1) Protocol Title

N-of-1 Trials Using mHealth in Chronic Pain *aka* PREEMPT (Personalized Research for Monitoring Pain Treatment)

- Phase I, Activity 3 – Pilot Trial
- Phase II – Randomized Clinical Trial

2) PREEMPT (Personalized Research for Monitoring Pain Treatment)

Author of Protocol

X UC Davis Researcher
☐ Researcher from other institution
☐ Private Sponsor
☐ Cooperative Group
☐ Other: _____

3) IRB Review History

N/A

4) Objectives

NOTE: The Grant outlines the study to be conducted in the following manner:

- Phase I Activity 1 – Focus Group (IRB Exemption #386259-2)
- Phase I Activity 2 – Mock N-of-1Trial (IRB ID: 446562-1, approved 6/11/2013)
- Phase I Activity 3 – Pilot Trial **(Submitted herein for IRB review)**
- Phase II – Randomized Clinical Trial **(Submitted herein for IRB review)**

The procedures for the pilot trial and the randomized clinical trial (RCT) are identical with the following exceptions: the pilot trial does not have a follow-up period; and a smaller incentive will be distributed to pilot participants since the trial length is shorter compared to RCT participants. Throughout the protocol, differences between the pilot trial and RCT are explained. The terms participants and patients are used interchangeably.

Importance of knowledge to be gained:

Our mobile web application (the **Trialist**) will allow patients and clinicians to jointly set up a personalized n-of-1 trial; will use state-of-the-art user interaction design to help patients collect, view, and understand their data; and will return n-of-1 trial results to the clinician and patient for joint decision making.

The **Trialist** App will support primary care and specialty clinicians at the point of service by highlighting alternative pain treatment options, including alternative opioids. Phase I, activity 3

of the study is concerned with the testing the **Trialist** App with a small number of patients. In Phase II of the study, a RCT will be conducted to examine the research questions stated below.

This IRB application is concerned with activity 3 of Phase I and Phase II.

The aim of the pilot trial is to assess the effects of participating in a mobile n-of-1 trial on participatory decision making between clinicians and patients, patient's treatment satisfaction, and adherence. Achieving this aim will set the stage for the RCT. The pilot will provide valuable information about the **Trialist** functionality, patient satisfaction, and patient willingness to complete the intervention (adhere to intervention treatments and daily intervention tasks). The pilot trial will not have a comparison group.

The aim of the RCT is to assess the effects of participating in a mobile n-of-1 trial (versus usual care) on clinical outcomes, participatory decision making, satisfaction, and adherence. Achieving this aim will set the stage for broader uptake of mHealth n-of-1 trials in chronic pain management as well as other chronic health conditions. Mobile n-of-1 trials applications will expand patient involvement in care and promote more personalized, patient-centered health care [1] (Appendix B).

From the population perspective, if mHealth based n-of-1 trials can help patients and clinicians achieve therapeutic success faster and with greater confidence, patients may require fewer subsequent office visits, tests, emergency room visits, and after-hours phone support, thus lessening the burden on health systems and restraining costs.

Hypotheses (RCT)

Hyp 1: Compared to usual care, patients randomized to the **Trialist** App will experience less pain interference at 6 months follow-up (primary outcome).

Hyp 2: Compared to usual care, patients randomized to the intervention arm (**Trialist** App) will experience less pain intensity, improved health-related quality of life, improved participatory decision making, greater treatment satisfaction, and more adherence to prescribed therapy at 3, 6, and 12-month follow-up (secondary outcomes).

5) Background

Chronic musculoskeletal pain (MSP) is an enormous problem; affecting more than 100 million Americans and costing upwards of $160 billion [2-6]. Current pharmaco-therapeutic strategies convey a mix of benefits and hazards. In usual practice, clinicians often begin with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), prescribing opioids when pain is severe or unresponsive [7]. When the analgesic response to the initial treatment is inadequate, clinicians can invoke step care, dose titration, opioid rotation, or augmentation with adjuvants such as anti-convulsants [7-9]. These approaches are usually employed in a trial-and-error fashion. Trial and error can work but may lead to poor therapeutic decisions in the long run. A treatment that appears effective over a short period may only seem so because of random fluctuation in the patient's underlying condition, uncontrollable external factors, or the placebo effect. N-of-1 trials are randomized controlled crossover trials conducted in a single patient. By crossing a patient back and forth between two treatments several times, clinicians can identify the more effective approach for that individual patient with greater precision than can be achieved in ordinary practice.

N-of-1 trials are especially useful when available therapies manifest substantial heterogeneity of treatment effects (HTE), implying significant variation across patients as to which treatment works best [10]. Many pain therapies display such HTE [11]. When HTE is large, average effects may mislead, calling for a more personalized approach that emphasizes individualized treatment effects [12]. N-of-1 trials are the most direct way to personalize therapeutic decisions, taking into account systematically the patient's own clinical responses to the therapies under consideration. And while the primary purpose is to inform personalized decision making, the results of n-of-1 trials can also be aggregated using Bayesian methods to inform care of populations beyond the n-of-1 trial participants themselves [13]. N-of-1 trials are an intuitively appealing and demonstrably successful way to compare the effectiveness and toxicity of one analgesic regimen with another, thus reducing patient and clinician uncertainty about "which treatment is best for me?" [14-16]. However, n-of-1 trials have not yet gained traction with clinicians, patients, and the scientific community. As described in the PI's prior work, a major barrier is the perception that such trials demand too much time and effort [1, 17, 18]. By making n-of-1 trials easier to accomplish, mobile health initiatives can address this perception and transform care (See Appendix B). Our goal is to provide patients and clinicians with tools for individualizing treatments for chronic MSP, and to evaluate this approach in terms of patient outcomes.

6) Inclusion and Exclusion Criteria

Patient criteria

Patients will be eligible to participate in the pilot or RCT if they are receiving clinical care at a participating site and have chronic musculoskeletal pain.

Inclusion criteria:

1. Chronic musculoskeletal pain (e.g., neck, back, extremities) operationalized as pain present for >=6 weeks and a pain score of >= 4 (on a 0-to-10 scale) on at least one-of-three items from the PEG pain scale [19]
2. Age 18-75 years
3. Own web-enabled Android or iOS phone with data plan
4. In judgment of treating clinician, pain potentially amenable to treatment with acetaminophen, NSAIDs, low-dose opioids, a complementary/alternative treatment such as massage or meditation, or a simple combination of these treatments
5. Ability to speak and read English

Exclusion criteria:

1. Treated with surgery, radiation or chemotherapy for cancer in past 5 years
2. Other medical conditions that in clinician's judgment would limit life expectancy to < 2 years or imperil patient safety
3. Pregnant or breastfeeding
4. Dementia, bipolar disorder, schizophrenia, active suicidality
5. Current alcohol or prescription drug abuse; history of disruptive behavior
6. Failed 5 or more analgesic medications because of lack of effectiveness or poor tolerability
7. Participated in the pilot trial (RCT only)

Because opioids will be offered as a menu option for clinicians to select, women will not be invited to participate if they are pregnant or breastfeeding (lactating). Subjects with a recent history of alcohol or prescription drug abuse will be excluded to prevent problems with inadvertent overdose from opioids. Patients with mental illness have a higher than normal incidence of opioid overdose. It is our intent to minimize their participation because this population is vulnerable in terms of morbidity and mortality from opioids.

The following populations will not be enrolled in the study

- Adults unable to consent
- Non-English speakers
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

Screening for Study Eligibility

Patients that are interested in participating in the study will initiate contact with the research team by telephone or email. Recruitment methods (below) detail the process for outreaching to potential study participants. Screening for study eligibility is a three step process.

1. At time of initial contact, patients will be screened for eligibility over the telephone or through completing an online questionnaire. At this initial contact, research staff will explain the study, ask the first set of screening questions (pp. 2-3 of Patient Eligibility Form, p. A025 of Appendix), and obtain verbal permission to contact patient's clinician. If the patient does not provide permission, the patient will be deemed ineligible for inclusion in the study.
2. In the second step of screening the patient's clinician will be contacted via secure email and/or a telephone call to verify patient is appropriate candidate for the study (page 4 of Patient Eligibility Form, p. A025 of Appendix).
3. Eligible patients will then be contacted by telephone and notified of eligibility; asked date/time of next clinic appointment to schedule an *Enrollment Interview* (see Section8-Patient Recruitment); and go over informed consent documents (see RA Screening Script, Patient Eligibility Form, pp. A017-A028 of Appendix).

7) Study-Wide Number of Subjects

Pilot trial: PI and Co-Investigators with clinical practices as well as close associates will identify 2-4 patients for enrollment. A total of 8 patients will be enrolled for the pilot study, and all will complete the **Trialist** App intervention.

RCT: Clinicians and participants will be enrolled from four primary sites, the UC Davis Family Medicine, UC Davis Internal Medicine, UC Davis Primary Care Network (UCD PCN), and the VA Northern California Health Care System (VANCHCS). Eligible clinicians will also include residents at the PG2 level or higher. We anticipate enrolling 50-60 clinicians across these sites in order to meet patient recruitment goal of 244 patients, with 122 randomized to intervention arm (**Trialist** App) and 122 to control group (Usual Care). Each enrolled clinician will have no more than 12 patients participating in the study. Enrollment in the study is defined as (1) completion of

the baseline questionnaire, (2) randomization to the intervention (**Trialist** App) or control arm, and (3) completion of one or more study-related visits. Allowing for 10% attrition, we will recruit 286 patients into the study with the expectation that 244 will complete all three enrollment procedures. For recruitment and participation through VANCHCS, separate IRB approval will be obtained.

EMR data will be obtained on enrolled patients within UC Davis Family Medicine, UC Davis Internal Medicine, the UC Davis Primary Care Network (UCD PCN), and VANCHCS. Separate IRB approval will be obtained from VANCHCS.

8) Study-Wide Recruitment Methods

Clinician recruitment

Clinicians representing UC Davis Family Medicine, UC Davis Internal Medicine, UCD PCN, and the VANCHCS will be solicited for participation in several ways including flyers, e-mail announcements, and presentations about the study in faculty and in-house staff meetings. (See pp. A003-A006 of Appendix for Recruitment materials).

Once clinicians indicate interest, informed consent will be obtained detailing their responsibilities in the trial and soliciting their consent to have their patients recruited in the Pilot and/or RCT and to guide their enrolled patients through the study. (See pp. A032-035, A041-045 of Appendix for clinician consent forms).

Patient recruitment

Patient recruitment will occur three ways. First, a clinician may ask their patients directly if they are interested in the study. Clinicians will provide interested patients with an informational sheet about the study, including research staff contact information, and patients will initiate contact with research staff if interested in participating (p. A008 of Appendix). At the point of initial contact, research staff will provide a description of the study and assess patient eligibility.

Second, informational flyers will be posted in waiting rooms of participating clinicians (p. A007 of Appendix). Interested patients can initiate contact with the research team or speak with their clinicians about the study. If a patient has a visit with a clinician (not yet enrolled in the study), the clinician may contact the researchers to complete clinician informed consent and enroll in the study. Once enrolled, the clinician can provide their patient with an informational sheet, and the patient can contact research staff. The screening process will proceed as described above.

A third recruitment strategy will be an informational letter distributed to patients of enrolled clinicians informing them about the study (p. A009 of Appendix). Included with the letter will be a business card size magnet with the study name, telephone number, email and website to provide accessibility for patients interested in contacting research staff for participation. The letter will be sent to patients seen through accessing UC Davis Family Medicine, UC Davis Internal Medicine and UCD PCN (VANCHCS enrolled participants will be handled separately through VA IRB approval). We request access to personal health information (PHI) through a waiver of HIPAA Authorization for the recruitment purposes only (See HIPAA section below). Patients meeting specific ‘International Statistical Classification of Diseases and Related Health Problems’ (ICD-9) codes will be sent a letter signed by their clinician or signed on their behalf (with clinician permission) by a study clinician (Dr. Kravitz or Dr. Wilsey). A list of patients

meeting ICD-9 criteria will be generated every four months and include a process to exclude duplicates within a 12-month period. The letter will inform patients about the study and ask them to contact the research team if they are interested in obtaining more information. (see p. A010-013 of Appendix for list of pain related ICD9 codes). With the change to ICD-10 in October 2015, mapping of the approved ICD-9 codes to ICD-10 was done. Recruitment letters will be based upon ICD-10 codes after October 2015. A list of applicable ICD-10 pain related codes is submitted for review.

Patients who indicate an interest in participation and meet study eligibility requirements will have an *Enrollment Interview* and *Treatment Planning Visit* scheduled to coincide with an upcoming primary care or pain management appointment with their clinician. During the telephone call to schedule this visit, research staff will go through the consent form with the patient. Then prior to this visit, informed consent and HIPAA Authorization will be mailed to the patient with an addressed, stamped envelope and the request to return to project office by mail. Alternatively, informed consent and HIPAA Authorization may be conducted in person at the CHPR offices, at the patient's home, or at a public location of mutual convenience and scheduled according to patient preference.

Enrollment Interview refers to the meeting between a member of the research staff and patient to administer the baseline survey. *Treatment Planning Visit* refers to the meeting with the research staff member, intervention patient, and the patient's clinician to set-up the **Trialist** App for the patient's personalized intervention trial. Patients randomized to the control arm will have an *Enrollment Interview* but no *Treatment Planning Visit*. (A patient recruitment flow chart is on page A014 of Appendix).

Patients in the pilot trial will not be randomized; instead all pilot trial participants will be assigned to the **Trialist** App (intervention arm) since the goal of the pilot is focused on the **Trialist** App functionality and patient adherence to the intervention.

Incentives

Pilot Trial: Patients will be provided up to $50 as incentives for participation in the pilot trial which includes completing baseline survey, daily mobile web surveys using the **Trialist** App during their n-of-1 trial and follow-up survey, which will be administered at the conclusion of their n-of-1 trial. The pilot follow-up survey is identical in content to the 3-month follow-up survey that will be used in the RCT. Incentives will be distributed in the following manner for the pilot: completion of baseline survey $10, completion of daily mobile web surveys $30, and completion of the follow-up survey $10.

RCT: Patients randomized into the intervention arm will receive up to $150 distributed in the following manner: $10 for completing each survey (baseline, 3-month, 6-month, and 12 month), up to $60 for completing daily mobile web surveys during their n-of-1 trial, $25 for completing a result review visit with their clinician, and $25 for completing the Post-Result Review Interview. The incentives will be provided upon completion of follow-up surveys. The amount of the incentive for completing daily mobile web surveys will be determined by the following scale: 0-59 percent completion of surveys: $20; 60-79 percent completion of surveys: $40; and 80-100 percent completion of surveys: $60.

Patients randomized to the control group (Usual Care) will be offered a payment of $50 at the completion of their 12 month survey. Control group incentives will be prorated for early

withdrawal or incomplete questionnaires. The prorated incentive schedule for control patients is: Baseline survey $10, 3 month survey $10, 6 month survey $20, 12 month survey $10.

Clinicians consenting to participate in this study will incur practice costs resulting from the extra time required to complete surveys and discuss the study with patients. In addition, for patients randomized to the Trialist (intervention) arm, clinicians will be required to participate in both trial set-up (beginning of n-of-1 trial) and results review (end of trial). Clinicians will be provided a $100 gift card for each patient they enroll in the study. Gift cards will be provided to clinicians at the end of the study after their participating patients have completed their n-of-1 trial. Clinicians agreeing to audio-record the Result Review Visit and completing the Post-Result Review interview will be provided a $25.00 gift card incentive for their time.

HIPAA

Access to personal health information is required for two purposes in the study. In the first instance, we request access to personal health information (PHI) through a waiver of HIPAA Authorization for recruitment purposes only. HIPAA Authorization is not practicable as a meaningful recruitment strategy for the study that would generate a high rate of participation and could not practicably be conducted without a waiver of the authorization. Without the ability to identify and contact eligible patients, we could not effectively recruit subjects for the study. CTSC cohort discovery and EMR data retrieval service would be utilized to obtain patient name and address for those patients meeting age and ICD-9 criteria for sub-acute and chronic musculoskeletal pain (ICD-10 code for pain used after October 2015 and applicable list of ICD-10 codes submitted) (See p. A010 of Appendix for list of ICD-9 criteria). A variety of methods will be in place to protect the PHI from improper use or disclosure. The following PHI would be requested: patient name, mailing address, date of birth, physician whom patient sees for chronic pain condition, ICD-9 (ICD-10) codes for primary and secondary diagnoses related to pain. Participant data and research materials which include and are not limited to demographics, study progress data, assessment data, and questionnaire data are managed using a defined set of integrated centralized database systems. All database systems, web-based or not, store data on secure, central servers. PHI acquired for the purposes of recruitment will not be disclosed to any other agency, party or individual. PHI obtained for recruitment purposes will be destroyed at the end of the recruitment period, which is estimated to be June 30, 2016.

A second purpose for accessing PHI will occur during the RCT to verify clinic visits, scheduling, medications prescribed, and associated costs. HIPAA Authorization will be obtained at the time of informed consent from enrolled patients seen at UC Davis Family Medicine, UC Davis Internal Medicine, UCD PCN and VANCHCS, which is being handled separately through the VA IRB. PHI that will be accessed includes laboratory reports, emergency medicine center reports, health care billing statements, diagnostic imaging reports, outpatient clinic records, and discharge summaries (See HIPAA Authorization Form, p. A052 of Appendix).

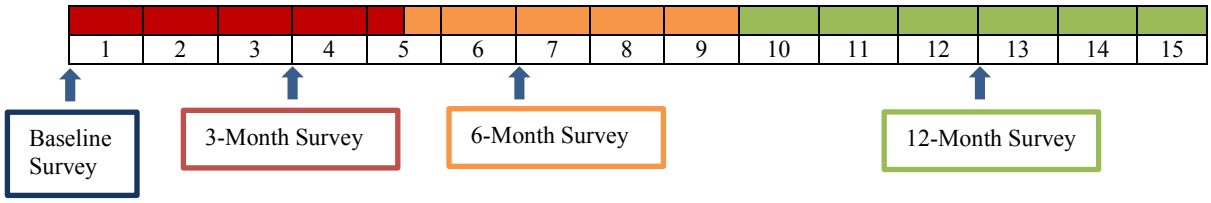
9) Study Timeline

Pilot Trial: Clinician and patient enrollment will begin September 2013 and is anticipated to continue for two months. Enrollment date is the date a patient signs the consent form. Duration in the pilot study will last approximately one month from enrollment, depending on the length of

the **Trialist** treatment chosen, and duration of patient participation is not expected to exceed two months.

The purpose of the pilot trial is to test the **Trialist** functionality, patient satisfaction, and patient willingness to complete the intervention (adhere to intervention treatments and daily intervention tasks). Since the pilot trial will not have a comparison group, extensive data analysis will not be done in this phase and estimated date of completion is February 1, 2014.

RCT: Clinician enrollment will begin September 2013. We anticipate beginning enrollment of patients in January 2014 with completion by March 2016. This will require enrolling approximately 2.5 patients per week. Once a patient is enrolled, study duration for any individual patient (if they complete all surveys and intervention tasks) will be 12-14 months from enrollment. For intervention patients, **Trialist** treatment may last between 4-12 weeks and begins once baseline assessment and *Treatment Planning Visit* are completed. Both control and intervention patients will complete 3-, 6-, and 12 month surveys. A grace period will be allowed for completion of each follow-up survey, such that the 3-month survey can be completed between 3-4.5 months; 6-month survey between 4.5-9 months; and 12-month survey between 9-15months. Patients failing to return a questionnaire during the corresponding time period will have missing data for the follow-up survey. Efforts will be made to obtain responses for the subsequent follow-up surveys. The timeline for survey follow-up periods is outlined below.



Patient participation ends upon completion of the 12-month survey. The clinician's primary involvement will end when all patients randomized to the **Trialist** intervention arm have completed the *Results Review* session. The clinician's formal participation will end once all enrolled patients have completed the 12-month survey. Clinicians will not be administering the follow-up surveys hence their primary participation ends after the **Trialist** intervention *Results Review* is conducted.

Primary Analysis (RCT)

The main outcome is pain-related interference using the PROMIS measure reported at 6 month follow-up. Primary analyses are expected to be completed within six months following the completion of the 6-month surveys.

Secondary Analyses (RCT)

The secondary analyses include pain reported at 3- and 12-months follow-up, and analysis of secondary constructs at all follow-up periods (3-, 6-, and 12-month). Secondary constructs are: health related quality of life, participatory decision making, patient treatment satisfaction, patient trust in clinician, adherence, and clinician trust in patient.

Analyses of pain reported at 3- and 12-months are expected to be completed within 6 months following the completion of the 12-month surveys. Analyses of the secondary constructs are expected to be completed within 12 months following the completion of the 12-month surveys.

10) Study Endpoints

Study endpoints

Pilot Trial: The primary study endpoint is the change in pain-related interference from baseline to follow-up survey.

RCT: The primary study endpoint for intervention and control participants is pain-related interference measured at the 6-month follow-up survey.

For intervention participants a secondary endpoint is the completion of the **Trialist** App. Additional study endpoints for control vs. intervention comparisons are baseline, 3 and 12 months surveys.

Safety Endpoints (Pilot Trial and RCT)

Potential safety endpoints will be reported by enrolled patients and/or their clinician and adjudicated by the Safety Monitoring Committee (see also section 14- Provisions to Monitor the Data to Ensure the Safety of Subjects). These include: patient has pain or medication-related ED visit or hospitalization during study period; or patient or clinician withdraws from study due to safety concerns.

11) Procedures Involved

The study design is a randomized clinical trial of n-of-1 trials using the **Trialist** smartphone application. After screening for eligibility and informed consent, patients will be randomized to Usual Care (control) or **Trialist** (intervention). Randomization will be stratified by clinician in blocks in order to balance numbers and minimize selection bias. Patients assigned to Usual Care will receive usual course of care as prescribed by their treating physician. Patients randomized to the **Trialist** will design the n-of-1 trial in collaboration with their clinician.

All patients enrolled in the pilot trial and RCT will receive a pain booklet based on Dr. Ward's prior work (pp. A066-A081 of Appendix), and complete surveys at baseline, and 3-, 6- and 12- months post baseline.

Patients randomized to the **Trialist** will meet with the treating clinician and study research staff at a *Treatment Planning Visit* to design the patient's n-of-1 trial. The *Treatment Planning Visit* will occur during a patient's normal clinic visit. Clinicians and patients will use the desktop interface of the **Trialist** to select two comparison treatments (see pp.A055-060 of Appendix for screen shots of the set-up screen). One important feature of the n-of-1 trial is that it can be tailored to the patient, and the participating provider's clinical judgment and negotiation with the patient determines which specific protocol to invoke in the study. The customized option allows patients and clinicians to select from among acetaminophen, ibuprofen, naproxen, or opioid combination products containing either hydrocodone or oxycodone, several of which are available in different FDA-approved doses. Other options include tramadol and complementary/alternative treatments such as massage, meditation or physical exercise. If a clinician attempts to select multiple treatments from one column that are deemed clinical inappropriate due to potential drug interactions the **Trialist** App will not allow their selection

(e.g. a codeine combination product such as Tylenol with codeine and a hydrocodone combination product such as Vicodin). A message will be displayed notifying the clinician of the inappropriate choice. The desktop interface will also provide links to current prescribing standards and recommendations for the available drug treatment options. The links, unallowable treatment options, and warning messages were developed by Dr. Barth Wilsey a pain medicine specialist and study researcher. See p. A065 for links on prescribing standards and recommendations available to clinicians within the desktop interface. Additionally, the Trialist desktop interface will display a pop-up advisory box for any patient trial including codeine, tramadol, hydrocodone or oxycodone as part of one of the treatment regimens. This advisory will acknowledge that codeine, tramadol, hydrocodone or oxycodone was selected as part of the treatment regimen, remind clinicians that good clinical practice is to increase or decrease opioids gradually over a few days to prevent withdrawal symptoms, and suggest that clinicians should consider using 2-week treatment periods for patients taking these medications. While clinicians already know these practices, this feature adds an additional safeguard for patient safety and was guided by the belief that clinicians may benefit from the reminder at the time of trial set-up.

Intervention arm (**Trialist** App) patients will also be advised that they will participate in a *Results Review Visit* following completion of their n-of-1 trial, which may last from 4 to 12 weeks following the *Treatment Planning Visit* date depending on the treatments selected. For patients enrolled from a UC Davis based clinical practice and sign the HIPAA Authorization Form at enrollment, the research assistant will have access the patient's EMR. This will help facilitate the scheduling of the *Results Review Visit*.

Once the n-of-1 trial is designed, and a start date is selected the **Trialist** will send tailored prompts reminding patients to take their medicines, rate their symptoms, and (optionally) examine graphic displays of secondary outcomes. Patients can choose the start date of their study. This allows the patient time to obtain prescriptions (if applicable) before they start their personalized trial. At the end of a given treatment period, the **Trialist** will instruct the patient to continue the same medication or to switch treatments. No washout period is planned due to the relatively short analgesic half-lives and multiple crossover design.

If a patient enrolls in the trial and then wants to change his/her comparison treatment, he/she will be allowed to select alternative treatments providing the personalized n-of-1 trial has not started. However, the patient's clinician must approve the change. Research staff will contact the clinician by telephone or email on the patient's behalf to request the change or the patient may contact the clinician directly to request the change. The research assistant will not update the patient's personalized **Trialist** treatment comparison without approval of the patient's clinician. All communication about changes to a trial will be recorded in the Treatment Change Log Sheet (p. A085 of Appendix). Once a patient has started a **Trialist** treatment comparison they will be unable to make changes. However, there may be circumstances where it is no longer appropriate for the patient to be enrolled in a trial comparing the initially selected treatments. In that case, the patient shall stop the current n-of-1 trial treatments and may, at the discretion of the clinician and the investigators, start a new n-of-1 trial.

A research assistant will be available to show the patient how to enter study data on his/her smartphone on a weekly basis regarding pain intensity, interference, and pain relief, as well as potential side effects such as fatigue, drowsiness, and nausea. This support will be provided by telephone and/or via email.

Upon completion of the n-of-1 trial, the **Trialist** will generate reports (available for printing or viewing on a desktop) that patients and clinicians can examine together during a follow-up office visit.

Pilot Trial: The patient will review data from the study with their clinician at a *Results Review Visit* to take place either at the UC Davis Center for Healthcare Policy and Research (CHPR) or at the clinician's office. The clinician will have access to the web application of the app via a desktop computer. The clinician and the patient will retrieve individual patient data using passwords to obtain the individual's responses to the survey during the study (see pp. A063-064 of Appendix for examples of the result displays).

RCT: For intervention arm (**Trialist**) participants, the Results Review Visit will occur during a regularly scheduled clinic visit after completion of the n-of-1 trial. The clinician will have access to the web application of the app via a desktop computer. The clinician and the patient will retrieve individual patient data using passwords to obtain the individual's responses to the survey during the study (see pp. A063-064 of Appendix for examples of the result displays). As the study does not require patients to schedule an appointment at the end of the trial but rather adds a study visit to an existing appointment, several options are provided to patient and clinician to facilitate the completion of the result review visit. This visit may be completed in the following ways: 1) held in person during a regularly scheduled clinic visit within eight weeks of the trial end date; 2) if an in person visit is not feasible, the visit may be held by telephone at a mutually convenient and agreed upon date/time by clinician and patient within 8 weeks of the trial end date; or 3) the result graphs will be sent to the clinician and patient prior to the end of the eight week window if neither an in-person nor telephone discussion can be scheduled.

Prior to the Result Review Visit, the patient and clinician will be asked for permission to audio-record the discussion of n-of-1 trial results during the Result Review Visit and complete an interview following the Result Review Visit. Informed consent will be obtained from both the patient and clinician in order to proceed. If both patient and clinician agree and consent to audio-recording, the research assistant present at the Result Review Visit will record the discussion with a digital recorder. Only the portion of the patient visit that pertains to the n-of-1 trial results will be recorded, and the research assistant will stop the recorder and leave the exam room for the remainder of the visit. Clinicians and patients can verbally decline continued recording at any time. The goal is to audio-record 25-30 Result Review Visits.

Clinicians will also be asked to complete an interview by telephone about a Result Review Visit. While we may record multiple Result Review Visit discussions for any individual clinician, as they likely have several patients randomized to the intervention, the clinician interview will be conducted only once with questions focusing on only the most recent Result Review Visit. Guiding questions for this interview are included for review. This interview will be audio-recorded and is expected to require 20-30 minutes. Interviews will be conducted by telephone and scheduled at the clinician's convenience.

Intervention patients will also be asked to complete an interview by telephone or in person, based upon patient preference, to learn about their experiences and what they learned by participating in their own n-of-1 trial. These interviews will be audio-recorded and should take approximately 30-45 minutes to complete. Guiding questions for these patient interviews are included for review. Questions asked of patients include their preferences for presentation of information; treatments compared for n-of-1 trial and guesses about which treatment would

be best and why; observations about Result Review Visit discussion with the clinician; and critique of the graphs provided for Result Review Visit discussion.

Follow-up surveys for both intervention and control patients will occur at 3-, 6-, and 12-month post enrollment. Patients will be contacted by telephone and/or email when a survey is due to be completed. Patients will have the option of completing the surveys online (e.g., Survey Monkey), through a mailed survey, or via a paper survey administered by the research assistant at CHPR. For intervention patients the 3-month follow-up survey will not be administered until the **Trialist** intervention is completed. Clinicians will complete a survey at baseline for each patient they enroll (pp. A101-104 of Appendix). Clinicians will have the option of completing the survey on-line, via a mailed survey, or paper survey at a meeting with the research assistant at CHPR or at their clinical practice.

Sources of materials

Materials include surveys (baseline, 3, 6, and 12 months), graphic illustrations of study data as presented by the clinician-facing **Trialist** system and the patient-facing system for episodic data entry, and EMR data. Patients in the Pilot trial will complete the **Trialist** intervention, baseline and follow-up measures (3-month survey administered as soon as the n-of-1 trial is complete). See pp. A087- 104 of Appendix for questionnaires, and p. A055-060 for the clinician-facing **Trialist** system (desktop interface) and p. A061-062 for the patient-facing system (App screen shots).

Patient participant materials. Pilot study participants will only complete the baseline and 3-month measures, where the 3-month follow-up will be administered as soon as the n-of-1 trial is complete. Materials administered to all patient participants include the following measures:

Construct	Measure	Baseline	3 mo	6 mo	12 mo
Pain Interference (primary RCT outcome)	PROMIS 8-item Pain Interference short form	☑	☑	☑	☑
Pain Intensity	PROMIS 3-item Pain Intensity short form 3a	☑	☑	☑	☑
Health-related Quality of Life	PROMIS Global Health Scale	☑	☑	☑	☑
Participatory Decision Making	CAHPS 12-month Medication Shared Decision Making	☑	☑	☑	☑
Satisfaction	Pain Treatment Satisfaction Scale	☑	☑	☑	☑
Patient Trust in Physician	Trust in Physician Scale	☑		☑	
Self-reported Adherence	Analgesic Adherence	☑	☑	☑	☑
Smartphone skills	Smartphone usage	☑			
Demographics	Age, gender, race/ethnicity, marital status, educational attainment,	☑			
Demographics	Employment status	☑	☑	☑	☑

Participants randomized to the intervention arm will also complete a Patient Expectations Questionnaire administered at the Treatment Planning Visit (pre-trial) and at the Result Review Visit (post-trial). The purpose of this questionnaire is to evaluate intervention patient

expectations and experiences with treatment and the extent to which patient expectations were met. Intervention patients will also be asked to complete the Trialist Acceptability and Satisfaction questionnaire to provide feedback on the use of the Trialist app and comments on the app features that they liked most or liked least to help improve the app for future use. The survey will be sent to participants after the n-of-1 trial is completed and can be completed either online or by pen/paper.

In addition, participants in the *intervention arm* will answer the following questions using the **Trialist** App:

Construct	**Measure**	**Daily**	**Weekly**
Daily Pain	Adapted version of PEG scale	☑	
Daily Sleep Disturbance	Adapted question from PROMIS Sleep Disturbance scale	☑	
Daily Fatigue	Adapted question from PROMIS Fatigue scale	☑	
Daily Drowsiness	Sleepiness and drowsiness	☑	
Daily Constipation	Constipation	☑	
Daily Cognitive Functioning	Adapted questions from PROMIS Cognitive functioning scale	☑	
Neuropathic Pain	Adapted questions form Neuropathy Pain Scale	☑	
Treatment Adherence	Adherence to n-of-1 trial treatment(s)		☑

Clinician participants sources of materials. Materials administered to clinician participants include the following measures administered at baseline and for the RCT only.

Construct	**Measure**	**Baseline**
Clinical Practice	Clinical Practice Characteristics	☑
Clinical Trial Experience	Clinical Trial Experience	☑
Demographics	Age, gender, race/ethnicity, educational attainment, employment	☑

12) Data and Specimen Banking

N/A

13) Data Management and Confidentiality

Data Analysis Plan

Due to the low *n* in the pilot study, extensive data analysis will not be completed on pilot data. The primary goal of the pilot study data will procedures to be utilized in the RCT.

The experimental design for Aim 2 (RCT) is a simple two-arm pragmatic randomized trial with patients nested within physicians, and physicians nested within clinics. In order to eliminate confounding effects of physicians and clinics, patients will be randomized so that each clinic and each physician receives an equal number of participants for each condition (control and intervention). Outcomes will be analyzed both as changes from baseline to a single time point and as longitudinal evolutions in time. For change at a single point, say, from baseline to 6 months, we will compare the groups by a t-test for continuous outcomes and chi-square test for binary outcomes. For the longitudinal outcomes, we will use a mixed model with fixed effects of time, treatment and their interaction as well as a random effect of time using the appropriate generalized linear model link function and distribution (normal for continuous outcomes; binomial for binary ones; Poisson for counts).

Secondary analyses will examine: (1) potential interactions of covariates such as age, gender, type of intervention, dosage, time on treatment, physician and clinic and; (2) outcomes that change from baseline to 3- and 12- months. The primary analysis will be intent-to-treat which uses all participants as randomized. When no endpoint is available (e.g., a month 6 pain measurement for a change to 6-month outcome), we will assume no change. Further analyses will employ multiple imputation to fill in missing values, particularly in covariate-adjusted models. The longitudinal models can accommodate missing outcomes under the assumption that data are missing at random.

Each patient enrolled into the intervention arm (**Trialist** App) will enter data for all periods including data for both treatments. At the end of each N-of-1 (**Trialist** App) study, statistical analysis will be performed in order to compare results on the two treatments and present these to the patient and clinician for use in deciding which works best. Because each patient's data requires a separate analysis and these analyses will be occurring frequently, the analyses will be automated to run in the background once each N-of-1 trial is completed. The analysis will consist of running different Bayesian models that make different assumptions about the nature of the data (e.g., data with and without correlation over time, with and without interactions between time and treatment, different assumptions about prior distributions of model parameters, etc.). The results of these models will be compared as to which best fits the data using features such as parameters that explain significant variation, testing for the effect of outliers, checks on how well the predictions derived from the posterior distribution mimic the data. Models that are robust will be preferred. Results from the model that fits desired criteria best will be chosen. Patient and clinician will be provided with the estimate of the treatment difference and a measure of its uncertainty (a 95% Bayesian confidence interval) as well as the probability that each treatment is the best for each outcome in both a numeric and graphical format.

Power Analysis

Sample size is based on the assumption that a 0.4 SD difference (4 points) on the PROMIS pain interference metric is clinically significant. Assuming that 10% of those who enter the study will not complete an endpoint and will therefore be assigned a change of zero, we wish to be able to detect a 3.6 point difference in the full sample (endpoint completers plus non-completers). A sample size of 122 in each group (**Trialist** App and Usual Care) will have 80% power to detect a difference in means of 4.0 points assuming that the common standard deviation is 10 with mean

68 out of 100 as in published chronic pain samples using a 2 group t-test with a 0.05 2-sided significance level. Enrollment in the study is defined as (1) completion of the baseline questionnaire, (2) randomization to the intervention (**Trialist** App) or control arm, and (3) completion of one or more study-related visits. Allowing for 10% attrition, we will recruit 286 patients into the study with the expectation that 244 will complete all 3 enrollment procedures. Approximately one-third of this number will be recruited at the VANCHCS.

Data security

Identical data safety measures will be utilized for the Pilot study and RCT. Multiple procedures for protecting against or minimizing risks will be put in place. All research staff will complete training for HIPAA and human subjects' protections regulations and procedures.

Confidentiality of participant data will be maintained through several mechanisms. All participants will be assigned identification numbers, and a list linking names and ID number will be stored separate from participant data in a locked file cabinet and electronically on a secure server at CHPR. Access to this list will be restricted to the principal investigator, project manager and research assistant. At the enrollment interview, all signed consent forms will be kept in a folder and bag for transportation separated from the baseline surveys. Upon returning to CHPR, the signed consent forms will stored separately from the completed surveys, and other research materials. Informed consent will be conducted in such a way that details of the study cannot be overheard by other patients and caregivers. Participants will be advised as to the risks to confidentiality during informed consent, namely how the privacy of their data may be compromised if their smartphone (for those randomized to **Trialist** App) is lost or stolen. Wireless data transfer will use encryption, and no personal health information will be captured during the initial study setup.

For the medical record abstraction, the patient's last name, DOB, and MRN will be used to verify identify the patients for the abstractor to insure the correct records are accessed and only those for whom the study has obtained HIPAA Authorization are included in the abstraction. This information will be completed prior to abstraction on a separate cover sheet. Once the information on pain diagnosis and medications has been abstracted, this cover sheet will be removed and stored with the consent forms and other identifying information. The information that is abstracted will include only study ID and be stored with other questionnaire data, separated from any identifying patient information.

Intervention patients in the pilot trial and RCT will use their own mobile phone and download the **Trialist** App. Before the clinician and patient can create a **Trialist** treatment plan, they will be provided with a username and password, and enter the patient's RCT number.

Any data the patient enters in the **Trialist** app is encrypted and uploaded to a secure server using TLS/SSL protocols. The mobile phone data as well as all the log data will be stored in a secure password-protected server running the Linux operating system (Ubuntu 12.04.2) that only the server administrators have access to via SSH keys. Study data servers will be updated daily for the latest operating system and security updates by the server administrator and will be closely monitored during the study.

For the **Trialist** system, security and privacy are paramount from the design level up to end-user operations and is built-into the Open mHealth architecture on which **Trialist** will be developed.

All data transfer will occur over HTTP secured by an SSL certificate (TLS 1.0 with 128-bit encryption) or SSH certificate (RSA-2048-based encryption). Login accounts will be established with only a username and password; no PHI will be stored with the user data in **Trialist**. In addition, user passwords will be stored using a one way hash created using Bcrypt with a random salt to randomize password hashing. This means that no one except the end user knows their password, and prevents against automated attacks where malicious software attempts to guess passwords by trying many login attempts. Passwords for login accounts must be a miniumum of 8 characters.

The server to run the mHealth software is housed in Amazon Web Services (AWS). Only server administrators with security training and access will be allowed to login to the machine for development or troubleshooting purposes. The server adminstrators report to Josh Selsky (see 23 Resources available) whom reports to co-PI Ida Sim (see 23 Resources available). This server will meet the following technical specifications: 1) limited logon access; 2) up-to-date operating system; 3) secure network connections through firewalls; and 4) capacity to remove unnecessary applications from the operating system (locking down servers) while running a minimal amount of software on top of Linux.

Separate servers are used to store the patient's personal information (e.g., master list) compared to the data entered into the **Trialist** App. The server storing the patient's personal information is stored at CHPR. For the **Trialist** system, the server will be housed in Amazon Web Services. These two servers will not be connected in any way. The only way to link patients data entered into the **Trialist** App is to manually compare the patients login name to the patients RCT (or pilot trial) number, and then compare the patients RCT (or pilot trial) number to the master list. This ensures only the principal investigator, project manager and research assistant can link data to an individual patient.

Access to a patient's EMR records will be limited to the research assistant, project manager, and principal investigator. Only the research assistant and project manager's desktop computers at CHPR will have access to the EMR system. Their computers are password protected and receive regular software and security updates.

All paper surveys will be stored in locked file cabinets at CHPR, and only the project manager, research assistant and principal investigator will have access to them. All identifiers will be destroyed by the project manager at completion of the study.

Data quality control

All data that requires manual entry (e.g., from a pen-and-paper surveys) will be entered by experienced researchers and checked for accuracy by comparing all entered data to the raw data. All statistical analyses will be reviewed by the researcher completing the analysis and by an additional researcher (either within, or external to the research team) to check analytical accuracy and integrity.

Data Storage

Screening and enrollment for the pilot and RCT will be conducted by UC Davis researchers at all research sites, and all consent forms and data will be stored at CHPR. All paper based study documents will be stored in locked file cabinets, and all electronic data will be stored on secure servers at CHPR with access limited to PI, Project Manager, and Research Assistant.

Data Transportation

In instances where signed consent forms are collected at the *Enrollment Interview*, signed consent forms will be stored in a folder separated from other study documents, such as surveys, and chain of custody will be observed at all times. Upon returning to CHPR, the study documents will be stored securely in separate locked file cabinets from signed consent forms.

14) Provisions to Monitor the Data to Ensure the Safety of Subjects

This is a low-risk study, as all treatments will be known to and approved by the participating patients' own clinicians. Nevertheless, because of the study's complexities, a Safety Monitoring Committee (SMC) will be established. Once the first subject is enrolled in the RCT, monthly SMC conference calls will be held, subject to cancellation at the discretion of the SMC chair if there are no adverse events, no unanticipated problems or no other issues for discussion. The SMC will consist of Naileshni Singh, MD (chair), Stephanie Hatten, RN, Barth Wilsey, MD, and Daniel Tancredi, PhD.

Unanticipated and adverse events will be detected and reported to the SMC in several ways. All patients and clinicians participating the in the clinical trial will have phone numbers of the Project Manager (Marois) and PI (Kravitz) available as part of the informed consent documents, and any reports are likely to be collected by telephone. The Project Manager and PI will enter all such contacts into a log for immediate reporting to the SMC chair and IRB if the matter is serious or urgent, or for routine consideration at the next scheduled meeting of the SMC. All such incidents will be reported to the UCD and VA IRB. In addition, the SMC will report adverse events considered related to the study directly to the NINR (National Institute of Nursing Research) Program Official within one week of the SMC meeting at which the event is discussed.

The Project Manager will be directly responsible for assuring that all IRB requirements are attended to, including conformance with informed consent requirements, maintenance of confidential project files and minimizing research related risk. She will work closely with study investigators to assure seamless operations and transparent reporting.

There are no planned interim analyses of the RCT as a whole. However, it is the nature of the n-of-1 trials that individual patients and their clinicians can review selected interim results of their own n-of-1 trial data at any time.

15) Withdrawal of Subjects

If a patient meets eligibility criteria and consents to participation, there are no likely circumstances under which they would be withdrawn from the research without their consent.

Pilot Trial: If a participant withdraws from the research before entering data into the **Trialist**, the patient will be replaced by an alternate selected during initial recruitment activity. Patients are free to opt out at any time and still be treated by their physician. If a participant withdraws once **Trialist** data collection begins, they will be considered a drop-out from the study and this information will be recorded along with the date of withdrawal. Participants will be asked, but

not required to provide a reason for withdrawal. SMC members will be notified of withdrawals on a monthly basis and if available, reasons for withdrawal.

RCT: If an intervention participant withdraws from the research after beginning a **Trialist** sequence (but not completing the entire treatment sequence), the patient data will be used to test the usability of the system, but the patient data will not be reviewed by a clinician.

In the event that a patient withdraws from the research before any **Trialist** data are collected, the patient will be replaced by an alternate selected during initial recruitment activity, and they will be classed as a screening failure.

Patients are free to opt out at any time and still be treated by their physician. If a participant withdraws from the study, they will be classified as a drop-out and the date of withdrawal will be recorded. Participants will be asked, but not required to provide a reason for withdrawal, and any collected data up to the day of their withdrawal will be used in analysis. SMC members will be notified of withdrawals on a monthly basis and if available, the participant's reason for withdrawal.

16) Risks to Subjects

Physical risk is minimal, since the patient and the clinician work collaboratively to select the best pain control therapies given the patient's preferences and clinical need. In some cases, patients may experience troublesome side effects that warrant a follow-up visit with the clinician. This is within the scope of standard care, and patients will be advised to follow up with their clinicians as they normally would. Patients will also be responsible for any co-pays resulting from follow-up care or research visits, which involve counseling and education as enhancements to usual care. However, the number of required visits is unlikely to exceed that which is required during usual care of patients with complex chronic painful conditions. The potential for legal risk is small since there is the potential for disclosure of private information on a smartphone, particularly if the phone is lost or stolen. There is a small potential risk of breach of confidentiality should the participant's personal health information be compromised. We believe we have established effective procedures to protect confidentiality through encryption and secure transfer and to minimize the legal risk for the participant or the study. No alternative treatments or procedures are available. We do not anticipate psychological risks beyond those encountered in ordinary clinical practice. (For risks and protection of patient data, see data security Section 13, Data Management.)

The pharmacologic treatment options available in the **Trialist** (acetaminophen, NSAIDS, tramadol, or opioid combination products containing either hydrocodone or oxycodone) are all FDA-approved drugs. These medications are commonly used in practice. When clinicians and patient selected treatments with the **Trialist**, "pop-up" precautions and contraindications will occur if the drug combination selected is not clinically appropriate (e.g., information to prevent the risk of hepatic and/or renal injury arising from taking excessive amounts of acetaminophen and/or NSAIDs), (Non-allowable drug combinations are included in pp. A065 of Appendix).

For some treatment combinations, there is a theoretical risk of withdrawal symptoms as the patient goes completely off his/her opioids. However, it is unusual to see opioid withdrawal when less than 30 mg per day of morphine-equivalents are administered [communication with

Barth Wilsey, co-Inv]. Additionally, the time it takes to become physically dependent varies with each individual, often making withdrawal a non-issue. Regardless, an advisory pop-up box will be displayed if a clinician chooses codeine, tramadol, hydrocodone or oxycodone as part of the treatment regimen; include reminders to increase or decrease opioids gradually over several days; and suggest using 2-week treatment periods to allow for ramping-up and/or tapering. Additionally, the consent form will be written with language letting patients know what symptoms to expect if they are experiencing opioid withdrawal, which may include agitation, anxiety, muscle aches, increased tearing, insomnia, runny nose, sweating, and yawning for early symptoms and abdominal cramping, diarrhea, dilated pupils, goose bumps, nausea, and vomiting for late symptoms of withdrawal. Opioid withdrawal reactions are very uncomfortable but are rarely, if ever, life threatening. In any case, if the patient experiences withdrawal symptoms, s/he will contact the treating clinician who will be able to place the patient immediately back on an opioid-containing preparation. In this way n-of-1 trials are distinctly different from conventional clinical research; the treating clinician and patient are in charge, and they can do whatever comports with good clinical care.

17) Potential Benefits to Subjects

The potential benefit of the research to the participants in the intervention condition is direct; they will receive information that should improve their cooperation and adherence to tailored pain control regimens. **In this way, n-of-1 trials differ from classic parallel group RCTs where participants enroll without any expectation of direct, personal benefit for decision making (See Appendix B).** Intervention participants may benefit from having clear visual displays of their pain scores and metrics that apply to treatment side effects and overall quality of life. These scores can be shared with their clinician and compared to the results they achieve on different pain control therapies. The intervention could also reduce the discomfort associated with participants' uncertainty about how to communicate with a clinician about pain symptoms and treatment. For participants in the control condition, the benefits are indirect, but we believe the value of a randomized experimental design with a control group improves the likelihood that we can adequately assess the effect of the patient's regular pain treatments.

18) Vulnerable Populations

N/A

19) Multi-Site Research

Dr. Barth Wilsey is a study co-investigator and the partnering principal investigator at the Department of Veterans Affairs, Northern California Health Care System (VANCHC). Dr. Wilsey will obtain IRB approval at the VANCHC, and provide copies of all IRB documentation to Dr. Kravitz, PI and the project manager. The project manager will be responsible for providing copies of all UC Davis approved IRB documents to Dr. Wilsey, including protocol modifications.

Dr. Wilsey and Dr. Kravitz (PI, UC Davis) will work closely together, and any modifications to the study will be overseen by them, and along with the project manager they will be responsible

for ensuring any modifications are implemented at all study locations. All communications (email, phone calls) to the research sites regarding modifications will be logged.

All clinicians will be informed once their patient's involvement in the study has finished (i.e., patient completes 12-month follow-up survey) via an email, telephone call, or letter.

20) Community-Based Participatory Research

N/A

21) Sharing of Results with Subjects

Pilot study: Participants will only receive results from the **Trialist** App. Due to the small number of participants to be recruited for the pilot, results from the baseline survey will not be provided to either participants or clinicians.

RCT: After completion of the n-of-1 trial with the **Trialist** App, patients and clinicians will generate reports (available for printing or viewing on a desktop) that they will examine together during a follow-up clinic office visit. Overall results from the RCT, including analysis of the follow-up surveys, will be provided as a brief report to clinicians and participants.

22) Setting

The study will be conducted at four practice sites within the Sacramento-Yolo, CA region, and include UC Davis Family Medicine, UC Davis Internal Medicine, UC Davis Primary Care Network (UCD PCN), and the VA Northern California Health Care System (VANCHCS). Clinicians working with chronic pain patients will be identified and approached for participation in the study, and patients will be identified and recruited through participating clinicians. Primary research procedures include baseline, 3, 6, and 12 month follow-up surveys, which will be self-administered via paper or online. These may be completed at the clinic, the project office at CHPR or patient's home according to individual preference. Patients in the **Trialist** App intervention arm will also complete daily and weekly entries into the **Trialist** App on their smartphone in his/her home at his/her convenience.

23) Resources Available

The following individuals will participate in the study:

Richard. L. Kravitz, MD, Principal Investigator
Dr. Kravitz will be responsible for the scientific integrity and conduct of the entire project. Dr. Kravitz is a general internist and health services researcher with more than 20 years of experience performing observational and experimental studies in primary care; he also spent a year consulting at RealAge.com, a health internet company. Recent work has focused on interventions to enhance patient engagement in advanced cancer and depression. He has published extensively on n-of-1 trials as a tool for estimating individual treatment effects. For the past year, he has been an active member of Open mHealth.org to create a versatile platform

for helping patients and clinicians track their own health data.

Deborah Ward, RN PhD, Co-Investigator
Dr. Ward is Associate Dean, Betty Irene Moore School of Nursing at UC Davis. Her most recent study evaluated a nurse-led, motivational-interviewing-based intervention for self-management of pain after spine surgery (funded by the RWJ foundation). She has bother operational and research experience in health care system design and operations with a focus on patient communication. Dr. Ward will provide input on design and conduct of the project in all phases. During Phase I she will provide the nursing perspective on design and optimization for the **Trialist**. She will assist with recruitment of clinicians particularly nurse practitioners and physician assistants. In the Phase II, she will contribute to the interpretation and dissemination of results.

Barth Wilsey, MD, Co-Investigator
Dr. Wilsey is a pain medicine specialist and researcher. He is currently holds a VA merit Award in support of a project evaluating cannabinoids for treatment of neuropathic pain. During Phase I of the project, Dr. Wilsey will advise the Development Team on the use of and deployment of clinical outcomes measures, particularly as they relate to pain and analgesic side effects. Building on his experience with the Prescription Opioid Documentation and Surveillance system (PODS), he will work closely with Open mHealth to design user interfaces for data entry and display that are clinically sensible, psychometrically valid, and user-friendly. During the RCT Phase he will serve as head clinical liaison at the VA, recruiting physicians and patients and supervising the VA research assistants. He will also participate in data analysis and dissemination.

Ida Sim, MD, PhD, Co-Investigator
Dr. Sim is a Co-Founder in Open mHealth. She will participate in this effort via subcontract to UCSF. Ida Sim, MD, PhD is a widely respected clinical informatician, health services researcher, and practicing general internist and a co-founder of OpenmHealth.org. She has extensive experience in clinical research and critical appraisal methods and specializes in the development of informatics technologies for evidence-based practice. As Co-Founder of OpenmHealth.org, she is building an open software architecture for mobile health that will promote and support best practices for mobile health interventions and evaluation methods.

Marc Schwartz, User Interface Expert (Consultant)
Marc Schwartz, is the founder and managing partner of IdeaSphere LLC. Based in New York City, IdeaSphere produces software systems and data centers facilitating many diverse projects for varying clients and communities. In the healthcare arena, Ideasphere's body of work ranges from electronic medical records systems to surgical simulators to mobile phone software for conducting scientific and medical clinical trials. Marc has a Master's degree from MIT and a BFA from The Rhode Island School of Design. Marc was also a US Fulbright Scholar in Japan, where he studied the cultural impact of mobile telephony.
Marc will provide for Participatory Design Management by conducting initial interviews with stakeholders (including the project investigators plus a subset of the 6 clinicians and 6 patients about their current technological landscape and the software they currently use. He will collect, organize and circulate conclusions from these interviews. He will develop and prioritize design

goals and criteria with stakeholders. He will create software prototypes to test and collect feedback through automated tracking, screen-sharing and interviews. He will continue to modify design based on the feedback and modify prototype for re-testing.

Josh Selsky, Software Designer Open mHealth (Consultant)
Josh Selsky holds a BS in Computer Science from the Illinois Institute of Technology and is a software developer with 15 years of professional experience working at startups, within academia, and at corporations both large and small. In addition to architecting the Open mHealth software ecosystem and working with its technical community, Josh currently holds a senior software engineering and management position at CENS where he collaborates with health and computer science researchers on mHealth applications and manages a team dedicated to turning research into professionally developed software. In coordination with Marc Schwartz, Josh will be responsible for programing the **Trialist** software as defined by the PREEMPT Development team.

Christopher H. Schmid, PhD, Co-Investigator
Dr. Schmid is a statistician and Professor of Biostatistics at the Center for Evidence Based Medicine Brown University. His research goals for many years have been directed to the development and application of statistical methods, particularly Bayesian, for research synthesis of both study-level and individual participant level data. He has participated in several large federally funded projects that have combined both randomized and non-randomized data from different studies and databases in order to develop predictive models and to evaluate the effect of interventions in different populations. The proposed project to develop a mobile application to facilitate the conduct of N-of-1 studies builds on his previous work to develop Bayesian methods for combining N-of-1 studies to improve individual and population predictions and on his experience in an N-of-1 clinical trial of treatments for fibromyalgia. That study developed Bayesian multilevel models to predict risk and to feed back information to patients and providers. The proposed study is a logical extension to implement these methods in a user-friendly tool with powerful analytic capabilities. In general, Dr. Schmid's expertise extends to analysis of large databases, conducting simulations to address methodological questions, developing novel statistical methods, designing and analyzing clinical trials and developing Bayesian models. He will be closely involved with development of the new methods as well as with developing computer programs to implement these methods. In addition, he will direct the statistical design and analysis of the RCT.

Zachary Holt, MD, Co-Investigator
Dr. Holt is the Internal Medicine Primary Care Director and an Assistant Professor in the Department of Internal Medicine. His clinical career places emphasis on the primary care of individuals with complex medical histories and significant psychosocial issues. He spends a significant amount of time caring for patients with chronic pain and chronic controlled substance prescriptions, a population for which he has had informal training from the Pain Management Division (a part of the Department of Anesthesia) and formal training via the Chief Resident Immersion Program (CRIT), facilitated by Boston University faculty with SAMSA funding. His role in the current study is to advise on the clinical aspects of the study execution, including strategies for working in the clinic and identifying suitable patients for the study population.

Anthony Jerant, MD, Co-Investigator
Dr. Jerant is a professor in the Department of Family and Community Medicine and researcher with the Center for Healthcare Policy and Research. Dr. Jerant's research expertise includes seeking ways of improving the health of people with chronic health conditions and eliminating disparities in the outcomes of such conditions. Given the difficulties chronically ill people face in obtaining consistent, timely access to primary care, a major focus of his work is in developing and evaluating technology-enhanced care delivery to effectively expand the primary care encounter in space and time. Using such tools to bolster patients' confidence in their ability to master self-management of their chronic conditions is a particularly strong current theme in his research. His role in the study is to advise on clinical aspects of study execution, facilitate study work in the clinic and assist with identifying suitable patients for participation.

Maria T. Marois MPH, PhD, Project Manager
Dr. Marois is an epidemiologist with over 15 years of experience managing a variety of research studies. She has managed all aspects of several field studies, including a longitudinal cohort study of occupational exposures and health status of migrant farm workers in California's San Joaquin Valley and a study examining pesticide exposure and respiratory health in Costa Rica. Dr. Marois will be responsible for the day-to-day management of the study. She will be responsible for the overall functioning of all project components; supervise staff; serve as the liaison between study staff, study participants, investigators and consultants; develop study instruments and data management protocols; and prepare study progress reports and manuscripts.

Colin Barr, Research Assistant
Colin Barr holds a Bachelor of Science in Psychology from the University of Auckland, New Zealand. He is experienced in IRB and data collection protocols. He is skilled at the "safe handling" practices for safeguarding Personal Health Information (PHI), maintaining data integrity and data destruction. Under the supervision of the Project Manager and PI, Mr. Barr will assist in meeting the daily needs of the project through schedule maintenance, document management, project data tracking and the maintenance of data collection and outcomes. He will assist with IRB modification/submissions, generate administrative documentation and presentations, and prepare and send recruitment/project materials. He will communicate verbally and in writing with team members, stakeholders and collect and store data.

Navjot Dhammi, Research Assistant
Navjot Dhammi holds a Bachelor of Science in Biological Sciences from the University of California, Davis. She has experience in patient recruitment, conducting research interviews, data collection and entering and processing data. Under the supervision of the Project Manager and PI, Ms. Dhammi will assist in meeting the daily needs of the project through patient recruitment, project data tracking and data collection.

Other Resources

Pilot Trial: A total of 8 participants and 2-4 clinicians will be recruited for the pilot study. Recruitment for the pilot trial is anticipated to require two months and will be conducted October-November 2013.

RCT: For the intervention, a total of 244 participants and 50-60 clinicians will be recruited for this study from 4 practice sites. To meet recruitment goals, 6-8 participants per clinician will be enrolled. The recruitment period will run March 1, 2014 – February 28, 2016, requiring enrolling approximately 2.5 patients per week during the two year period. Recent studies have suggested that 13% of physician visits are related to chronic pain, suggesting over 20,000 patient visits due to chronic pain at the recruitment sites, providing a feasible number of potential subject to meet recruitment goals. Additionally, an estimated 500-600 patients are taking opiates for pain within the PCN (personal communication).

The facilities for study are more than adequate to assure project success. The study is based at the Center for Healthcare Policy and Research (CHPR) and includes office space, work stations, statistical services and other data management and quality control services. All research personnel complete human subjects and HIPAA training, and undergo training with the investigators and project manager, and participate in weekly meetings with the PI and research team to ensure all research procedures are implemented according to protocol and maintain patient confidentiality.

24) Prior Approvals

N/A

25) Provisions to Protect the Privacy Interests of Subjects

Screening for Eligibility

When a patient contacts the research team about the study, the patient can make contact via email or telephone. The patient will be provided a brief summary about the study and asked if they would like proceed with the screening questions, and if they have any questions. The potential participant will have the option to re-schedule for a more convenient time when they are asked the screening questions, or to complete them via an online survey. Potential participants will not be required to answer any questions they are uncomfortable answering. However, non-response to a screening question will likely result in exclusion from participation since researchers will not be able to determine eligibility. Allowing the potential participant to answer questions via telephone, or an online survey provides them with the chance to use an interface they are most comfortable with.

Informed Consent

Before signing the consent form participants will be provided an opportunity to read it and ask any questions they may have. Participants will have the choice to sign the consent form, or sign the consent form at a later date if they are unsure about participation.

Participants will be informed that if they sign the consent form, they have the right to withdraw from the study at any time, and do not have to provide researchers with a reason for withdraw. Participants will be provided a copy of the consent form to keep, which will contain the contact details of the PI and project coordinator, and the UC Davis and VANCHC IRB. Participants will be informed they can contact any of these people/institutions with any concerns they have about the study.

Study Procedures

Participants will not have to complete any study procedures or answer any questions that they are uncomfortable with answering. For the baseline, 3-, 6-, 12-month surveys, participants can skip questions they do not wish to answer. Researchers will not have access to the participant's **Trialist** password, and participants will not enter personal contact details into the **Trialist** App. Participants will not be able to see other participant's data entered into the **Trialist** App.

26) Compensation for Research-Related Injury

For reasons advanced earlier, this study is considered "no more than minimal risk." The reasons are that all treatments are FDA approved, treatment choice and administration are entirely at the discretion of the treating clinician, and other study procedures (surveys) carry no risk. Thus, except for the rare instance of opioid withdrawal among patients who choose to compare an opioid-containing regimen with a non-opioid regimen, the study conveys no risk beyond usual care. (We believe opioid withdrawal will be rare because: 1) many patients will choose to compare two non-opioid containing regimens; 2) most other patients will choose to compare one opioid-containing regimen with another opioid-containing regimen; 3) the vast majority of patients on opioids will be taking less than 30mg of morphine equivalents, the generally accepted threshold below which opioid withdrawal virtually never occurs; and 4) patients who develop early symptoms of opioid withdrawal can simply start taking their opioid again.)

Patient consent forms for both the pilot study and RCT inform patients of the following:

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

This information is contained in the section, "What else do I need to know?" on page 5, paragraph 4 of the RCT patient consent form and page 5, paragraph 3 of the pilot study patient consent form.

There is no risk of research-related injury to clinicians enrolled in either pilot study or RCT.

27) Economic Burden to Subjects

Patients will be responsible for any co-pays resulting from follow-up care, which involve counseling and education as enhancements to usual care. This information will be clearly stated in the consent form. Patients will require a smartphone with a data plan to be enrolled in the study. Patients will be responsible for all data charges they inccur using the **Trialist** App. It is estimated that the App will use 1.5 MB of data per month. In comparison, watching a 4 minute YouTube music video uses an average of 11MB of data [24]. Patients will be informed that the research team accepts no responsibility of data overage fees from their smarthphone carrier.

28) Consent Process

Clinician consent will be obtained through a variety of ways. Interested clinicians will be provided with informed consent at presentations about the study, in-house staff meetings and other personal contacts. Drs. Kravitz and Wilsey will be available to discuss the clinician role and responsibility in participating in the study as well as answer any questions.

For eligible patients, the consent form will be mailed, discussed by telephone with the patient by the Research Assistant or Project Manager, and mailed back to the study office at CHPR prior to the *Enrollment Interview*. If a patient does not mail the signed consent form back prior to the *Enrollment Interview*, it will be collected from them in the clinic setting at the *Treatment Planning Visit*. Individuals listed in the application as being involved in the consent process will be familiar with the study and all procedures as well as the informed consent process in order to clearly answer questions and discuss all aspects of the study. Patients will be allowed to review the consent document and research staff will follow SOP: Informed Consent Process for Research (HRP-090).

Upon being provided the consent form, potential participants will have an opportunity to review and ask any questions of the research team. Staff will go through sections of the consent form with participants, ask questions to assess patient's understanding, insure patients are aware of their rights, and take the necessary time to review and make a decision about participation. The timing should allow potential participants as much time they require making their decision, up to the end of the recruitment period, or when maximum enrollment is reached.

A waiver or alteration of the consent process is not required. The following groups of people will not be enrolled.

Non-English Speaking Subjects –N/A, only English speaking subject will be recruited as software is only available in English at this time.

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)—N/A

Subjects who are not yet adults (infants, children, teenagers)-- N/A – Subjects will be over the age of 18 years.

Cognitively Impaired Adults-- N/A

Adults Unable to Consent -- N/A

29) Process to Document Consent in Writing

Research staff will follow the SOP: Written Documentation of Consent (HRP-091) to document consent in writing (see pp. A032-A054 for copies of all consent forms).

30) Drugs or Devices

N/A.

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