Study Protocol for Comparative Effectiveness of Pain Cognitive Behavioral Therapy and Chronic Pain Self-Management Within the Context of Opioid Reduction: The EMPOWER Study

ClinicalTrials.gov: NCT03445988
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Project Summary

The purpose of this pragmatic clinical trial is to transform care, reduce health risks, and improve outcomes for patients with chronic pain who are taking long-term prescription opioids. Our proposed study will address several critical evidence gaps that currently hinder patients and physicians from making informed decisions about pain care. This project will provide both patients taking opioids and their prescribers with the specific evidence needed to choose the most effective strategies for reducing opioid doses and minimizing pain, reducing pain interference, and improving role function.

For patients interested in reducing opioid use, we aim to: (1) reduce prescription opioid use while maintaining pain control; and (2) compare the effectiveness of the Chronic Pain Self-Management Program (CPSMP), cognitive behavioral therapy for chronic pain (pain-CBT), and no behavioral treatment, all within the context of patient-centered collaborative opioid tapering. The acronym EMPOWER stands for *Effective Management of Pain and Opioid-Free Ways to Enhance Relief.*

[Please note: Along with the EMPOWER randomized controlled trial, PCORI funded a separate sub-study involving a national observational study of people taking daily prescription opioids (not tapering). As this observational sub-study was not part of the randomized controlled trial, it is not described in this protocol.]

General Information

Stanford University Institutional Review Board (IRB) Protocol Title: Comparative Effectiveness of Pain Cognitive Behavioral Therapy and Chronic Pain Self-Management Within the Context of Opioid Reduction

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Study Goals and Objectives

Aim 1: Reduce or Contain Prescription Opioid Use While Maintaining Pain Control.
Hypothesis 1a. At one year, 40% of participants in the Taper Only group (no behavioral treatment) will successfully reduce prescription opioids by ≥50% in MEDD without worsening pain intensity, pain interference, or satisfaction with social roles and activities at 12 months.
Hypothesis 1b. Success with patient-centered opioid tapering will not be associated with the starting MEDD.

Aim 2: Compare the Effectiveness of (1) Taper + CPSMP, or (2) Taper + pain-CBT, or (3) No Behavioral Treatment (Taper Only) within the Context of Patient-Centered Collaborative Opioid Tapering.
Hypothesis 2a. Participants receiving behavioral interventions (Taper + pain-CBT or Taper + CPSMP) will be more likely to reduce their opioid dose than those in the Taper Only group (no behavioral intervention).
Hypothesis 2b. There will be no significant differences in dosage reduction or the percentage of participants reducing dosage between the Taper + pain-CBT and Taper + CPSMP groups.
Hypothesis 2c. Participants in the Taper + pain-CBT group will experience less pain, less pain interference, and decreased depression compared to those in the Taper + CPSMP or Taper Only groups.
Hypothesis 2d. Participants in the Taper + CPSMP group will show greater improvements in satisfaction with social roles and activities and self-efficacy compared to those in the Taper + pain-CBT or Taper Only groups.

Exploratory Hypothesis 2e. Opioid escalation will be less common among participants in the behavioral intervention groups (Taper + pain-CBT or Taper + CPSMP) compared to those in the Taper Only group.

Study Design

This is a pragmatic, prospective, longitudinal, multi-center, three-arm, randomized controlled clinical trial. The study will include 594 patients receiving daily prescription opioids in primary care and pain clinics at EMPOWER study sites (see Table 1 for a list of study locations).

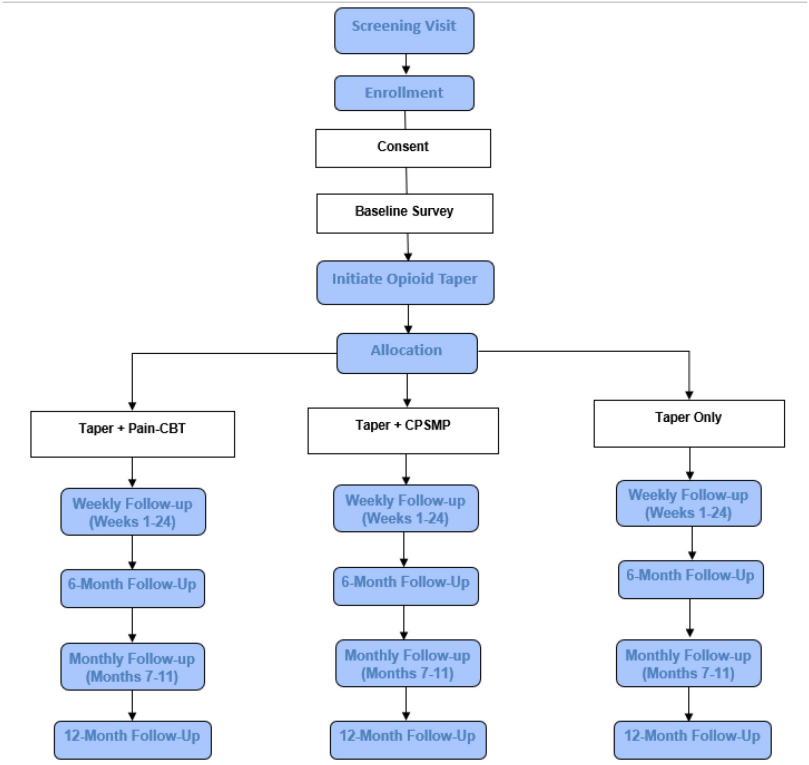
Table 1. Study Sites

Study Site	Setting	Payer System	Type	Location
Stanford Pain Management Center	Pain Clinic	Open	Academic Regional Org.	Redwood City, CA
Stanford Primary Care	Primary Care	Open	Academic Regional Org.	Palo Alto, CA
Phoenix Veterans Affairs Health Care System	Pain Clinic	Closed Network	Veteran Healthcare	Phoenix, AZ
Stieg Pain Clinics/MedNOW Clinics	Pain Clinic	Open	Private Practices	Colorado
Intermountain Health	Primary Care	Closed Network	Regional Org.	Layton, UT
Kaiser Permanente Oakland	Primary Care	Closed Network	Regional Org.	Oakland, CA
Lehigh Valley Health Network	Pain Clinic	Closed Network	Regional Org.	Allentown, PA

Methodology

At all sites, patient recruitment will occur through the following methods: identifying eligibility in medical records, in-house advertising, external community-based advertising, and use of the CHOIR database at Stanford University.[1] Study coordinators will review the clinic schedule daily to identify eligible patients based on pain and opioid information available in the electronic medical record. Clinicians will discuss EMPOWER with patients and obtain permission from interested patients to be contacted by study staff. Study coordinators will then obtain informed consent and register participants in the CHOIR research learning health system database to initiate survey deployment. After completing the baseline survey, participants will be randomized to one of three intervention arms: (1) EMPOWER Taper Only (no behavioral treatment); (2) EMPOWER Taper + pain-CBT; or (3) EMPOWER Taper + CPSMP. Block randomization with variable block sizes, stratified by study site, will be utilized. The Executive Research Team, including the Principal Investigator and the data analytic team, will remain masked to intervention assignment throughout recruitment, enrollment, and data collection. Participants, EMPOWER clinicians, and study coordinators will be aware of intervention assignment. For the study flow diagram, see Figure 1.

Figure 1. Study Flow Diagram



Eligibility Criteria. Inclusion criteria are: adults aged 18–85 years, diagnosed with chronic non-cancer pain (lasting at least six months), and actively taking prescription opioids (at least 10 MEDD) for at least three months at any of our seven study sites. Eligibility will not be restricted to specific pain conditions. Exclusion criteria include: clinician-determined moderate or severe opioid use disorder (OUD) as defined by a brief screening tool;[2] inability to provide informed consent; inability to meaningfully participate in group interventions (e.g., due to cognitive impairment or lack of English fluency); or known disruptive behavior that could interfere with the group learning experience and treatment outcomes for the cohort. Patients with moderate to severe OUD will be referred for addictionology consult or triaged per local systems.

Patients with active substance use disorder (SUD) may enroll and local systems will refer them for SUD evaluation and treatment as clinically indicated. No special vulnerable populations will be recruited (e.g., children or patients pregnant at the time of enrollment). All research procedures will take place at the seven clinical sites, with data collection and some treatment elements occurring online.

Consent Procedures. Electronic consent will be administered through CHOIR[1] following completion of the screening visit. Participants will provide consent by entering their full name and date on the consent form webpage in CHOIR after reviewing the form with study staff. A copy of the consent form will be securely emailed to the participant. Two study sites (Phoenix Veterans Affairs Health Care System and Kaiser Permanente Oakland) will administer consent locally.

Participant Compensation. Participants will receive a $25 Amazon gift card code for completing assessments at baseline, month 6, and month 12, and $5 for completing weekly surveys from weeks 1–24 and monthly surveys from months 7–11 (29 total surveys).Total possible compensation for study participation is $220. For participants who do not complete their 12-month survey and do not respond to any of the contact attempts made by the study team including the EMPOWER clinician we will offer an additional $50 incentive for completing the last survey.

Learning Health System and Informatics Platform. CHOIR (https://choir.stanford.edu/) is an electronic informatics platform that serves multiple study functions.[1] It is a secure (password-protected), HIPAA-compliant platform hosted by the Stanford University School of Medicine. CHOIR will collect patient-reported data at each time point using surveys tailored to the study and will be standardized across all study sites. Additional CHOIR functions include obtaining online consent, automated post-enrollment randomization, deployment of tailored surveys based on treatment arm assignment, a patient-reported outcomes data system that minimizes response burden using computer adaptive testing for NIH PROMIS measures, a centralized study database, an automated electronic payment system for survey completion, real-time display of patient progress for study clinicians, generation of personalized opioid tapering plans, monitoring for patient adverse events, and deployment of alerts to various stakeholders to address patient risks, minimize missing data, and manage participant payments. Clinicians will be able to view individual patient progress and longitudinal data in real time. Paper surveys will be mailed to participants who lack access to email, computers, or smartphones, and study staff will input the data into the electronic database.

Weekly CHOIR surveys: All patients will receive weekly CHOIR e-surveys via email to assess taper discomfort symptoms or other issues, with the explicit purpose of informing clinical care, symptom triage, and any necessary adjustments to their taper plan. Taper-related symptoms of moderate severity will trigger an automated e-alert to the prescriber, study site director, site coordinator, and study manager. Patients will also receive automated e-response messages with recommended actions, such as calling the clinic for telephone triage or scheduling an in-clinic visit. At each follow-up visit, taper discomfort symptoms will be reviewed and confirmed by the prescribing clinician as either related or unrelated to the taper. Moderate and severe symptoms will be reported to the local IRB, the Data Safety and Monitoring Board (DSMB), and the study sponsor.

Monthly CHOIR surveys: Patients will be assessed monthly for satisfaction with the study, current opioid use, hospital or emergency medical visits, depressive symptoms, suicidality, and other factors that may indicate symptom worsening and require follow-up. Suicidality will trigger e-alerts to the prescribing clinician, site director, site coordinator, study manager, and the overall principal investigator. Site-specific messages will provide patients with instructions for non-emergency triage (e.g., calling the clinic for telephone or in-person follow-up) and emergency triage options in their community (e.g., calling 911), rapid contact with clinic staff, and crisis hotlines.

Weekly and monthly surveys will ensure careful monitoring of patients, triage of issues, and close connections with study staff and prescribing providers to enable rapid taper adjustments and address any additional needs. Study clinicians may securely access EMPOWER CHOIR via a web browser to review patient responses and coordinate participant activities. Comprehensive patient-reported survey batteries will be administered at baseline and at six and 12 months, including data on opioid use.

Randomization. Each site will conduct a site-specific randomized controlled trial using a randomized design, allowing rapid accrual of patient cohorts (N=8–18 per cohort) assigned to the same intervention arm and timely delivery of behavioral interventions. Patients entering the study will be automatically assigned to the currently open intervention arm. The ordering of intervention arms will remain blinded to patients and clinicians, who cannot choose or direct group assignment. Study coordinators, while unblinded, will be trained to maintain clinician and patient blinding. After enrollment and baseline measures, group assignments will be revealed to participants. A statistician unaffiliated with patient care will create unique randomization schemes for each site, enabling prompt receipt of behavioral interventions for those assigned to such arms (ideally within two to ten weeks of taper initiation). Behavioral intervention timing will be recorded.

Study Outcomes

Primary Outcome (Aim 1) – Taper Success at 12 months

Taper success will be defined as a ≥50% reduction in MEDD from baseline to 12 months without significant pain intensity increase (≤1-point increase) or no opioid increase with significant pain relief (≥2-point decrease in pain intensity). Please see Appendix A, Data Measurement Plan, for more details.

Secondary Outcomes (Aim 2) – Pain Characteristics for the Three Intervention Arms at 12 months

Taper success (MEDD and pain intensity), pain interference, pain self-efficacy, and depression and satisfaction with social roles and activities will be assessed (for more details, see Appendix A). Specifically, depression and satisfaction with social roles and activities will be assessed using National Institutes of Health PROMIS short-form measures which are commonly used in pain research. These domains were identified by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials as core outcomes.[3,4] Web-based PROMIS assessment center software will calculate short-form T scores using Item Response Theory scoring algorithms that apply the Bayesian expected a posteriori method.

EMPOWER Patient-Centered Opioid Taper (received by all three study arms). Following study enrollment, all participants will engage with their EMPOWER clinician in a patient-centered prescription opioid tapering program. All opioid prescribing will be managed by the EMPOWER clinician. Opioid dose data will be sourced from study surveys and the patient's electronic medical record. All aspects of tapering will be individualized, including the timing of taper initiation, the dose reduction goal (set collaboratively with the patient), and the pace of the taper. The basic patient-centered opioid taper protocol will mirror the pilot methods described in Darnall et al.[5] Importantly, complete opioid cessation will only be a goal if the patient chooses it. The recommended taper speed will be a 5% reduction of the starting dose, with one dose decrease per month until the patient is stable, without physical discomfort or psychological distress. Patients will be assessed at each visit; dose decreases or increases in taper speed will only occur after consultation with and consent from the patient. Patients will have the choice to set the pace of their taper, pause their taper, or withdraw from the taper or the study at any time. The taper will not be unidirectional: EMPOWER will not restrict needed opioid increases for acute pain or for patients with poor responses to the taper. Participation in the study will not prevent patients from receiving any needed medical care. Patients will not be removed from the study if they increase their opioid dose; on the contrary, we will seek to follow these patients to understand their experiences, responses, and unmet treatment needs.

Clinicians may use the electronic CHOIR opioid taper tool to create a taper schedule that remains flexible based on patient responses to prior dose reductions. Micro-dose reductions will be recommended for the first few decrements, followed by dose reductions as tolerated, not exceeding a 10% opioid dose reduction per month. Recommendations will include tapering one opioid at a time and avoiding

concurrent tapering of other medications. Participants will receive in-person or online medical follow-ups with their EMPOWER clinician approximately every three to four weeks. Participants will complete weekly and monthly CHOIR symptom surveys, which will be reviewed during medical follow-ups to determine whether reported withdrawal symptoms are related to the taper or are unrelated (e.g., seasonal allergies). If CHOIR detects severe or worsening symptoms indicative of participant struggle or deterioration, immediate (real-time) electronic alerts will be sent to the participant, clinic, and prescribing clinician, with follow-up actions based on symptom severity.

The study protocol will encourage the use of adjuvants within the scope of normal clinical practice and training and will not restrict other analgesic prescribing, such as initiating SNRI medications. The protocol will provide guidance on reducing short- and long-acting opioids and recommend tapering one medication at a time. Concurrent tapering of other medications will be discouraged.

The EMPOWER taper program may only be administered by a prescriber clinician trained in EMPOWER methods.

CHOIR Opioid Taper Tool. EMPOWER will include an electronic taper calculator allowing clinicians to input the patient's current dose, number of daily doses, desired taper timeframe, taper goal, and taper pace. The tool will generate precise guidance for doses/pills per dose daily over several months. Because the taper will be flexible, the opioid taper tool can be used multiple times to recalculate a patient's taper plan based on new circumstances, such as a desired taper pause or a patient's request to adjust the taper speed.

Study Arms

(1) EMPOWER Taper + Cognitive Behavioral Therapy for Chronic Pain (pain-CBT).[6] Pain-CBT is a behavioral treatment that reduces chronic pain and its impacts through patient education, skills acquisition, and social support. Research on pain-CBT indicates benefits for reducing pain intensity, pain catastrophizing, depression, and the social impact of pain.[7] CBT is considered the gold-standard psychobehavioral treatment for pain, with other behavioral treatments demonstrating non-inferiority but not superiority.[8-9] A general pain-CBT therapist manual and corresponding patient workbook were developed for the EMPOWER study (EMPOWER CBT). A relaxation MP3 audio file accompanies the patient workbook. Consistent with general pain-CBT, the EMPOWER CBT protocol includes interactive discussion, pain education, relaxation training practice, goal setting, cognitive restructuring, problem-solving, and action planning, with home exercises incorporated into each session. Participants will learn to effectively manage their pain and symptoms while working towards achieving the goals that matter to them. A mental health will deliver the eight-week group intervention to cohorts of patients (N=8–18) assigned to this arm. Intervention sessions will be delivered weekly and last two hours. To ensure consistency across all study sites and cohorts, therapists will be trained in the common eight-session CBT protocol, with competency assured by Director Dr. Heather King. The structured format of the CBT intervention ensures treatment fidelity, with the trained therapists using PowerPoint slides (for didactic content), corresponding worksheets from the participant workbook, and optional reading from an additional book. The study coordinator will be present at each treatment session and facilitate intervention fidelity by ensuring participants have corresponding materials, including the relaxation audio. Participants assigned to this intervention arm will not receive CPSMP during the study period. No other aspects of pain care will be constrained.

(2) EMPOWER Taper + The Chronic Pain Self-Management Program (CPSMP).[10-11] CPSMP is an evidence-based behavioral treatment delivered by two certified healthcare clinicians or peer co-leaders with lived experience in successful pain self-management. Certification as a CPSMP leader requires 24 hours of training over four days. The CPSMP manualized protocol includes patient education about pain and strategies for effective self-management of pain, its impacts, and other symptoms. Based on self-efficacy theory, CPSMP is delivered in six weekly 2.5-hour group sessions to cohorts of 8–18 participants. All participants receive a book on pain self-management and an exercise CD. Like pain-CBT, CPSMP incorporates interactive discussions, relaxation training, action planning, and home exercises into each session. Patients learn to live better with chronic pain by making daily choices that support improved health and function. Participants assigned to this arm will not receive group pain-CBT during the study period. No other aspects of pain care will be constrained, including individual psychological treatment; receipt of non-study treatments will be tracked.

Prior research has shown that pain-CBT and CPSMP have both shared and distinct effects, suggesting some individuals may respond better to one treatment than the other. However, no evidence currently exists to guide a best-practice choice between the two. While pain-CBT and CPSMP are both effective for chronic pain, they have not been tested within an active opioid reduction protocol. We hypothesize that these behavioral interventions will help patients reduce opioids and associated risks, manage pain, and restore function in ways superior to opioid reduction alone.

(3) EMPOWER Taper Only (usual care). Participants assigned to this intervention arm will participate in the voluntary EMPOWER patient-centered opioid tapering program and will not receive group pain-CBT or CPSMP during the 12-month study period. No other aspects of pain care will be constrained.

Virtual Format for Behavioral Treatment Groups

Background: In March 2020, the COVID-19 pandemic led to social distancing safety requirements, which prevented the continuation of in-person delivery of our behavioral treatment groups. In response, with PCORI approval, we demonstrated the feasibility of virtual groups by piloting a virtual option with participants who were already enrolled in the study (i.e. enrolled prior to 03/26/2020). We now offer virtual (live, online) delivery of our behavioral treatment groups as another option for all participants including new enrollments. Due to ongoing and unpredictable COVID-19 restrictions on group gatherings, live virtual treatment delivery is essential to ensure successful completion of our RCT.

Content: Virtual pain-CBT and CPSMP treatments are delivered exactly as outlined in the protocol where the same content and materials (e.g., participant workbooks, presentation slides, etc.) by live facilitators with live participants. The only difference between virtual and in-person is the video format in the virtual groups and materials are distributed via traditional mail instead.

Platform – Each site delivers the virtual treatments using a HIPAA compliant and secured platform endorsed by their respective institution (Zoom at Stanford and Colorado, VA Video Connect at the Phoenix VA, and WebEx at Intermountain Health). The platforms are broadly utilized for telehealth at the sites.

Facilitator Training – To assure high-quality and standardized delivery, the facilitators who conduct the in-person groups at each site, are also the same facilitators delivering the virtual treatments. Additionally, we centralized our virtual system across Stanford Pain, Stanford Primary Care and Colorado where we have Stanford psychologists (or Telligen peer leaders) leading a cohort comprised of both Stanford and Colorado participants. As closed payer systems, Phoenix VA and Intermountain Health do not permit external services. The facilitators practiced delivering the programs on the virtual platform up to three times before the start of the first series.

Participant Training – The facilitators, study coordinators, and the core manager collaborated in developing materials to prepare participants to successfully engage in the virtual groups. Before the first session, the local study coordinator conducts an orientation with each participant to review how to use the platform and etiquette expectations (e.g., be situated in a private, quiet place during each session). Please see accompanying documents (Study Coordinator Procedures/Script, Group Telehealth Agreement, Facilitator Work Flow and Guidelines, Welcome to the Group, Welcome Letter, and Zoom Application Instructions).

Patient-Centered Opioid Tapering (taper-only, no behavioral treatment)
Virtual Format - Each recruitment site enhanced their clinic schedules to make virtual medical visits more accessible to patients at the onset of the COVID-19 pandemic in March 2020. Participants continue to have the option to schedule an in-person or virtual appointment for their follow-up visits with their EMPOWER clinician. All sites had an established telehealth system, which allowed a smooth transition into conducting more virtual visits. Video and messaging features are included in the telehealth system. For participants who do not have access to a smartphone or computer, the Phoenix VA loans tablets to patients to address this issue.

Institutional Review Board (IRB). The study will adhere to the common protocol and procedures approved by local IRBs at all study sites.

Sample Size Calculations and Study Power

The power calculation is primarily based on the study aims for comparative effectiveness. The original power calculation was for N = 850, with N = 750 patients completing the month-12 survey. The study sample size was later reduced to N = 489 participants completing the month-12 survey (n = 163 patients per intervention arm on average). As a result, the study's power is lower than initially planned but remains adequate for the objectives, summarized as follows:
Hypothesis 1a. N = 163 Taper Only participants provide 80% power to confirm that the taper success rate is above 40% at a two-sided significance level of 0.05, when the true success rate is 51.5%.
Hypothesis 1b. Comparing the taper success rate between n = 140 Taper Only participants with an initial dose < 200 MEDD and n = 23 Taper Only participants with an initial dose $\geqslant$ 200 MEDD, the expected 95% confidence interval (CI) for the difference in success rates is [-22%, 22%], assuming a true taper success rate of 50% independent of the initial dose. The width of the CI increases by only 24% due to the sample size reduction.
Hypothesis 2a. N = 163 participants per intervention arm provide 80% power for detecting a taper success rate difference of 40% versus 53.5% at a two-sided significance level of 0.05.
Hypothesis 2b. N = 163 participants per intervention arm yield an expected 95% CI of [-11%, 11%] for estimating the difference in taper success rates between the Taper + pain-CBT and Taper + CPSMP arms, assuming a taper success rate of 50% in both arms.
Hypothesis 2c and 2d. N = 163 participants per intervention arm provide 80% power to detect a between-group difference of 0.311 standard deviation in the 12-month change of continuous outcomes using a two-sample t-test at a two-sided significance level of 0.05.

We also assume an annual drop off rate is less than 19% and we will include all drop outs in our ITT analyses. We will enroll a total of 594 patients to assure the minimum group size requirements for analysis of comparative effectiveness.

Statistical Analysis Plan

Aim 1: Reduce or contain prescription opioid use while maintaining pain control.
Hypothesis 1a: We will estimate the proportion of patients achieving patient-centered opioid taper success and test whether this proportion exceeds 40% (treatment success estimate derived from Darnall et al.[5]). We will estimate the binomial proportion of patients with opioid taper success and use the exact test to test whether the proportion is greater than 40%.
Hypothesis 1b: We will compare opioid tapering success rates among patients in different initial opioid dose categories: Low (10–49 MEDD), Moderate (50–89 MEDD), High (90–199 MEDD) and Super-High (≥200 MEDD).

Aim 2: Examine the balance in key patient characteristics such as initial opioid dose, pain intensity, and functional measures separately for the three interventions arms. We will use Chi-square or Fisher's exact tests to compare success rates between opioid dose groups.
Hypothesis 2a: We will compare the intervention success rate of 500 patients in behavioral intervention arms (pain-CBT and CPSMP) with 250 patients receiving patient-centered opioid tapering only (no behavioral intervention; Taper Only). We will use a Chi-square test to compare the success rate between groups. We will apply logistic regression to adjust for baseline covariates.
Hypothesis 2b: We will estimate the difference in intervention success rates between pain-CBT and CPSMP arms using an intention-to-treat procedure and construct 95% CIs for the difference.
Hypothesis 2c: We will compare changes in pain intensity, pain interference, and depression scores (baseline to 12 months) between the pain-CBT and Taper Only as well as between the pain-CBT and CPSMP arms using two-sample t-tests. We will apply an analysis of covariance based on multiple regression to adjust for baseline covariates.
Hypothesis 2d. We will compare improvements in satisfaction with social roles and activities, and self-efficacy for Taper + CPSMP against Taper + pain-CBT and Taper Only.

We will compare the intervention success rate between participants who received the behavioral interventions with participants who received Taper Only using Fisher's exact test. The difference in success rates between Taper + pain-CBT and Taper + CPSMP will be assessed with 95% confidence intervals (CI) to determine equivalence. Secondary outcomes—including pain intensity, pain interference, depression, self-efficacy, and satisfaction with roles and activities—will be compared between Taper + pain-CBT and Taper Only and between Taper + pain-CBT and Taper + CPSMP at months 6 and 12 using mixed effects model for repeated measurements regression. This analysis will incorporate baseline, month 6, and month 12 outcomes as dependent variables, with an unstructured variance–covariance matrix for within-subject correlations.

Exploratory Hypothesis 2e: We will separately estimate the probability of opioid escalation by intervention arm (pain-CBT, CPSMP and Taper Only).

For exploratory hypotheses, the probabilities of opioid escalation by intervention group will be estimated and compared with Fisher's exact test. Post-hoc analyses will use logistic regression to examine associations between baseline characteristics and tapering success. There is no correction for multiple comparisons. Heterogeneity of treatment effects will be explored by splitting the population into training and validation sets of equal sizes. Logistic regression with lasso regularization will identify baseline features predicting tapering success in each intervention group. These models will be applied to testing sets to identify the subgroup with the highest predicted success under Taper + pain-CBT, and success rates will be compared across intervention arms within the subgroup. Intervention effects will be also estimated in predefined subgroups.

Heterogeneity of treatment effects will be explored for each intervention arm considering gender, age, race, initial opioid dose, baseline depression, and anxiety level.

Access and Intervention Participation. The comparison across interventions will be performed according to the intention-to-treat principle. Additional comparisons based on the actual intervention received will be conducted as a sensitivity analysis. We will also study the effect of intervention participation and on treatment outcomes. To this end, we will perform regression analyses to examine the association between the success rate for opioid weaning and other outcomes with session attendance for the pain-CBT and CPSMP arms, separately, while adjusting for identified confounding factors affecting compliance. We will also investigate how baseline factors, such as socioeconomic status, affect the level of compliance.

Virtual Behavioral Treatment Groups: Comparison of participants who receive in person vs. virtual treatment - We will examine mode of delivery as a potential covariate in our analytic models, and study statistician Lu Tian will both advise and implement. Outside of this issue of treatment delivery mode, we must also recognize that COVID itself has introduced a new variable in the study. We will be examining COVID impacts, as well. In regards to the group size and effectiveness of the intervention, the size of the virtual groups are comparable to the size of the in person groups where most groups have an average size of 4 participants. Facilitators stated larger groups (more than 4 participants per cohort) usually provide a more dynamic experience with diverse interactions. While in smaller groups, participants have a chance to go into more detail regarding the skills they are learning and using and any barriers that arise.

Sensitivity Analysis. We will perform sensitivity analyses to account for missing data and non-completion of behavioral interventions. In addition, we will consider an alternative definition of taper success, replacing the 50% reduction in opioid dose with a 30% reduction in opioid dose. A 30% change has been cited as a benchmark for a moderately clinically important difference in the chronic pain literature. Similar analyses will be conducted with this new endpoint as part of the sensitivity analyses.

Statistical analysis will be completed using SAS Enterprise Guide Version 8.3 and R Version 4.1.1.

Project Management

As the principal investigator, Dr. Darnall oversees the project along with the site co-investigators (Drs. De Bruyne, Edelson, Flood, Kim, Mackey, Mardian, Moore, Nicholson, and Porter). Luzmercy Perez serves as the project manager. Additional study staff include Corinne Jung,

who facilitates IRB regulation, and study coordinators. Juliette Hong assists with statistical analyses and organization under the supervision of Prof Lu Tian. The study site IRBs provide local regulatory compliance oversight. An independent Data Safety and Monitoring Board will meet twice yearly to review the project status and adherence to the Data Safety and Monitoring Plan.

Ethics
As detailed in the Safety Considerations section, ethical considerations include the potential (though unlikely) discomfort when completing surveys. This is addressed by making all survey items optional. For increased withdrawal symptoms, a plan to triage participant needs has been outlined.

Informed Consent Forms
The approved Informed consent form is included below (see Appendix B).

Appendix A. Data Measurement Plan

Name of Measure	Brief Measure Description	Baseline	Weekly (first 6 months)	Monthly*	Months 6, 12
Pain Catastrophizing Scale (PCS)[12-13]	13-item scale assesses severity of trait pain catastrophizing tendencies on a 5-point scale (0 = "not at all"; 4 = "all the time").	x			x
Pain Self-Efficacy Questionnaire (PSEQ)[14]	2-items measure self-confidence to manage pain and engage in life activities despite pain.	x	x	x	x
NIH PROMIS Measures	Pain intensity (one-item rates average pain intensity during the previous 7 days on a scale of 0 (no pain) to 10 (worst pain imaginable);[15-16] depression; and satisfaction with social roles and activities (The National Institutes of Health Patient-Reported Outcomes Measurement Information System short form versions will be used to assess depression and satisfaction social roles and activities. Questions will be framed according to the experience of symptoms or functioning over the past 7 days, and higher scores signify greater severity of these symptoms. Scores will converted from raw scores to t-scores (M = 50 and SD = 10), consistent with their initial publications).[17-18]	x	x	x	x
Taper collaboration	Patients rate how much their input was considered by their doctor and overall collaboration in their opioid taper.	x	x	x	x
Alcohol & Substance Use	AUDIT alcohol abuse screen,[19] DAST illicit drug abuse screen, tobacco use.[20]	x			x
New Medical Problems or Surgery	New medical issues are assessed, such as dental surgery that might cause a new opioid prescription.	x		x	x
Subjective Opioid Withdrawal Symptom Scale (SOWS)[21] and correlates	Weekly for the first 6 months questions will assess mood, anxiety, sleep, physical function, pain interference, medication use, discomfort with opioid reduction, and any emergent medical problems.		x	x	x
Beck Depression Inventory[22] (single suicide risk item)	This question is deployed at baseline and also prompted in the weekly survey (SOWS) when the PROMS depression question is answered with "often" or "always".	x		x	x
Group Intervention Attendance	Pain-CBT and CPSMP participants will report whether they attended their treatment class in the past week (attendance also recorded by staff).		x**	x**	
Satisfaction with Group Intervention	Pain-CBT and CPSMP participants will rate their level of satisfaction with their assigned intervention, and separately, with their group instructor on a 7-point rating scale (0 = "not at all satisfied" to 6 = "extremely satisfied").		x***	x***	
Life Changes survey	Items assess changes to employment, disability status, and/or major life events (new child, loss of a loved one, divorce, major illness, etc.).				x
Study Satisfaction	Patients will rate their level of satisfaction with the study (0 = "not at all satisfied" to 6 = "extremely satisfied"). They may input free text responses and we will monitor these closely.				x
Study Effects	Assesses patient-reported effects (positive and negative) as a result of participating in the study.				x
Patient's Global Impression of Change (PGIC)[15]	Single item assessing patient's impression of general improvement as a result of participating in the study.				x
COVID-19	Assesses impact of COVID-19 on participants.	x		x	x
Pain Interference	A nine-item Brief Pain Inventory questionnaire measures the level of pain-related interference during the past twenty-four hours across seven domains (such as mood, general activity, etc.) on a scale of 0 (does not interfere) to 10 (completely interferes). Higher scores signify worse pain interference. A total pain interference score will be created by averaging the seven domain scores for each participant.[23-24]	x		x	x
Opioid Dose	Participants will self-report their daily prescribed opioid type(s) and dose(s). Daily opioid doses will be converted to a total standardized morphine equivalent daily dose (MEDD) using the 2016 CDC Guidelines for conversion factors including using the escalation of the factor for methadone (i.e. methadone's conversion factor increases at higher doses).[25]				

* Monthly questionnaires will be distributed at months 1–5 and 7–11. They will not be distributed at months 6 and 12.
** Group Treatment Attendance Form will only be completed while participant is currently in pain-CBT or CPSMP interventions.
*** Satisfaction with Group Intervention Form will be distributed following the first and final session of the intervention course only.

Appendix B. Stanford Informed Consent Form

STANFORD UNIVERSITY Research Consent Form Protocol Director: Dr. Beth Darnall	*IRB Use Only* Approval Date: March 22, 2022 Expiration Date: March 22, 2023
Protocol Title: Opioid Taper Study	

This is a study for people who want to use less or no opioids. A health care professional will help everyone slowly taper their opioids. You will have a say in the speed of the taper. The EMPOWER study is funded by the Patient-Centered Outcomes Research Institute (PCORI, https://www.pcori.org/)

In addition to tapering, everyone will be randomized to either:

- Cognitive Behavioral Therapy for Chronic Pain
- Chronic Pain Self-Management Program
- No education for the first year (after that you can choose to attend either program)

Both of the study treatment classes have been shown to help people with chronic pain live better lives, and have more control over their pain and symptoms.

PURPOSE OF RESEARCH

You are invited to participate in a research study of the effectiveness of the Chronic Pain Self-Management Program (CPSMP), Cognitive Behavioral Therapy for chronic pain (pain-CBT), and no behavioral treatment within the context of patient-centered collaborative opioid tapering (PCOT). We hope to learn effectiveness of these therapies to reduce patient prescription opioid use while maintaining pain control. You were selected as a possible participant in this study because you have experienced chronic pain and are interested in reducing your prescription opioid use.

If you decide to terminate your participation in this study, you should notify the research team at (650) 724-9319.

This research study is looking for 865 participants experiencing chronic pain that are interested in voluntarily reducing their prescription opioid use. Enrollment for this study will take place across the Western United States. Stanford University expects to enroll 392 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 5 years to complete. Participation will last a total of 12 months. Participants will be asked to complete a set of questionnaires lasting

approximately 30-60 minutes at baseline, 6, and 12 months. For the first 6 months each participant will also be asked to complete weekly questionnaires lasting approximately 10 minutes. For the final 6 months of participation, we will send out monthly questionnaires similar in nature and content to the weekly questionnaire.

PROCEDURES

If you choose to participate, Dr. Beth Darnall and her research study staff will ask you to participate in the following steps.

Step 1: Eligibility Visit

The first step is to confirm your eligibility with the research team. This is to make sure you are a good fit for the study. Once your eligibility is confirmed and you have signed this consent, you will be asked to fill out a battery of questionnaires assessing medication use, pain and symptoms, coping mechanisms, mood, sleep, general health and well-being, and psychological traits. This set of questionnaires take approximately 30-60 mins to complete.

At this visit, we will also mark the launch of the brief weekly questionnaires (e.g., 12 items). The weekly questionnaires will be administered weekly for the first 6 months of study participation and will include assessments of patient symptoms, satisfaction, and side effects of the opioid taper program. For the final 6 months of participation we will send out monthly questionnaires similar in nature and content to the weekly questionnaire. All questionnaires will be administered online to reduce participant burden.

Step 2: Opioid Taper

All participants engaging in a patient-centered opioid taper will collaborate with their physician to determine the strategy of the tapering program. Duration of the opioid taper is up to 12 months to assure patient comfort, though some patients may end their taper sooner. The goal of the taper is to achieve the lowest comfortable dose for each patient with patients informing the pace of opioid reduction.

Step 3: Intervention

Roughly 2-6 weeks following step 1, you may be randomly assigned to one of the following groups. Your chance of receiving each intervention is random and determined by a number of factors.

1. Pain-Cognitive Behavioral Therapy (pain-CBT+PCOT)

   A trained psychologist delivers pain-CBT to groups of patients. Group treatment is delivered across 8 weekly sessions that last for 2 hours each. Pain- CBT incorporates interactive discussion, practice of relaxation training, action planning, and home exercises into each session. Pain-CBT is effective for reducing pain intensity, pain catastrophizing, depression and social impacts.

2. Chronic Pain Self-Management Program (CPSMP+PCOT)

   The CPSMP is delivered by 2 trained peers who are certified CPSMP leaders. The CPSMP consists of six weekly 2-hour group sessions in which two peer co-leaders provide patient education about pain, effective self-management, pain impacts, and other symptoms from a highly structured manual. CPSMP incorporates interactive discussion, practice of relaxation training, action planning, and home exercises into each session.

3. Patient-Centered Opioid Taper (PCOT)

   Participants allocated to this arm will engage in a physician-guided, patient-centered opioid tapering program without additional behavioral intervention.

Step 4: Follow-up questionnaires

6 and 12 months following enrollment you will be asked to fill out a battery of questionnaires similar to those completed in step 1. They will assess medication use, pain and symptoms, coping mechanisms, mood, sleep, general health and well-being, and psychological traits. This set of questionnaires take approximately 30-60 mins to complete.

Longitudinal Arm:

If you are not interested in participating in the interventions or reducing your current prescription opioid medications but are otherwise eligible and interested we may ask you to participate in a 12-month observational arm of the study. You will be asked to complete a battery of questionnaires at baseline, 6 months, and 12 months following enrollment.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to begin the study after the onset of your next menstrual period. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.

- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify the research team at (650) 724-9319.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director, Dr. Beth Darnall, if you have any questions.

- Patients who enter the study and engage in patient-centered opioid tapering may experience physically uncomfortable and/or distressing opioid withdrawal symptoms (e.g., drug craving, anxiety, insomnia, increased pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection). Our study is designed to mitigate these negative symptoms by tapering at a very slow rate and at the patient's pace.
- Patients may experience anxiety, mood changes, or greater pain with opioid changes, though patients may experience these symptoms as a consequence of opioid use, as well.

- A financial burden may be imposed in the form of copayments if randomization procedures allocate the patient to pain-CBT.
- There is a low risk that patients may experience discomfort in the group treatment related to content or group discussions, or interpersonal interactions.
- There is a risk you may feel uncomfortable answering some of the questions on the questionnaires. You have the right to refuse to answer particular questions.

Additional Risks

- You may be inconvenienced due to being assigned to a treatment that is not your first choice, or to the PCOT taper only.
- Traveling may be a possible inconvenience. There are multiple sessions involved in each intervention.
- Part of our screening process involves asking about illegal drug use. The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.
- It is possible that based on information gained from this study, the researchers may have serious concerns (relating to matters such as severe depression, physical abuse, etc.) about your health and/or safety; in such a case, the researchers may contact you and provide a referral for your care. Additionally, the researchers may be required to report information (e.g., information relating to suicide, physical or sexual abuse) to the appropriate authorities.

POTENTIAL BENEFITS

Long-term opioid use is associated with increased pain, depression, and disability. Participants enrolled in the study may decrease their opioid medication use and in turn reduce their risk of increased pain, depression, and disability. Patients may also reduce their pain as a result of the interventions.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

Alternatives to tapering include switching medication class or maintaining current dose. The study does not constrain prescribing of any other medications while engaging in the opioid taper. As such, participants are free to explore any alternative procedures or standard courses of treatments while participating in the study.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your authorization. If you verbally indicate your consent, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before completing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to investigate the comparative effectiveness of group Pain-CBT and CPSMP in individuals who volunteer to participate in a patient-centered opioid taper program.

The longitudinal observational arm of this study will be characterizing individuals who are ineligible for the opioid tapering program, either because the patient is disinterested in reducing their dose, or due to other factors, such as inability to attend treatment classes.

Do I have to complete this authorization form?

You do not have to provide oral authorization at the end of this oral consent process, but if you do not, you will not be able to participate in this research study, including receiving any research-related treatments.

Completing the form is not a condition for receiving any medical care outside the study.

If I provide authorization, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for

the research use or disclosure of your health information in this study, you must write to: Dr. Beth Darnall at 1070 Arastradero Rd. Suite 200, Palo Alto Ca. 94304

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your name, contact information, demographics, date of birth, medical history, medications and treatment use, and responses to questionnaires. We may also access your medical record to obtain additional information about your pain condition, current and past treatments, other conditions that may affect your pain, and symptoms.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Beth Darnall
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The funding agency - Patient-Centered Outcomes Research Institute
- Collaborating institutions

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

FINANCIAL CONSIDERATIONS

Payment

Payment will be administered in the form of Amazon gift cards.

Participants will be compensated a maximum of $220 for completion of patient- reported outcome (PRO) surveys.

- Baseline, 6-month, and 12-month follow-up surveys will be worth $25 each, totaling $75.
- Weekly questionnaires will be worth $5, and will be administered weekly over the course of the first 6 months of study participation and then monthly for the final 5 months of study participation (29 total surveys), totaling up to $145.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor

Patient-Centered Outcomes Research Institute is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment - whether routine or experimental - involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by completing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Beth Darnall at (650) 721-2104. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact the study team at (650) 724-9319.

Alternate Contact: If you cannot reach the Protocol Director, please contact the Core Manager, Luzmercy Perez, at (650) 497-1095.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

If you agree to participate in this research, please verbally indicate this to the researcher.

The extra copy of this consent form is for you to keep.

Yes, subject agrees to participate.
No, subject does not agree to participate.

Enter Name of Subject

Enter Name of Person Obtaining Authorization

Enter today's date

Are you participating in any other research studies?

Yes
No

May we contact you about future studies that may be of interest to you?

Yes
No

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