kann jedoch nicht garantieren, dass diese Zusicherung eingehalten wird.

9.2 Sicherer Umgang mit den Daten und Proben während der Studie

Die Sponsorin PD Dr. phil. Cosima Locher ist verantwortlich für den sicheren Umgang mit Ihren Daten aus dieser Studie. Sie ist verantwortlich dafür, dass die geltenden Gesetze, z.B. die Datenschutzgesetze, eingehalten werden. Die Daten werden mittels eines Codes verschlüsselt. Alle Daten, welche Namen oder andere persönliche Identifikationsmerkmale enthalten (wie zum Beispiel die Einverständniserklärungen), werden separat gelagert. Alle Dateiordner werden mit einem Passwort gesichert. Das Passwort ist nur Mitgliedern des Studienteams bekannt.

In dieser Studie werden Ihre Daten auch elektronisch erfasst und übermittelt. Die Daten sind auf einem Server in der Schweiz gespeichert. Trotzdem gibt es immer ein gewisses Restrisiko, dass fremde Personen auf Ihre persönlichen Daten zugreifen (z.B. Risiko von «Hacking»).

Mit der Einwilligung am Schluss des Dokuments erlauben Sie den Austausch dieser Informationen.

9.3 Sicherer Umgang mit Daten und Proben nach der Studie

Die Sponsorin bleibt auch nach Ende der Studie verantwortlich für den sicheren Umgang mit Ihren Daten. Das Gesetz schreibt vor, dass alle Studiendokumente, z.B. die Datenerhebungsbögen, für mindestens 10 Jahre aufbewahrt werden.

Nach Abschluss einer Studie werden die Ergebnisse meist in wissenschaftlichen Zeitschriften veröffentlicht. Dazu werden die Ergebnisse durch andere Fachpersonen begutachtet. Ihre verschlüsselten Daten müssen dabei an diese Fachpersonen weitergeleitet werden. Die Daten dürfen allerdings nicht für neue Forschungszwecke weiterverwendet werden. Dafür würde es Ihre separate Einwilligung brauchen (siehe 9.4).

9.4 Weiterverwendung Ihrer Daten und Proben in anderen, zukünftigen Studien

Ihre Daten aus dieser Studie sind für die zukünftige Forschung sehr wichtig und können möglicherweise zur Beantwortung von anderen Fragestelllungen zu einem späteren Zeitpunkt für andere Studien weiterverwendet werden.

Für diese Weiterverwendung bitten wir Sie, ganz am Ende dieses Dokuments eine weitere Einwilligungserklärung zu unterzeichnen. Diese zweite Einwilligung ist unabhängig von der Teilnahme an dieser Studie.

9.5 Einsichtsrechte bei Kontrollen

Die Durchführung dieser Studie kann überprüft werden. Die Überprüfung geschieht durch Behörden wie die zuständige Ethikkommission. Auch die Sponsorin muss solche Überprüfungen machen, damit die Qualität dieser Studie und die Ergebnisse gesichert sind.

Dafür erhalten wenige, speziell dafür ausgebildete Personen Einblick in Ihre persönlichen Daten und in Ihre Krankengeschichte. Für diese Überprüfung sind die Daten also nicht verschlüsselt. Die Personen, die Ihre unverschlüsselten Daten sehen, unterliegen der Schweigepflicht.

10. Versicherungsschutz

Sie sind versichert, wenn Sie durch die Studie – also durch die in der Studie durchgeführten Interventionsmethoden – einen Schaden erleiden. Das Vorgehen ist gesetzlich geregelt. Dafür hat die Sponsorin eine Versicherung abgeschlossen bei der Zürich Versicherungs-Gesellschaft AG. Wenn Sie meinen, dass Sie einen Schaden durch die Studie erlitten haben, wenden Sie sich bitte an Ihre Prüfperson oder direkt an die Versicherung.

Teil 4:
Einwilligungserklärungen

Diese Einwilligung besteht aus zwei unabhängigen Einwilligungserklärungen:

- Einwilligungserklärung zur Teilnahme an dieser Studie: Konditionierte offene Placebos zur Erleichterung der Reduktion opioider Schmerzmittel bei Patient*innen mit chronischen nicht krebsbedingten Schmerzen: Eine randomisierte kontrollierte Studie
- Einwilligungserklärung für die Weiterverwendung von Daten aus dieser Studie in verschlüsselter Form

Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie uns, wenn Sie etwas nicht verstehen oder wenn Sie noch etwas wissen möchten. Für die Teilnahme ist Ihre schriftliche Einwilligung notwendig.

Einwilligungserklärung zur Teilnahme an der Studie Konditionierte offene Placebos zur Erleichterung der Reduktion opioider Schmerzmittel bei Patient*innen mit chronischen nicht krebsbedingten Schmerzen: eine randomisierte kontrollierte Studie

BASEC-Nummer **SNCTP-Nummer** **Clinicaltrials.gov-Nummer**	2023-02327 SNCTP000005853 NCT06350786
Titel der Studie	Konditionierte offene Placebos zur Unterstützung der Reduktion opioider Schmerzmittel bei Patient*innen mit chronischen nicht krebsbedingten Schmerzen: Eine randomisierte kontrollierte Studie
Laienverständlicher Titel	*Mind-Body Management: Ein Ansatz, der Sie bei der Reduktion von Opioiden unterstützt*
Verantwortliche Institution (Sponsorin mit Adresse)	PD Dr. phil. Cosima Locher Universitätsspital Zürich Klinik für Konsiliarpsychiatrie und Psychosomatik Haldenbachstrasse 16 / 18 8091 Zürich
Ort der Durchführung	Haldenbachstrasse 16 / 18 8091 Zürich

Prüfperson am Studienort Name und Vorname in Druckbuchstaben:	
Teilnehmer*in Name und Vorname in Druckbuchstaben: Geburtsdatum:	

- Ich habe mündlich und schriftlich Informationen über die Studie bekommen, und zwar von der Prüfperson, die unten unterschreibt.
- Die Prüfperson hat mir den Zweck, den Ablauf und die Risiken der Studie erklärt.
- Ich nehme freiwillig an der Studie teil.
- Die Prüfperson hat mir erklärt, welche möglichen Standardbehandlungen es ausserhalb der Studie gibt.
- Ich hatte genügend Zeit, um diese Entscheidung zu treffen. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich kann jederzeit meine Teilnahme beenden. Ich muss nicht erklären, warum. Auch wenn ich die Teilnahme beende, bekomme ich weiter meine medizinische Behandlung. Die Daten, die bis dahin gesammelt wurden, bleiben gespeichert und werden im Rahmen der Studie ausgewertet.
- Wenn es besser für meine Gesundheit ist, kann mich die Prüfperson jederzeit von der Studie ausschliessen.
- Ich wurde darüber aufgeklärt, dass mit einzelnen Proband*innen ein Interview zu Studienende durchgeführt wird, bei dem eine Tonaufnahme stattfindet.
- Ich habe verstanden, dass meine Daten nur in verschlüsselter Form weitergegeben werden. Die Sponsorin sorgt dafür, dass der Datenschutz nach Schweizer Standard eingehalten wird.
- Bei Ergebnissen, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, bespreche ich das mit meiner Prüfperson.
- Die zuständigen Fachpersonen der Sponsorin und der Ethikkommission dürfen meine unverschlüsselten Daten zur Kontrolle einsehen. Alle diese Personen unterstehen der Schweigepflicht.
- Die Zürich Versicherungs-Gesellschaft AG versichert mögliche Schäden.

Ort, Datum	Name und Vorname Teilnehmer*in in Druckbuchstaben Unterschrift Teilnehmer*in

Bestätigung der Prüfperson: Hiermit bestätige ich, dass ich dieser Teilnehmerin / diesem Teilnehmer Art, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle mit dieser Studie in Verbindung stehenden Verpflichtungen nach Schweizer Recht zu erfüllen. Sollte ich im Verlauf der Studie von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin / des Teilnehmers zur Studienteilnahme beeinflussen könnten, werde ich sie / ihn umgehend darüber informieren.

Ort, Datum	Name und Vorname der Prüfperson in Druckbuchstaben Unterschrift der Prüfperson

Einwilligungserklärung für Weiterverwendung von Daten in verschlüsselter Form

Diese Einwilligung betrifft Sie nicht im Sinne der persönlichen Teilnahme an einer Studie. «Weiterverwendung» meint, dass Daten über die Zeit Ihrer Studienteilnahme hinaus aufbewahrt und in verschlüsselter Form für weitere Forschung verwendet werden können. Das heisst, Ihre Daten können für die Beantwortung von anderen Fragestellungen zu einem späteren Zeitpunkt weiter verwendet werden.

BASEC-Nummer **SNCTP-Nummer** **Clinicaltrials.gov-Nummer**	(2023-02327) SNCTP000005853 NCT06350786
Titel der Studie	Konditionierte offene Placebos zur Unterstützung der Reduktion opioider Schmerzmittel bei Patient*innen mit chronischen nicht krebsbedingten Schmerzen: Eine randomisierte kontrollierte Studie
Laienverständlicher Titel	*Mind-Body Management: Ein Ansatz, der Sie bei der Reduktion von Opioiden unterstützt*
Teilnehmer*in Name und Vorname in Druckbuchstaben: Geburtsdatum:	

- Ich erlaube, dass meine verschlüsselten Daten aus dieser Studie für die Forschung weiterverwendet werden dürfen. Die Daten werden an der Klinik für Konsiliarpsychiatrie und Psychosomatik des Universitätsspitals Zürich gelagert werden. Sie stehen dann für zukünftige, weitere Forschungsprojekte auf unbestimmte Zeit zur Verfügung.
- Ich habe verstanden, dass die Daten verschlüsselt sind und der Schlüssel sicher aufbewahrt wird.
- Ich bin damit einverstanden, dass die verschlüsselten Daten nach Abschluss des Forschungsprojekts zum Nachweis der sogenannten «guten wissenschaftlichen Praxis» einem Daten-Archiv übergeben werden.
- Die Daten können nur in der Schweiz ausgewertet werden und in einer Datenbank hier gespeichert werden.
- Ich entscheide freiwillig und kann diesen Entscheid zu jedem Zeitpunkt wieder zurücknehmen. Wenn ich zurücktrete, werden alle meine Daten anonymisiert. Ich informiere lediglich meine Prüfperson und muss diesen Entscheid nicht begründen.
- Normalerweise werden alle Daten zusammengefasst ausgewertet. Wenn sich zufällig ein Ergebnis zeigt, das für meine Gesundheit sehr wichtig ist, werde ich kontaktiert. Wenn ich das nicht wünsche, teile ich dies meiner Prüfperson mit.

Ort, Datum	Name und Vorname Teilnehmer*in in Druckbuchstaben Unterschrift Teilnehmer*in

Bestätigung der Prüfperson: Ich bestätige, dass ich der Teilnehmerin / dem Teilnehmer Art, Bedeutung und Tragweite der Weiterverwendung von Daten erläutert habe.

Ort, Datum	Name und Vorname der Prüfperson in Druckbuchstaben Unterschrift der Prüfperson

Supplemental Material B: Informed Consent – English translation

University Hospital Zurich

Department of Consultation Liaison Psychiatry and Psychosomatics

Haldenbachstrasse 16 / 18

8091 Zurich

Request for Participation in Research

Study title: Conditioned Open-Label Placebos to Facilitate Opioid Reduction in Patients with Chronic Noncancer Pain: a Randomized Controlled Trial

Lay Title: Mind-Body Management: An Approach to Support You in Reducing Opioid Use

Dear Sir or Madam,

We would like to inform you about our research project and ask whether you would be interested in participating. Before a new intervention method can be implemented, it must first be studied to understand how it works.

Such research is referred to as a clinical trial. In our study, we aim to investigate whether so called open-label placebos (OLP), in combination with a mind-body management intervention, can be used as a supportive measure to help reduce the use of opioid pain medication. The term OLP means that the placebo is administered with full disclosure that it contains no pharmacologically active ingredients. In other words, the placebo is taken with the knowledge that it is inactive.

You are currently experiencing chronic non-cancer-related pain and are taking opioid pain medication. You are motivated to reduce your opioid use. You are already under the care of a primary treating physician, with whom you will carry out the reduction. Therefore, we would like to ask if you would be willing to participate in this study.

Your participation is voluntary. The following patient information is intended to help you make an informed decision. Any questions regarding the study can be discussed with the study investigator. That is the term we use for the researchers responsible for this study and for supporting you throughout the process. If you decide to participate, please sign the consent form at the end. By signing, you confirm that you have read and understood the patient information. If anything is unclear, please ask the study investigator.

The patient information and consent form consist of four parts:

Part 1 **A Brief Summary of the Most Important Points**

Part 2 **Detailed Information about the Study**

Part 3 **Data Protection and Insurance Coverage**

Part 4 **Consent Form**

Reading **part 1** will give you an overview of the study. **Part 2** explains the entire process and background of the study in detail. **Part 3** contains information on data protection and insurance coverage. By signing **part 4** at the end of the document, you confirm that you have understood everything and agree to participate.

This study is funded by the Swiss National Science Foundation. The study is led and overseen by PD PhD Cosima Locher.

Your contact persons for this study are:

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Part 1:
A Brief Summary of the Most Important Points

11. Why Are We Conducting this Study?

In cases of chronic non-cancer-related pain, it is essential to support the reduction of opioid pain medication in order to minimize or avoid unwanted side effects.

In this study, we are investigating whether a mind-body management intervention, in combination with the use of placebos, can serve as a supportive measure to aid in reducing opioid pain medication and thereby help reduce undesirable side effects. The mind-body management intervention is based on the assumption that the body and mind influence each other. You can learn more about the scientific background of this study in Chapter 4.

12. What Will You Need to Do if You Participate?

Your participation in this study will last a maximum of 9 weeks. The study is divided into a pre-assessment phase and an intervention phase. The pre-assessment phase lasts up to 3 weeks, and the intervention phase lasts 6 weeks. Throughout the entire 9-week period, we will invite you to attend 6 appointments. Two of these appointments may take place on-site, while the others will be conducted online.

Pre-Assessment Phase:

- Initial contact via telephone to provide study information and make preliminary assessments of eligibility (approx. 30 minutes)
- Online questionnaire for initial assessment (approx. 30 minutes)

Intervention Phase:

- First intervention session via telephone or video call, including a group-specific intervention and an online questionnaire (approx. 90 minutes)
- Second session via telephone or video call, including a group-specific intervention and online questionnaire (approx. 75 minutes)
- Third session via telephone or video call, including a brief group-specific intervention and an online questionnaire (approx. 75 minutes)
- Final session via telephone, video call, or in person, with completion of an online questionnaire (approx. 90 minutes)
- At the end of the final session, a small number of participants will be invited to take part in a final interview (approx. 30 minutes). This interview will be audio recorded.

You can find a detailed schedule of appointments in Chapter 5.

If you decide to participate, you will be randomly assigned to one of two groups: the OLP group or the control group. Both groups will receive a group-specific intervention. In the OLP group, you will receive placebos in addition to your opioid pain medication, whereas the control group will not receive placebos. Regardless of which group you are in, you will track your opioid intake electronically throughout the entire duration of the study (electronic monitoring). Participants in the OLP group will also track their placebo intake electronically.

More information about the study procedure can be found in Chapter 5.

If you complete your participation in the study, you will receive a compensation of CHF 100 (plus CHF 15 for participating in the final interview).

Your primary care physician will be informed about your participation in the study. Regardless of the study intervention, they will continue to manage your pain medication reduction and overall treatment.

13. What Are the Benefits and Risks of Participation?

Benefits

- Participation in this study may provide you with support in reducing your opioid medication and help to alleviate the side effects associated with reduction.
- You may benefit from the ongoing electronic monitoring of your medication intake by receiving feedback about your intake patterns.
- Your participation will contribute to a better understanding of how to manage opioid reduction in individuals with chronic non-cancer-related pain.
- The results of this study could benefit other individuals with chronic pain who are using opioid pain medication.

Risks:

- No specific risks related to the study are expected, as it involves the use of placebos without any pharmacological effect and ongoing electronic monitoring.
- During the process of reducing your opioid medication and participating in the study interventions, you may become more aware of your chronic non-cancer-related pain. This could lead to heightened symptom awareness but may also contribute to improve symptom management and ultimately to the improvement of your chronic pain.

Additional information on risks and burdens can be found in Chapter 6.

Part 2:
Detailed Information about the Study

14. Scientific Background of the Study

14.1 Background: Why Are We Conducting this Study?

In our study, funded by the Swiss National Science Foundation (SNSF), we are investigating a mind-body management intervention to support the reduction of opioid pain medication in individuals with chronic non-cancer-related pain. This intervention teaches participants helpful strategies that work on two levels: the body and the mind. Placebos are used as the investigational substance in this context. Previous studies have shown that placebos can be successfully used to support the reduction of opioid medication in acute pain scenarios. Only participants in the intervention group will receive placebos. Both the OLP group and the control group, record the intake of medication electronically on an ongoing basis. This electronic monitoring allows for feedback regarding the use of opioid medications and placebos, which can in turn support a positive attitude toward reducing opioid intake.

We are looking for individuals who have experienced chronic non-cancer-related pain for more than six months, have been taking opioid medications for at least three months, and would like to reduce them. That is why we are inviting you to take part in this study.

Our study is based on the concept of health promotion, with a focus on strengthening participants' ability to act autonomously (empowerment). It is also based on the assumption that the body and mind are interconnected and influence each other. These interactions mostly happen unconsciously and can affect how pain is perceived.

14.2 Study Structure: How Are We Proceeding?

In our study, participants will be randomly assigned to one of two groups. This process, known as randomization, is important to ensure reliable results. Each group will receive different treatment. The two study groups are:

- Group 1 (OLP Group): This group receives a mind-body management intervention along with placebos. The placebo used has no pharmacological effect and is approved in Switzerland. It is called "P-Tabletten blau" (engl.: "p-tablets blue") by Zentiva and contains lactose, table sugar and glucose. In addition to receiving the placebos, the intake of both opioids and placebos will be electronically monitored.
- Group 2 (Control Group): This group does not receive placebos. Only the daily intake of opioid pain medication will be monitored electronically.

You will record your medication (and placebo, if applicable) intake daily using the SEMA3 app. This data will be reviewed and discussed during your study visits.

Open-label placebo studies have shown that such placebos can support opioid reduction. However, we still know little about their effectiveness in cases of chronic non-cancer-related pain. Our study aims to determine whether open-label placebos can facilitate opioid reduction. You will be clearly informed that the placebos you may receive have no pharmacological effect.

In both groups, your primary physician remains responsible for prescribing opioids, creating a reduction plan, and implementing it. The study team will not interfere with your doctor's medical treatment plan.

14.3 Regulations for Scientific Research Involving Humans

We are conducting this study in accordance with Swiss laws (Human Research Act, data protecting regulations) and follow all internationally recognized guidelines. The responsible ethics committee has reviewed and approved this study.

This national study conducted in Switzerland with 86 participants. A description of the study is also available on the Swiss Federal Office of Public Health's website: www.kofam.ch (SNCTP-Nr.: SNCTP000005853 / BASEC-Nr.: 2023-02327).

15. Study Procedure

15.1 What Is Required if You Choose to Participate?

Participation in the study is voluntary and will last a maximum of 9 weeks. You are expected to follow the schedule (→ see Chapter 5.2) and comply with your assigned study instructions. This includes attending all scheduled appointments, completing questionnaires, and recording your daily opioid use via the app.

You are also expected to inform your study contact if,

- your health status changes (e.g., worsening symptoms or new complaints), even if you decide to leave this study early (→ see Chapters 5.3 und 5.4),
- you start, stop, or change the dosage of any medications during the study,
- you receive any current treatments from other healthcare providers.

15.2 What Happens During the Appointments?

You will have a total of six study appointments. Two of them are part of the pre-assessment phase, and the other four are part of the intervention phase. For the intervention, you will come to our site twice and we will meet twice remotely (via telephone or video conference). Alternatively, all appointments may take place remotely. Appointment durations vary between 15 and 90 minutes.

Pre-Assessment Phase (max. 3 weeks):

- Initial contact (by telephone): we will explain the study and conduct a preliminary screening (approximately 30 minutes).
- Online questionnaire (approximately 1 week later): you will complete a questionnaire to assess eligibility (approximately 30 minutes).

Intervention Phase (6 weeks):

- If you are eligible to participate in the study, the first visit will take place either at our location at Haldenbachstrasse 16 / 18 in Zurich or the intervention appointment will take place by telephone or video conference. This appointment will last approximately 90 minutes in total. We will inform you which study group you have been assigned to and begin with the study intervention. As part of this, we will discuss with you the procedure in your group (approximately 15 minutes). If you are assigned to the OLP group, you will also receive the placebos after the appointment. Afterwards, you will complete a questionnaire. Completing the questionnaire takes approximately 60 minutes. Finally, we will explain to you how to enter your daily intake of opioid pain medication using the SEMA3 app. The next meeting will take place one week after this first intervention appointment by telephone or video conference. The study intervention will be continued and depends on which group you belong to. In addition, you will receive feedback from us regarding your intake of opioid pain medication. The telephone call or video conference will last approximately 30 minutes. Following this appointment, you will again complete an online questionnaire (duration approximately 20 minutes). Altogether, this appointment will last approximately 50 minutes.

- After another two weeks, a further appointment will take place by telephone or video conference. During this appointment, we will discuss your questions and provide you with feedback regarding your intake of opioid pain medication since your last meeting with us. This appointment will last approximately 30 minutes in total

- The final visit will again take place either at our location at Haldenbachstrasse 16 / 18 in Zurich or by telephone or video conference. During this appointment, we will conclude your participation in the study with a final discussion, and you will be compensated with CHF 100. At the final appointment, you will also complete a questionnaire. Completing the questionnaire will again take approximately 20 minutes. Altogether, this visit will therefore last approximately 90 minutes.

- In addition to the final study visit with us, a small portion of study participants will take part in an interview (duration approximately 30 minutes). You will be informed at your first appointment whether you have been selected for this concluding interview. An audio recording of this interview will be made. For participating in the interview, you will be compensated with an additional CHF 15.

Through these assessments, we will see how well the OLP intervention works in comparison to the intervention of the control group with regard to opioid reduction.

The schedule on the next page shows all appointments. While the columns highlighted in blue represent the appointments of the pre-study phase, the columns of the appointments and study visits of the actual study intervention are highlighted in green. The checkmarks indicate the activities of each appointment.

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Schedule

Appointment / Study Visit	1	2	3	4	5	6
Phase	**Pre-Assessment**		**Study Intervention**			
Date	max. 3 weeks prior		Study start	1 week later	3 weeks later	6 weeks later
Duration	30 min	30 min	90 min	50 min	30 min	90 min
Where	Telephone	Online	On site / Online	Online	Online	On site / Online
Study Information	✓					
Questionnaire		✓	✓	✓		✓
Group-specific Intervention			✓	✓	✓	✓
Interview						(✓)

We will schedule the appointments together with you. You will receive a detailed overview of the appointments. We rely on the appointments being kept. We ask you to inform us in good time if you need to reschedule an appointment for important reasons.

15.3 When Does Participation in the Study End?

Your participation lasts a maximum of 9 weeks. You may also end your participation earlier at any time (→ see Chapter 5.4). You do not need to explain why you no longer wish to participate. If you wish to end your participation early, please speak with your study investigator.

Even if you end your participation early, you will continue to receive medical care and support from your primary treating physician. In that case, please return all study medications and study materials (placebos and empty placebo packaging and blister packs) that we gave you.

If your participation ends early, we will still evaluate the data collected up to that point (e.g., monitoring data on opioid pain medications and placebos, questionnaires) for the study.

In rare cases, it may happen that we have to exclude someone from the study early. This is the case, for example, if your health condition unexpectedly and seriously worsens. In this case, we will discuss the further course of action together with your treating physician.

15.4 What Happens if You Do not Want to Participate?

If you do not wish to participate in the study, there are established options available to support the reduction of opioid pain medication in cases of chronic non-cancer-related pain, about which your primary treating physician can inform and advise you.

15.5 Pregnancy

Should you become pregnant during the study, you must inform your study investigator immediately. In this case, you will also be asked to inform your primary treating physician. The study investigator will discuss the further course of action with you.

16. Risks, Burdens, and Side Effects

16.1 What Risks and Burdens May Occur?

No study-specific risks are to be expected, as this involves an open administration of placebos without pharmacological effect and the continuous recording of opioid pain medication. Engaging with your chronic non-cancer-related pain may possibly lead to an increased perception of symptoms but may also lead to better symptom management and thereby to an improvement in chronic pain. We will ask you about this.

17. Funding and Compensation

This study is initiated by the sponsor PD PhD Cosima Locher and fully funded by the Swiss National Science Foundation.

The researchers involved do not have any direct financial benefit from conducting this study.

If you take part in this study, you will receive the following compensation for full participation: 100 CHF. Expenses such as travel costs incurred due to participation are already included in the compensation. Participants of the interview at the final appointment will be additionally compensated with 15 CHF. There are no costs incurred by participating in this study for you or your health insurance.

18. Results from the Study

There are results that concern you personally. These results will be communicated to you by your study investigator. There are also incidental findings. Incidental findings are “accompanying results” that are not intended. This may be a risk for a disorder (e.g., depression). However, it would only be a risk for a condition, which should be further clarified by professionals. The study team does not make diagnoses. If you do not wish to be informed about this, please speak with your study investigator before the study begins.

There are also the overall results of the study, which are based on the data from all participants. This includes, for example, that we gain more knowledge about the use of open-label placebos in connection with chronic non-cancer-related pain (→ see Chapter 4.1). These results do not concern you or your health directly. Your study investigator can provide you with a summary of the overall results at the end of the study.

Part 3:
Data Protection and Insurance Coverage

19. Protection of Data and Samples

We protect your data (e.g., information about medication intake from your medical history). In Switzerland, there are strict legal regulations for the protection of data and samples.

19.1 Encryption of Data

In every study, data are generated from the assessments (e.g., questionnaires, electronic monitoring). These data are documented. This usually takes place electronically in large tables, the so-called “data collection sheets.” All data are documented in encrypted form. “Encrypted” means that personal information is stored separately from the assessment results. For this, there is a list that identifies each person with a unique code. This means, for example, that your name, date of birth, or place of residence do not appear directly in the data collection sheet. This list is kept for a duration of 10 years at the Clinic for Consultation-Liaison Psychiatry and Psychosomatics at the University Hospital Zurich. No one else has access to this list.

At the end of the study, your data will be fully anonymized, at the earliest at the end of the legally prescribed retention period. This means that it will no longer be possible to identify you without disproportionate effort. Various measures are used for anonymization, including the destruction of the code and the list.

The servers of the SEMA3 app, which is used for electronically recording the intake of opioids and placebos, are located at the University of Melbourne, Australia. Your personal details (such as name, telephone number, email address) are not stored on the app platform. Members of the study team can identify you only through a code that is linked to your encrypted email address. The code is used to check whether you already have a SEMA3 user account. Data protection law in Australia is less strict than in Switzerland. The University of Melbourne affirms in its privacy policy that it complies with EU data protection standards, which are equivalent to Swiss law [https://sema3.com/privacy.html]. However, the University Hospital Zurich cannot guarantee that this assurance will be upheld.

19.2 Secure Handling of Data and Samples During the Study

The sponsor, PD PhD Cosima Locher, is responsible for the secure handling of your data from this study. She is responsible for ensuring that the applicable laws, such as data protection laws, are complied with. The data are encrypted using a code. All data containing

names or other personal identifying characteristics (such as the consent forms) are stored separately. All file folders are password protected. The password is known only to members of the study team.

In this study, your data are also collected and transmitted electronically. The data are stored on a server in Switzerland. Nevertheless, there is always a certain residual risk that unauthorized persons could access your personal data (e.g., risk of “hacking”).

With the consent at the end of this document, you permit the exchange of this information.

19.3 Secure Handling of Data and Samples After the Study

The sponsor remains responsible for the secure handling of your data even after the end of the study. The law stipulates that all study documents, such as the data collection sheets, must be retained for at least 10 years.

After the completion of a study, the results are usually published in scientific journals. For this purpose, the results are reviewed by other professionals. Your encrypted data must be forwarded to these professionals. However, the data may not be reused for new research purposes. For that, your separate consent would be required (→ see Chapter 9.4).

19.4 Reuse of Your Data and Samples in Other, Future Studies

Your data from this study are very important for future research and may possibly be reused at a later time to answer other research questions in other studies.

For this reuse, we ask you to sign an additional consent form at the very end of this document. This second consent is independent of participation in this study.

19.5 Right of Access for Audits

The conduct of this study may be reviewed. The review is carried out by authorities such as the responsible ethics committee. The sponsor must also carry out such reviews in order to ensure the quality of this study and its results.

For this purpose, a few specially trained individuals will have access to your personal data and your medical history. For this review, the data are therefore not encrypted. The individuals who view your unencrypted data are subject to confidentiality.

20. Insurance Coverage

You are insured if you suffer harm as a result of the study — that is, through the intervention methods carried out in the study. The procedure is regulated by law. For this purpose, the

sponsor has taken out insurance with Zürich Insurance Company Ltd. If you believe that you have suffered harm due to the study, please contact your study investigator or the insurance company directly.

Part 4:
Consent Declarations

This consent consists of two independent declarations of consent:

- Consent to participate in this study: *Conditioned Open-Label Placebos to Facilitate the Reduction of Opioid Pain Medication in Patients with Chronic Non-Cancer Pain: A Randomized Controlled Trial*
- Consent for the reuse of data from this study in encrypted form

Please read this form carefully. Please ask us if there is anything you do not understand or if you would like to know more. Your written consent is required to participate.

Consent to Participate in the Study Conditioned Open-Label Placebos to Facilitate the Reduction of Opioid Pain Medication in Patients with Chronic Non-Cancer Pain: A Randomized Controlled Trial

BASEC Number **SNCTP Number** **Clinicaltrials.gov Number**	2023-02327 SNCTP000005853 NCT06350786
Title of the Study	Conditioned Open-Label Placebos to Support the Reduction of Opioid Pain Medication in Patients with Chronic Non-Cancer Pain: A Randomized Controlled Trial
Lay Title	*Mind-Body Management: A Method to Support You in Reducing Opioids*
Responsible Institution (Sponsor with Address)	PD PhD Cosima Locher University Hospital Zurich Clinic for Consultation-Liaison Psychiatry and Psychosomatics Haldenbachstrasse 16 / 18 8091 Zurich
Place of Conduct	Haldenbachstrasse 16 / 18 8091 Zurich

Investigator at Study Site Name and First Name in Block Letters:	
Participant Name and First Name in Block Letters: Date of Birth:	

- I have received verbal and written information about the study, from the study investigator who signs below.
- The study investigator has explained to me the purpose, procedure, and risks of the study.
- I am participating in the study voluntarily.
- The study investigator has explained to me what possible standard treatments exist outside the study.
- I had sufficient time to make this decision. I will keep the written information and receive a copy of my written consent form.
- I can end my participation at any time. I do not have to explain why. Even if I end my participation, I will continue to receive my medical treatment. The data collected up to that point will remain stored and will be evaluated within the framework of the study.
- If it is better for my health, the study investigator may exclude me from the study at any time.
- I have been informed that an interview will be conducted with individual participants at the end of the study, during which an audio recording will be made.
- I understand that my data will only be passed on in encrypted form. The sponsor ensures that data protection in accordance with Swiss standards is observed.
- In the case of results that directly concern my health, I will be informed. If I do not wish this, I will discuss it with my study investigator.
- The responsible professionals of the sponsor and the ethics committee may view my unencrypted data for monitoring purposes. All of these individuals are bound by confidentiality.
- Zürich Insurance Company Ltd insures against possible harm.

Place, Date	Name and First Name of Participant in Block Letters Signature of Participant

Confirmation by the Study Investigator: I hereby confirm that I have explained the nature, significance, and scope of the study to this participant. I assure that I will fulfil all obligations associated with this study according to Swiss law. Should I become aware of any aspects during the course of the study that could influence the participant's willingness to continue participation, I will inform them immediately.

Place, Date	Name and First Name of the Study Investigator in Block Letters Signature of the Study Investigator

Consent for Reuse of Data in Encrypted Form

This consent does not concern your personal participation in a study. “Reuse” means that data will be stored beyond the duration of your participation in the study and may be used in encrypted form for further research. This means that your data may be reused at a later time to answer other research questions.

BASEC Number **SNCTP Number** **Clinicaltrials.gov Number**	(2023-02327) SNCTP000005853 NCT06350786
Title of the Study	Conditioned Open-Label Placebos to Support the Reduction of Opioid Pain Medication in Patients with Chronic Non-Cancer Pain: A Randomized Controlled Trial
Lay Title	*Mind-Body Management: A Method to Support You in Reducing Opioids*
Participant Name and First Name in Block Letters: Date of Birth:	

- I consent to my encrypted data from this study being reused for research purposes. The data will be stored at the Clinic for Consultation-Liaison Psychiatry and Psychosomatics of the University Hospital Zurich. They will then be available for future, additional research projects for an indefinite period of time.
- I understand that the data are encrypted and that the key is securely stored.
- I agree that the encrypted data may be transferred to a data archive after completion of the research project for the purpose of demonstrating so-called “good scientific practice.”
- The data may only be evaluated in Switzerland and stored in a database here.
- I make this decision voluntarily and can withdraw it at any time. If I withdraw, all of my data will be anonymized. I will only inform my study investigator and do not need to give a reason for this decision.
- Normally, all data are evaluated in aggregated form. If a result should emerge by chance that is very important for my health, I will be contacted. If I do not wish this, I will inform my study investigator.

Place, Date	Name and First Name of Participant in Block Letters Signature of Participant

Confirmation by the Study Investigator: I confirm that I have explained to the participant the nature, significance, and scope of the reuse of data

Place, Date	Name and First Name of the Study Investigator in Block Letters Signature of the Study Investigator

Supplemental Material C: Qualitative Interview

Experiences with the OLP-Intervention

1. *Please think back to the time during the Mind-Body Management intervention. How did you experience this phase? Please share your experiences.*

2. *When you think of specific moments during the Open-Label Placebo or Mind-Body intervention, what situations or aspects stand out positively? What helped you or was particularly useful?*

3. *Were there any moments or experiences during the intervention that you found challenging? What was difficult to implement or hard to cope with?*

Acceptance of the OLP Approach

4. *At the beginning of the intervention, you were given an explanation (rationale) of how and why Open-Label Placebos work. When you think back to that explanation, what aspects did you particularly understand well? What thoughts did you have about it?*

5. *Now that you have experienced the intervention: Can you imagine using Open-Label Placebos again in the future? Under what circumstances would this be conceivable for you? Please share your thoughts.*

6. *Think about people in your social environment: Would you share your experiences with placebos with them or recommend that they try it? How do you imagine such conversations would go?*

Prerequisites, Ideas, and Concerns Regarding the Practical Implementation of OLP

7. *When you think about your daily routine: How could a Mind-Body intervention personally fit into your everyday life? Please describe how this could look in practice.*

8. *Imagine you are in a clinic where other patients are also undergoing a Mind-Body intervention. How do you think they would respond to this intervention? Please tell us what you imagine.*

9. *If doctors prescribe Open-Label Placebos to patients: What do you think they should particularly pay attention to? What would be important to ensure the intervention is well accepted?*

Supplemental Material D: Table 1

Table 1. Study Outcomes and Measuring Points

Study Schedule									
			Screening		**Intervention**				**On-going intake**
			Pre-Screening	Screening	Learning phase	Dose-extension phase	Dose-extension phase	Dose-extension phase	
		Visit	1	2	3	4	5	6	
		Timepoint	t-2	t-1	t0	t1	t2	t3	
		Days	-21	-14	0	7	21	42	
		Location	Phone	Online	On-Site/ Phone	Phone	Phone	On-Site/ Phone	Daily monitoring with App SEMA3
		Assessments			Baseline	Interim	Booster	Post	
Group specific intervention	Treatment rationale				x	x			
	Electronic monitoring feedback					x	x	x	
Screening	Study information		x						
	Informed Consent		x						
	Screening			x					
Contact Physician	Physicians' treatment expectancies			x					
	Physicians' acceptability of OLP			x					
Randomisation	Randomisation				x				

Primary Outcome	Opioid medication capture				x				
	Opioid medication intake								x
Secondary Outcomes	Subjective opioid withdrawal (SOWS)				x	x		x	
	Pain severity (ICD-11)				x	x		x	
	Pain disability (PDI)				x	x		x	
	Anxiety (GAD-7)				x	x		x	
	Depression (PHQ-9)				x	x		x	
	Pain Opioid Analgesics Beliefs (POABS-CA)				x				
	Intervention Expectancy				x				
Evaluation Outcomes	Rationale credibility (OLP group only)							x	
	Placebo understanding							x	
	Patient Provider Connection (HEAL)							x	
	Non-Opioid Medication intake				x			x	
	Intervention Implementation				x	x	x	x	
EM-related Outcomes	Placebo medication intake								x
	Opioid adherence								x
Qualitative Outcomes	Qualitative interview							x	

Safety Outcomes	Safety Outcomes					x	x	x	