Protocol

Study Title: A Patient-Centered Intervention to Improve Opioid Safety

NCT02791399

This protocol contains the original statistical analysis plan excerpted from the funded research proposal.

04/24/2019

Details of the final protocol and recruitment outcomes are in the following publication:

Morasco, B.J., Adams, M.H., Maloy, P.E., Hooker, E.R., Iacocca, M.O., Krebs, E.E., Carr, T.P., Lovejoy, T.I., Saha, S., & Dobscha, S.K. (2020). Research methods and baseline findings of the Improving the Safety of Opioid Therapy (ISOT) cluster randomized trial. *Contemporary Clinical Trials, 90*, 105957.

A Patient-Centered Intervention to Improve Opioid Safety

SPECIFIC AIMS

With the increased use of prescription opioid medications to treat chronic pain,[1] there is growing and appropriate concern about impacts of their use. Prescription opioids are associated with increased risk of adverse medical effects, including cardiovascular events, fractures, hospitalization, and mortality.[2-7] Up to two-thirds of patients prescribed opioids will exhibit some type of prescription opioid misuse, such as taking more medication than prescribed, obtaining early refills or medication from others, taking opioid for purposes other than analgesia, or sharing with friends or family.[8,9] Prescription opioid abuse, which includes concurrent alcohol abuse or illicit substance use, occurs in 10-35% of patients with chronic pain.[10] VA/DoD Clinical Practice Guidelines for patients prescribed chronic opioid therapy for pain recommend screening all patients with urine drug tests (UDT) for prescription opioid abuse and adherence prior to and during opioid therapy.[11] Recent reports from the VA Office of Inspector General and Under Secretary for Health additionally highlight the need to be more thorough in screening for adherence to prescription opioids. However, UDTs are currently administered to fewer than 25% of patients who initiate chronic opioid therapy.[12] Reasons for the limited use of UDTs may include clinician discomfort, uncertainty about interpreting or responding to results, and lack of clear data on effectiveness of screening to reduce prescription opioid abuse.[13,14]

We propose a randomized trial of a multifaceted intervention designed to optimize a patient-centered approach for improving adherence to prescription opioids, "Improving the Safety of Opioid Prescriptions (ISOT)." Primary care clinicians and PACT (Patient Aligned Care Team) nurses will be randomized to ISOT or the control condition; patients will be nested by clinician status. Clinicians and PACT nurses in both groups will participate in an interactive workshop on reducing prescription opioid abuse and enhancing safety. In addition, clinicians assigned to ISOT will work with a nurse care manager (NCM) who will maintain a registry of enrolled patients, track UDT administrations and results, examine state Prescription Drug Monitoring Program data, monitor medical records, and collaborate with an internist and substance abuse specialist to provide decision support when patients demonstrate evidence of prescription opioid misuse or abuse. The NCM will also meet with intervention patients to discuss strategies for reducing opioid adverse effects and preventing diversion, and to provide rationale for prescription opioid adherence monitoring. Thus, our intervention targets system, clinician, and patient levels. A research goal is to enhance patient-centered pain care and improve the quality of the communication and relationship between the patient and the primary care team pertaining to this challenging topic. The main objectives of this study are to evaluate the efficacy and acceptability of a multifaceted intervention (ISOT) to enhance opioid safety in patients with chronic pain.

SPECIFIC AIMS

Aim 1: Evaluate to what extent a multifaceted intervention (ISOT) enhances prescription opioid safety.

Hypothesis 1: At 12 months, ISOT patients will have lower rates of prescription opioid abuse, as assessed via multiple methods (self-report, clinical interview, urine drug testing), compared to patients of clinicians randomized to the control condition.

Hypothesis 2: At 12 months, ISOT patients will experience fewer adverse events (defined in this proposal to include emergency room visits, overdoses, falls, motor vehicle accidents).

Aim 2: Assess to what extent assignment to ISOT impacts pain treatment-related processes of care.

Hypothesis 1: ISOT patients will have more modifications to clinical care documented in the medical record, including more frequent UDTs and queries to state prescription drug

monitoring programs.

Hypothesis 2: ISOT patients will report greater trust and satisfaction with their PCP related to opioid prescribing and treatment of chronic pain, relative to patients in the control condition.

Aim 3: Explore to what extent ISOT is associated with changes in pain intensity, function, quality of life, and depressive symptoms.

Hypothesis: ISOT patients, relative to patients in the control condition, will not experience worse significant adverse outcomes in pain intensity, function, quality of life, or depressive symptoms.

If ISOT is effective, we will additionally examine intervention impacts on VA healthcare utilization and costs.

The **overall significance** of this project is to test the efficacy, satisfaction, and cost-effectiveness of a multifaceted patient-centered intervention designed to enhance opioid safety. Results will inform the utility of team-based care and risk mitigation strategies for chronic opioid therapy. If results are significant, clinicians will have a pragmatic evidence-based treatment that improves adherence to prescription opioids, reduces adverse events, does not result in impairments, and enhances the clinician-patient relationship.

BACKGROUND

The use of prescription opioid medications to treat chronic pain continues to increase.[15] Data on opioid efficacy for chronic pain is limited.[16] Studies indicate one-half of patients prescribed opioids will receive up to 30% improvement in short-term pain intensity.[17,18] Less data are available on the long-term benefit of opioids.[19,20]

Recent statistics are emerging about harms associated with the use of prescription opioids – this includes issues of misuse, abuse, diversion, and opioid-related adverse events. Prescription opioid misuse includes taking more medication than prescribed, requesting early refills, or using opioids for a non-prescribed purpose; this may occur in up to two-thirds of patients prescribed chronic opioid therapy (COT).[8,9] More severe prescription opioid abuse, which includes concurrent illicit substance use and alcohol abuse, occurs in 10-35% of patients prescribed COT.[10,21] Concurrent use of prescription opioids and alcohol or illicit substances increases likelihood of adverse effects, including overdose, and inhibits effective pain treatment.[23]

Common adverse effects associated with opioid initiation include constipation, nausea, somnolence, and vomiting[23] and up to 50% of patients discontinue opioids due to intolerance or insufficient pain relief.[17,23] Patients maintained on COT may be exposed to additional adverse effects, including psychosocial and medical harms.[24] Opioids are associated with increased likelihood of cardiovascular events, fractures, hypogonadism, sleep-related breathing disorders, and death.[7] Unintentional overdose deaths quadrupled between 1999 and 2007, and in 16 U.S. states, more people die from prescription opioid overdose than automobile accidents.[22] The dose of opioids is a major contributing factor in adverse effects[3,4,6] and recent studies highlighted the relationship between opioid dose and elevated risk of overdose death.[2,5]

Attempts to Reduce Harms from Prescription Opioids: Empirical studies and consensus guidelines support the routine use of urine drug tests (UDT) to assess adherence and screen for prescription opioid abuse among patients prescribed COT.[25-27] The 2010 Department of Veterans Affairs Guidelines for treatment of patients prescribed COT recommend UDTs for all patients prior to initiating COT and periodic testing in stable patients. Increased frequency of UDT is recommended for patients at higher risk of abuse.[11] These recommendations were highlighted by recent reports from the VA Office of Inspector General and Under Secretary for

Health.[22]

Despite common calls for routine screening, regular UDT is uncommon. In prior research, we demonstrated that 26% of VA patients prescribed COT receive a UDT in a one year period.[21] Among patients at higher risk for prescription opioid abuse (such as patients with a substance use disorder), less than half receive UDT.[21] These data replicate findings from other settings indicating UDTs are infrequently used.[12,28-30]

Clinicians who routinely utilize UDT for all patients will encounter aberrant results in up to 40% of tests.[31] Even among patients who appear compliant with COT, approximately 20% will test positive for an illicit drug or another non-prescribed opioid.[26] These findings suggest clinicians over-estimate their ability to predict risk for prescription opioid abuse. Aberrant UDT results provide an opportunity to initiate discussions about treatment adherence and may lead to safe and appropriate changes in treatment.

Reasons for limited use of UDT in standard practice include clinician discomfort with requesting UDTs, uncertainty about what to do with results, and lack of data on the effectiveness of UDT to reduce abuse.[12,13] Beyond low rates of ordering UDTs, additional reasons for the limited utility of UDTs to reduce prescription opioid abuse include limited evidence-based treatments for patients who have aberrant UDT results.[14]

There is a need for evidence-based treatments to reduce prescription opioid abuse in primary care. Prior research has tested methods to reduce prescription opioid abuse. These include intensive specialty care services,[32,33] the Opioid Renewal Clinic (developed at Philadelphia VAMC[34]), and a multidisciplinary disease management program.[35] These studies suggest that higher intensity multidisciplinary interventions designed to reduce prescription opioid abuse are acceptable to patients and may be effective. However, these programs are costly, labor-intensive, and not feasible in busy primary care settings. Testing of pragmatic lowerintensity interventions designed for primary care and other general practice settings is urgently needed.

We propose a randomized trial of a multifaceted intervention to improve the safety of opioid prescribing. The intervention will have focus on enhancing the patient-clinician relationship, rather than placing patients and clinicians in conflict with one another about prescription opioid adherence monitoring. Primary care providers (PCPs) and PACT nurses will be randomized to the intervention, “Improving the Safety of Opioid Prescribing (ISOT)”, or the control group; patients will be nested within PCP status. All PCPs will participate in a workshop on reducing harms and misuse of prescription opioids, and maintaining open communication with patients. PCPs and PACT nurses assigned to ISOT will additionally collaborate with a nurse care manager (NCM) who will maintain a registry of enrolled patients, track UDT administrations and results, examine state Prescription Drug Monitoring Program (PDMP) data, monitor medical records, and collaborate with an internist and substance abuse specialist to provide decision support when patients demonstrate evidence of prescription opioid misuse or abuse. The NCM will also meet individually with enrolled participants to discuss strategies for reducing opioid adverse effects, preventing diversion, and providing rationale for prescription opioid adherence monitoring. Thus, the proposed treatment intervenes at the system, clinician, and patient levels.

Our intervention is informed by the PRECEDE Model of health promotion,[36] which posits that interventions likely to alter clinician behaviors and result in improved patient outcomes include three parts: predisposing (clinician education), enabling (feedback and monitoring), and reinforcing (system support) factors. Thus, the PRECEDE model indicates that system support and ongoing education or feedback is necessary to provide enabling and reinforcing components.[37]

The intervention has a focus on shared-decision making and patient-centered care. Shared-decision making has been recommended to respect patient values and improve treatment

outcomes.[38] Patient-centeredness includes taking a biopsychosocial approach, viewing the patient as an individual, sharing power and responsibility with the clinician, acknowledging the clinician is also a person, and maintaining a working alliance.[39] Clinicians are often hesitant to use UDTs, for fear of damaging the patient-clinician relationship[40] and screening for prescription opioid adherence may appear non-patient centered, particularly if framed as a mechanism to police activities or if screening is used to justify removal of prescription opioids. There are multiple mechanisms built into ISOT to support a patient-centered approach. Patient-centered interventions that have consistently resulted in improvements include the core components of effective communication, partnership, and health promotion.[41] We will test whether randomization to ISOT, which includes collaboration with a NCM, will result in improvements in patient-centeredness.

We propose a multifaceted intervention that operates at the patient, clinician, and system levels. Improving opioid safety necessitates collaboration and shared goals.[43] Collaborative interventions have been effective in treating depression,[44] severe mental illness,[45] Alzheimer's disease,[46] diabetes,[47] and other chronic diseases. We found that a collaborative care intervention improved pain, function, and depressive symptoms in veterans.[48] Where prior research focused on a disease, the proposed study is unique in that we are addressing the safety of a treatment. We will increase evaluations for adverse effects and screenings for prescription opioid adherence, including follow-up with clinicians to ensure treatment changes are enacted. These interventions will be conducted in a way that enhances trust and rapport in the clinician-patient relationship.

RESEARCH DESIGN AND METHODS

Overview: We propose a randomized trial of multifaceted intervention designed to reduce adverse effects from prescription opioids, *Improving the Safety of Opioid Prescriptions* (ISOT). PCPs and PACT nurses will be randomized to ISOT or control; patients will be nested by clinician status. All clinicians will participate in an educational workshop on reducing harms of prescription opioid therapy and communicating with patients. Clinicians assigned to ISOT will collaborate with a nurse care manager (NCM) who will maintain a registry of enrolled patients, track UDT administrations and results, query prescription drug monitoring databases, monitor other evidence of potential problems, and collaborate with expert consultants to provide decision support when patients have evidence of prescription opioid misuse or abuse. The NCMwill also have a one-time appointment with patients to discuss methods to reduce opioid adverse effects, prevent misuse and diversion, and provide rationale for prescription opioid adherence screening. The study will be conducted in the primary care clinics of the VA Portland Health Care System (VAPORHCS). A maximum of 80 PCPs, 80 PACT nurses, and 350 patientswill participate. We will randomize by clinician and patients will be nested within clinician intervention status. We will recruit participants who are currently prescribed chronic opioid therapy (defined below). Outcomes will be measured 6 and 12 months after enrollment.

Summary of the Intervention: ISOT is based on the Chronic Illness Model,[69] opioid treatment guidelines,[11,16] and recent empirical research[14,48]. It is designed to optimize approaches for prescription opioid adherence monitoring, increase and support response when patients abuse opioids, and reduce adverse effects, all within a patient-centered context. Reducing harms from prescription opioids is complex and requires a multipronged approach.[16,25,43] ISOT's effectiveness will be enhanced by intervening with patients, clinicians, and the medical system. The chronic illness model enhances productive collaboration between patients and clinicians via education and activation, information systemschanges, care management, and decision support.[69] This model has been effective in treating diverse chronic health conditions.[44-48]

Study Eligibility: **Clinicians**: All PCPs and their PACT nurse at the VAPORHCS will be eligible (~n=80 PCPs and ~n=80 nurses). In order for a PACT nurse to participate, the PCP s/he is

assigned to work with must also participate. **Patients**: All patients enrolled in primary care clinics will be potentially eligible.

Inclusion Criteria: Participants must be enrolled in primary care at the VAPORHCS and be receiving chronic opioid therapy for chronic pain unrelated to a life-limiting disease. Chronic opioid therapy is defined as receiving an opioid prescription in three consecutive months or six prescriptions in the last year with a current prescription.[20] The only other inclusion criterion is the ability to read and write in English. Exclusion Criteria: Age younger than 18 years, opioid therapy for palliative or end-of-life care, current enrollment in an opioid substitution program, or lack of telephone access. In order to identify potentially-eligible patients, we will request a waiver of informed consent, to access clinical diagnostic and pharmacy data. These data will be obtained for VA patients from the Corporate Data Warehouse, which will be accessed and analyzed within the secure user-restricted VINCI study site workspace.

Recruitment: **Clinicians:** PCPs and PACT nurses will be recruited through email, discussions at practice meetings (the PI or a member of the research team will make a presentation during a weekly staff meeting and/or during the monthly meeting for all PCPs), and direct contact by the investigators. **Patients:** We will ask participating PCPs for permission to recruit patients. Using data from the electronic medical record, we will identify patients at the VAPORHCS who potentially meet our inclusion/exclusion criteria. Consistent with the VAPORHCS's policy on recruiting participants for research studies, we will include a signed letter from the clinic manager where the patient receives his/her primary care, or director of primary care. The information sent to patients will include an accompanying letter from the research team, which will describe the study and invite patients to participate in a telephone screening session. Patients will be asked to return enclosed addressed and stamped letters, or to call our research office telephone number if interested in being screened.

During the screening telephone call, the study research assistant will provide a brief overview of the study purpose (including clear statements that participation involves research and participation does not provide clinical treatment), review inclusion/exclusion criteria, describe what participation in the study would entail, and schedule participants for a study appointment session. If the patient is interested in participating and eligible, the patient will be scheduled for a baseline assessment (participants will also receive reminder phone calls and/or letters prior totheir scheduled appointment). To enhance the likelihood of participants attending the study evaluation session, we will offer a $50 payment in compensation for time and/or travel to attend the research visit. The baseline assessment and all follow-up evaluations will be conducted either in person or via telephone.

During the telephone screening visit, if the participant is ineligible, but is interested in receiving additional clinical services, s/he will be referred to the study PI to contact for information about relevant clinical resources.

During the assessment sessions, the research assistant will provide another overview of study participation, administer informed consent and HIPAA authorization, and instruct the participant to complete study measures.

Follow-up: In addition to the baseline assessment, all participants will complete follow-up assessments every 6 months. During these research visits, participants will complete all study measures (described below). Research visits must be completed within 1 month of the scheduled follow-ups (i.e., the 6-month follow-up must be completed between 5-7 months from baseline and the 12 month follow-up must be completed between 11-13 months from baseline).

Randomization: We will randomize by PCP; patients will be assigned to intervention or control based on randomization of their PCP and PACT nurse. At the VAPORHCS, each PACT nurse is assigned to a single PCP and each PCP has one PACT nurse. Thus, contamination effects by PACT nurses working with a PCP assigned to the control condition will not be a concern.

We will randomize dyads of PCPs and PACT nurses to receive ISOT versus control. We will initially recruit PCPs to participate. Of the PCPs who choose to enroll, we will then attempt to recruit the PACT nurse who is assigned with that PCP (if the PACT nurse chooses not to participate, the consenting PCP will remain eligible). We will randomly assign consenting PCPs and their PACT nurse (if they choose to participate) to receive ISOT versus control after stratifying by PCP type of training (physician versus nurse practitioner/physician assistant) and proportion of patients in PCP's panel receiving opioid prescriptions (high vs low, based on median eligible clinician population). Using a permuted block randomization and maximizing the number of PCPs (clusters) should prevent major uneven distribution of caseload size and unmeasured confounders across the arms and increase precision.[72] The statistician will perform the randomization prior to patient recruitment. Research assistants will be blind to intervention status of patients and clinicians.

ISOT Team and Training: ISOT is a multifaceted intervention. The individual components of ISOT have been adapted from recommendations made as part of clinical practice guidelines[11,16], our preliminary studies, and prior experience in conducting multifaceted intervention studies in primary care.[48,51] The unique aspect of this intervention is its integration of different treatment recommendations into a single package. This method of treatment development and adaptation is similar to other effective multifaceted interventions.[73]

A research nurse care manager (NCM) will be hired to participate in this study. The NCM will be employed full-time. S/he will have clinical training as a registered nurse (R.N.) and have a clinical background in chronic disease management and outpatient treatment. The individual will receive extensive training in chronic pain management, prescription opioid safety, and research procedures.

ISOT Intervention Components

Clinician Education and Activation:

a. Dr. Erin Krebs (Co-Investigator) who has expertise in chronic pain treatment, screening for prescription opioid adherence, and patient-centered care, will conduct the interactive workshop for PCPs and PACT nurses. She has experience providing trainings on this topic. Workshop goals will be designed to optimize clinician interactions via education and activation, while providing system support. We will educate clinicians about prescription opioid adherence monitoring, screening for adverse effects, and enhancing patient-centered care, with a focus on enhancing shared decision making.[74,75] Clinical recommendations for modifying care in instances of opioid misuse/abuse will be based on our pilot work.[14] The workshop will include brief lecture, demonstration, and participatory skill development. The workshop will be conducted one time, during normal business hours, at the VA Portland Health Care System main campus. The session will be video-recorded. Clinicians who wish to participate in the study, but are not able to attend the in-person session, may view the recording.
b. The NCM will meet with each PCP and PACT nurse to discuss the intervention, identify attitudes about screening for prescription opioid adherence, and best practices for communicating about these topics.
c. The primary care pain specialist (Dr. Carr) and substance abuse specialist (Dr. Lovejoy) will provide consultation to Dr. Krebs in the development of the training workshop and help facilitate role-play components of the training. They will also consult with the NCM throughout

the intervention as needed.

d. The NCM will monitor medical records for all enrolled participants to examine potential opioid non-adherence behaviors (e.g., lost prescriptions, early refills, multiple providers, seeking opioids from the ER). For patients with prescription opioid abuse, the NCM will offer decision support to PCPs about treatment options. The NCM will also follow-up to ensure successful implementation of changes in the treatment plan.
e. Because there is variation in how clinicians approach preventing harms from opioids, ISOT will take a flexible approach to accommodate clinician preferences; we will collect information about PACT team preferences for communication with the intervention team and opinions on opioid prescribing and monitoring prior to initiating the study.[53] The NCM will provide feedback to each PACT team member in a manner consistent with preferences (i.e., discussion, chart note, secure email, voicemail message, etc.).
f. An email list serve (using encryption and within security firewall), managed by the PCP pain specialist and substance abuse psychologist, will be used to communicate information and facilitate dialogue among intervention clinicians. In our prior research, clinicians appreciated the opportunity to discuss (non-identifying) patient management strategies.

Patient Assessment and Activation:

a. The NCM will perform a chart review of each ISOT patient and schedule a one-time appointment.
b. With each patient, the NCM will review strategies for increasing opioid safety and discuss adverse effects of prescription opioids, including overdose, falls, interactions with other medications or alcohol/illicit substances, and opioid withdrawal. The NCM and patient will discuss treatment goals, options, and self-management approaches. Supplemental writtenmaterials will describe risks and benefits of opioids. With PCP authorization, the NCM will facilitate completion of opioid treatment agreements, as needed.
c. The NCM will talk with patients about the rationale behind screening for adherence to prescription opioids with UDTs, and focus on patient safety and risk-benefit of opioids.[76]
d. Patients will receive information about common ways in which opioids are diverted (e.g., taken by friends or family, loaning to others) and potential harms associated with diversion. Recommendations will be provided about methods for limiting opioid diversion, including details about medication take-back programs.
e. Patients will be provided with an easy-to-read brochure that describes adverse effects of opioids, methods for reducing the likelihood of adverse events, rationale for prescription opioid abuse screening, and strategies for preventing diversion.

System Assessment and Intervention:

a. The NCM will maintain a registry of all enrolled patients and track UDT administrations. For patients that have not been administered a UDT in 12 months or more, the NCM may assist the PCP by placing an order for UDT in the medical record.
b. The NCM may write the UDT order for the PCP to sign, if requested. The NCM will recommend checking state PDMP data for patients without a past-year check. (In Oregon, only prescribers are authorized to check PDMP data, so the NCM could not query the database him/herself.) PDMP checks are recorded in the medical record, so the research team will be able to track frequencies. If requested, the NCM may collaborate with pharmacy services to query state PDMP databases.
c. The NCM will provide support about methods for talking with patients about prescription opioid adherence monitoring. This will include providing written information, such as scripts that clinicians can follow. In pilot interviews, PCPs requested these types of materials to assist with improving adherence to opioid regimens.
d. The NCM will track all UDTs, notify the PCP of the results, and provide recommendations

about potential next steps in care. With collaboration from the primary care pain specialist and substance abuse specialist, the NCM will provide decision support to clinicians for patients with prescription opioid abuse about options for modifying treatment. The NCM will also follow-up to ensure treatment recommendations are implemented.

e. With input from the NCM, some patients may be referred for supplemental treatment. This may include referral to the substance abuse treatment program, mental health clinic, or specialty pain service.
f. The NCM may identify potential side effects or risky prescribing practices that have not been addressed.

Follow-up: Participants will complete assessments at baseline, 6 months, and 12 months post-baseline. During research visits, participants will complete all study measures, the structured clinical interview, and provide a UDT.

In the course of the study, a PCP or PACT nurse who is enrolled in the study may leave their position at the Portland VA. Clinical patients who are "attached" with these clinicians and already enrolled in the study will remain eligible to participate. Clinical recommendations that are made regarding patient's care will continue to be forwarded to PACT team members who remain involved in each patient's treatment.

Participants will also be reimbursed for their participation. This includes a $50 payment for each of the three research visits. This reimbursement amount is intended to cover time to complete the research visit and/or costs of travel to and from the hospital for the visit. This payment amount is consistent with other research studies of similar duration and intensity and do not appear to put undue pressure on prospective subjects to participate. The payment amount and terms of payment are specified in the consent form.

Study Measures: Research staff collecting outcome data will be blinded to participant and clinician intervention status. The ISOT intervention team will not have access to data obtained by the research team, except if a patient's safety becomes a concern.

Measures of Prescription Opioid Misuse/Abuse (*Aim 1*): The primary outcome will be responses to the Current Opioid Misuse Measure (COMM), a 17-item self-report measure that assess several constructs that place individuals at risk of opioid misuse and abuse.[80] The COMM has been well-validated[81] and previously used in treatment outcome studies. [33] The COMM has also been validated for detecting prescription opioid abuse using cut-off scores ≥ 13.[82] The Timeline Followback (TLFB; Sobell & Sobell, 1992) is a frequently used assessment method that uses calendar prompts to elicit frequency and intensity of substance use within a specific timeframe. The TLFB has demonstrated good test-retest reliability and validity for assessing multiple substances at one time (Ehrman & Robbins, 1994; Fals-Stewart et al., 2000). This study will assess use of alcohol, marijuana, methamphetamine, cocaine, heroin, opioid medications, and other prescription medications in the past 30 days. The Structured Clinical Interview for DSM-IV(SCID) will be used to assess current alcohol and substance use disorders.[83] The Overdose Risk Behavior (ORB) questionnaire is a newly-developed 14-item self-report measure that assesses behaviors and activities that place an individual at higher risk of accidental overdose to prescriptionopioids. Participants will complete Urine Drug Tests, to evaluate for the presence of substances ingested by participants. UDTs will evaluate for cannabis, cocaine, amphetamines, benzodiazepines, barbiturates, opioids, and opiates. Confirmatory testing will be conducted for all UDT screens with unexpected results. The purpose of UDT is to have confirmation of certain prescribed andillicit substances that have been ingested by study participants. Research staff will review medical record data prior to research visits to confirm medication status. Participants will be asked to validate pharmacy data aboutprescription status, as well as medications prescribed outside VA.

Measures of Opioid-Related Adverse Events (Aim 1): Prior to appointments, research staff will review medical record data for participants to track adverse effects. This includes emergency room visits, falls, and overdoses. Participants will also be queried about these effects and motor vehicle accidents at each research visit.

Processes of Care Measures (Aim 2): At the conclusion of each patient's participation, we will extract medical record data on treatment received. This will include data in the year prior to treatment and the year during treatment on number of urine drug tests administered as part of clinical care and queries to state prescription drug monitoring programs. Results from UDTs administered as part of clinical will be extracted from VA laboratory data. For PDMP data, clinicians must provide documentation in the medical record when they check PDMP data; research staff will review medical record data of enrolled participants to evaluate incidence and frequency of PDMP checks. For patients with documented prescription opioid abuse, research staff will evaluate any potential changes in care that occurred following detection of prescription opioid abuse, including referrals to the substance abuse treatment program, mental health clinic, or specialty pain service; follow-up monitoring; and treatment changes (such as change in opioid or dose, cessation of opioids, etc.).

- Although the research team will monitor UDTs administered in clinical practice, these data will not be used as outcome to reflect prescription opioid abuse. UDTs will also be administered by the research team to all participants at all three research visits. These UDTs will be ordered under a unique study identification number. Patient identifying information will never be attached to or associated with these research UDT sample.

Measures of the Clinician-Patient Relationship (Aim 2): Trust in one's clinician will be examined with the Trust in Physician Scale, an 11-item self-report measure assessing interpersonal trust in patient-clinician relationships.[84] This has been used extensively as an outcome measure in prior studies examining patient-centered care and shared decision-making, and has evidenced strong psychometric properties.[85] The Participatory Decision Making Style is a brief self-report measure designed to assess level of patient involvement in medical decision making.[86] Both of these measures have been shown to be responsive to interventions directed towards by PCPs and allied health professionals.[87] The Positive Regard Scale is a recently-developed 5-item self-report measure that evaluates patients' perceptions of their relationship with their primary care provider.

Clinician Data (Aim 2): At baseline and 12 months, PCPs and PACT nurses will be queried about barriers to screening for prescription opioid abuse. Clinicians and PACT nurses will also be asked about their satisfaction with and ways to improve ISOT, how ISOT affected their relationships with patients, and their encounters with patients prescribed opioids (see Appendix II for the questionnaire, which is based on our prior research[48]).

Measures of Pain, Function, and Quality of Life (Aim 3): The Chronic Pain Grade (CPG) will be used to assess pain intensity and function. The CPG is a commonly used and well-validated measure that provides global scores of pain intensity and function.[88,89] Quality of life will be measured with the Veterans RAND 12-Item Health Survey (VR-12),[90] a 12-item well-validated self-report measure of quality of life that is sensitive to changes in veterans and has been usedin numerous epidemiological studies. The Patient Health Questionnaire (PHQ), a brief and psychometrically valid measure, will be used to assess depressive symptoms.[91,92] The Generalized Anxiety Disorder-7 (GAD-7) Scale is a self-report measure designed to assess theseverity of anxiety symptoms, and has been validated as a robust predictor of the different anxiety disorders (Spitzer, Kroenke, & Williams, 1992; Kroenke, Spitzer, Williams, Monahan, &Lowe, 2007). Side effects from opioids will be assessed with the side effects subscale of the Pain Treatment Satisfaction Scale.[93]

Basic demographic characteristics that will be assessed include age, gender, race, ethnicity, marital status, employment, socioeconomic status, disability status, and VA service-connection.

Medical utilization data will be obtained from the medical record (e.g., physical therapy, surgery, osteopathic manipulation, acupuncture, etc.) and self-report (non-pharmacological interventions, complementary and alternative medicine approaches to pain[140]). Text data obtained from notes in the clinical record may also be reviewed, in order to conduct analyses of natural language processing. Based on pilot testing of this battery, we anticipate that all of the above questionnaires will be completed by participants in less than 60 minutes.

Data Analysis

Before analyses are conducted, data will be audited for quality, including missing data patterns and evaluation of distributions with reference to planned models. The evaluation of distributions includes the detection of outliers and checking distributions of variables to ensure they meet the assumptions of planned analyses. Power calculations (below) are based on comparisons that account for data clustering. The analyses will incorporate covariate information, in particular baseline data on age, gender, depressive symptoms, history of substance use disorder (SUD), and pain intensity, which will enhance power. Analyses will be conducted with all enrolled participants regardless of attrition (intent-to-treat).

Management of Missing Data: The pattern of missingness will be examined and baseline responses compared between those with and without missing data. Variables related to missingness will be included in the analyses which should yield valid inferences.[94] We will complete sensitivity analyses comparing the main analyses results with results from analyses with completers only and based on multiple imputation.

Aim 1: Evaluate to what extent a multifaceted intervention (ISOT) enhances prescription opioid safety. For Aim 1, we use 8.9 as an estimated standard deviation (SD) for change in COMM score from baseline to 12 months.[95] This SD estimate is based on SD's in prior intervention research.[33] For each group, an estimated SD for change was obtained using the two SD's and a within-subject intraclass correlation coefficient of 0.5. Averaging the corresponding variances leads to an estimated variance of 78 (SD=8.9). Power calculations were performed based on 28 or 32 (we may recruit as many as 40 PCPs, but do not anticipate that many will consent to participate) clinicians per intervention group and 4 or 5 patients per clinician. Table 1 displays differences in mean COMM change that can be detected under various values for the intraclass correlation coefficient. Our targeted sample size is 32 PCPs per group and an average of 5 patients per PCP. With a loss of 4 PCPs per group and 1 patient per PCP, we have power to detect small differences (able to detect < ½ SD change) in COMM score. For Aim 1, we plan to conduct analyses for self-report data (COMM), clinical interviews to assess current substance use disorders (SCID), and results from research-administered UDTs. With n=320, 28-32 PCPs per group, and 4-5 patients per PCP, we have statistical power greater than 80% to detect differences in percentages between groups of about 20% for binary outcomes from the SCID and UDT (see Table 2 below for similar calculations for Aim 2).

Table 1. Mean differences in COMM change from baseline to 12 months (80% power, α=0.05).

Intra-class correlation	Mean detectable difference in COMM change, n=4 patients per clinician, 28 clinicians per intervention	Mean detectable difference in COMM change, n=4 patients per clinician , 32 clinicians per intervention	Mean detectable difference in COMM change, n=5 patients per clinician, 28 clinicians per intervention	Mean detectable difference in COMM change, n=5 patients per clinician, 32 clinicians per intervention
0	3.4	3.2	3.0	2.8
0.02	3.5	3.3	3.2	2.9
0.04	3.6	3.4	3.3	3.1
0.10	3.9	3.6	3.6	3.4

Analyses for Aim 1: For comparison of mean COMM change between groups, we will use mixed longitudinal models with a random effect for PCP and patient, to allow for correlation between

observations on different patients of the same PCP and for repeat observations on the same patient. Transformations of the outcome will be applied to meet distributional assumptions. In linear mixed models, we will include baseline measures of patient age, sex, depressive symptoms, history of SUD, and pain severity as covariates. We will also adjust for baseline COMM score and the stratification variables: PCP training type (MD/DO vs NP or PA) and proportion of clinician panel prescribed opioids (high vs low). In addition to testing formal hypotheses, we will report 95% confidence intervals for the differences in mean outcomes between groups at 6 and 12 months. For comparing the percentages classified as abusing opioids at any time during follow-up (combining information from 6 and 12 months) based on SCID and UDT, we will use generalized-linear mixed models (or GEE as needed) to incorporate correlation between patients of the same PCP. We will adjust for baseline measures of the outcome along with the covariates listed above. We will report group comparisons on all three primary outcomes (COMM, SCID, and UDT). Assuming 15% of the sample has current SUD (consistent with other research), we will not conduct interaction analyses, but will present descriptive information for each outcome (COMM, SCID, UDT) on treatment outcomes by SUD status.

Data on opioid-related adverse events will be obtained from the medical record and participant self-report. We will collect data on opioid overdoses, falls, motor vehicle accidents, and ER visits related to pain. Descriptive information on opioid-related events will be provided for each group (numbers and percentages of participants with each event). Because the number of adverse events is expected to be small, we will use Fisher's Exact test to compare adverse event percentages between groups. We will compare both percentages for each individual type of event as well as percentages of individuals experiencing any adverse event between groups.

Aim 2: Assess to what extent assignment to ISOT impacts pain treatment-related processes of care. The power for comparing the percentage of patients receiving at least one UDT (Table 2) during the follow-up period assumes that 40% of patients in the control group will receive a follow-up UDT.[21] This is based on prior research in which 26% of patients had a UDT and our expectation that the percentage will be higher in the control group after clinicians participate in the workshop. We hypothesize that clinicians randomized to ISOT will have much higher rates of administering UDTs. Regarding checks to state PDMPs, currently 3-5% of VAPORHCS patients receive a query. The ISOT protocol prompts the clinician to conduct PDMP queries and we expect dramatic differences in percentages between the two intervention groups. We have 80% power to detect differences of 17-21% on binary outcomes. Here we expect differences to be much greater.

Table 2. Urine drug test percentage in the intervention group that can be detected (80% power, α=0.05) *compared to a usual care percentage of 40%*.

Intra-class correlation	Urine drug test % that can be detected in the intervention group, n=4 patients per clinician, 28 clinicians per intervention	Urine drug test % that can be detected in the intervention group, n=4 patients per clinician, 32 clinicians per intervention	Urine drug test % that can be detected in the intervention group, n=5 patients per clinician, 28 clinicians per intervention	Urine drug test % test that can be detected in the intervention group, n=5 patients per clinician, 32 clinicians per intervention
0	59%	57%	57%	56%
0.02	59%	58%	57%	56%
0.04	60%	58%	58%	57%
0.10	61%	60%	60%	58%

Aim 2: Assess to what extent assignment to ISOT impacts the quality of the clinician-patient relationship. Using estimated standard deviations of 14.2 for the Trust in Physician Scale[84] and

28.9 for the Participatory Decision Making Style,[86] we have 80% power at level 0.05 to detect mean differences between groups at 12 months of 4.7 to 5.6 and 9.6 to 11.3, respectively, using 28 to 32 clinicians per intervention group, 4 to 5 patients per clinician, and assuming an intraclass correlation of 0.02. If we focus on change from baseline, the power for comparisons at each follow-up time-point would be greater, provided the correlations between baseline and follow-up are greater than 0.5.

Clinicians will also be queried about perceived barriers and potential effectiveness of screening for prescription opioid abuse. With 32 pairs of clinicians and intra-class correlations of 0 to 0.1, we would have 80% power to detect differences of 0.50 to 0.53 SDs in mean summary scores between intervention groups.

Analyses for Aim 2: We will use GEE methods to compare between intervention groups the average numbers of clinical care documentations, UDT's, and queries to state prescription drug monitoring programs while adjusting for the baseline covariates (age, gender, depressive symptoms, history of SUD, and pain intensity) and the stratification variables. For patient level data, the approach for analysis of Aim 2 outcomes will be the same as that for Aim 1, using mixed models and/or GEE for comparisons, while adjusting for baseline covariates (age, sex, depressive symptoms, history of SUD, and pain severity), baseline measure of the outcome, and stratification variables (training type, proportion of panel prescribed opioids). Analyses will be conducted for scores on the Trust in Physician scale and Participatory Decision Making Style.

For clinician and PACT nurse data on barriers to use of UDTs, we will report descriptive information for each of the 10 questions. For each group and question, we will report the percentage of clinicians with scores at each of the five levels at baseline and follow-up, as well as the corresponding descriptive change information in follow-up scores. We will report the mean (and SD, min, max) of change for each question. We will obtain an overall survey score, by averaging the 10 question scores for each clinician and report the mean (and SD, min, max) survey score for each group at baseline and follow-up, along with the mean change (and SD, min, max) in survey score. We will use linear mixed models on the change scores to compare groups, while adjusting for clinician age, clinician training type, sex, panel size, summary survey score at baseline, and stratification variables. We will include a random pair effect to allow for correlation between the PCP and PACT nurse within each pair. P-values and 95% confidence intervals for the differences between groups in change scores will be provided. Similar analyses will be conducted for examining survey data on clinician satisfaction with ISOT.

Aim 3: Explore to what extent ISOT is associated with changes in pain intensity, function, quality of life, and depressive symptoms. Our goal is to improve opioid safety while not adversely impacting pain or quality of life. Power calculations were performed for pain intensity based on 28 or 32 clinicians per intervention group and 4-5 patients per clinician, using data indicating a baseline mean pain intensity score of 66 and estimated SD of change from baseline of 13.1.[48] Here we are interested in tests of non-inferiority; specifically we aim to show that the reduction in mean pain intensity for the ISOT group is no more than one-half standard deviation less than that for the control group. Considering the same set of conditions given in Tables 1-2, the worst case scenario (n=4 patients per clinician, n=28 clinicians per intervention and intraclass correlation of 0.10), results in power greater than 80% at level 0.025 for testing non-inferiority of pain intensity if the true mean change for ISOT patients is not more than 0.9 units less than the control group. Similarly for change in pain-related function, quality of life, and depressive symptoms, we considered a one-half SD difference in change to be the appropriate non-inferiority limit.[96,97] We have power greater than 80% at level 0.025 for testing non-inferiority, if the mean change in function, quality of life, and depressive symptoms for the ISOT group are no more than 1.8, 0.9, and 0.4 units, respectively, less than those for the control group. These are based on estimated SD's for change assuming a 0.5 correlation between baseline and follow-

up.

Analyses for Aim 3: For analysis of pain intensity, we hypothesize that the mean reduction in pain (measured by CPG pain intensity scale) for patients randomized to ISOT is no more than 6.6 points less than the control. Although we will conduct a formal test of this non-inferiority hypothesis, our primary goal is to estimate the difference in mean reductions between the groups at each time-point, anticipating that the differences will be small. Construction of a lower bound (97.5%) corresponds specifically to the non-inferiority hypothesis of interest, but we will also obtain the corresponding (97.5%) upper bound. As with comparison of continuous outcomes for the other aims, mixed models will be used for hypothesis testing and confidence interval construction and we will adjust for covariates measured at baseline (patient age, sex, depressive symptoms, history of SUD, and pain severity), stratification variables, and baseline score. We will use the same approach to examine potential differences between groups on measures of pain-related function, quality of life, and depressive symptoms.

REFERENCES

1. Kuehn BM. Opioid prescriptions soar: Increase in legitimate use as well as abuse. JAMA. 2007;297:249-251.
2. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305:1315-1321.
3. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med. 2010;170:1425-1432.
4. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: A cohort study. Ann Intern Med. 2010;152:85-92.
5. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171:686-691.
6. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010;25:310-315.
7. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170:1968-1976.
8. Meltzer EC, Rybin D, Meshesha LZ, et al. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug use disorder. Pain Med. 2012;13:1436-1443.
9. Morasco BJ, Dobscha SK. Prescription medication misuse and substance use disorder in VA primary care patients with chronic pain. Gen Hosp Psychiatry. 2008;30:93-99.
10. Morasco BJ, Gritzner S, Lewis L, Oldham R, Turk DC, Dobscha SK. Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. Pain. 2011;152:488-497.
11. Department of Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. . 2010. Accessed 4/1/11.
12. Starrels JL, Becker WC, Alford DP, Kapoor A, Williams AR, Turner BJ. Systematic review: Treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. Ann Intern Med. 2010;152:712-720.
13. Bair MJ, Krebs EE. Why is urine drug testing not used more often in practice? Pain Pract. 2010;10:493-496.
14. Morasco BJ, Krebs EE, Cavanagh R, Hyde S, Crain A, Dobscha SK. Treatment changes following aberrant urine drug test results for patients prescribed chronic opioid therapy. J Opioid Manage, In press.
15. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. 2011.
16. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113-130.
17. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain. 2004;112:372-380.
18. Machado LA, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Analgesic effects of treatments for non-specific low back pain: A meta-analysis of placebo-controlled randomized trials. Rheumatology 2009;48:520-527.
19. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med. 2007;146:116-127.

20. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008;24:521-527.
21. Morasco BJ, Duckart JP, Dobscha SK. Adherence to clinical guidelines for opioid therapy for chronic pain in patients with substance use disorder. J Gen Intern Med. 2011;26:965-971.
22. The Department of Veterans Affairs, Office of Inspector General (OIG). Healthcare Inspection – VA Patterns of Dispensing Take-Home Opioids and Monitoring Patients on Opioid Therapy (Report NO 14-00895-163).
23. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. CMAJ. 2006;174:1589-1594.
24. Sullivan MD, Von Korff M, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. Pain. 2010;149:345-353.
25. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: Prediction and identification of aberrant drug-related behaviors: A review of the evidence for an American pain society and American academy of pain medicine clinical practice guideline. J Pain. 2009;10:131-146.
26. Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg. 2003;97:1097-102, table of contents.
27. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med. 2003;349:1943-1953.
28. Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA. Opioids and the treatment of chronic pain in a primary care sample. J Pain Symptom Manage. 2001;22:791-796.
29. Bhamb B, Brown D, Hariharan J, Anderson J, Balousek S, Fleming MF. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. Curr Med Res Opin. 2006;22:1859-1865.
30. Boulanger A, Clark AJ, Squire P, Cui E, Horbay GL. Chronic pain in Canada: Have we improved our management of chronic noncancer pain? Pain Res Manag. 2007;12:39-47.
31. Michna E, Jamison RN, Pham LD, et al. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. Clin J Pain. 2007;23:173-179.
32. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: A randomized trial. Pain. 2010;150:390-400.
33. Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM, Howard MO. Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: Results from an early-stage randomized controlled trial. J Consult Clin Psychol 2014;82:448-459.
34. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: A primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. Pain Med. 2007;8:573-584.
35. Chelminski PR, Ives TJ, Felix KM, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. BMC Health Serv Res. 2005;5:3.
36. Green L, Kreuter M, Deeds S, et al. Health education planning: A diagnostic approach. Am Demogr. 1980;2:100-129.
37. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA.

1995;274:700-705.
38. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: What does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44:681-692.
39. Mead N, Bower P. Patient-centeredness: A conceptual framework and review of the empirical literature. Soc Sci Med. 2000;51:1087-1110.
40. Matthias MS, Krebs EE, Collins LA, Bergman AA, Coffing J, Bair MJ. "I'm not abusing or anything": Patient-physician communication about opioid treatment in chronic pain. Patient Educ Couns. 2013;93:197-202.
41. *Constand MK, MacDermid JC, Bello-Haas VD, Law M. Scoping review of patient-centered care approaches in healthcare. BMC Health Services Res 2014;14:271.*
42. *Argoff CE, Viscusi ER. The use of opioid analgesics for chronic pain: Minimizing the risk for harm. Am J Gastroenterol 2014;10:3-8.*
43. Ballantyne JC. "Safe and effective when used as directed": The case of chronic use of opioid analgesics. J Med Toxicol. 2012;8:417-423.
44. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: A cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med. 2006;166:2314-2321.
45. Reilly S, Planner C, Gask L, et al. Collaborative care approaches for people with severe mental illness. Cochrane Database Syst Rev. 2013;11:CD009531.
46. Callahan CM, Boustani MA, Unverzagt FW, et al. Effectiveness of collaborative care for older adults with Alzheimer's disease in primary care: A randomized controlled trial. JAMA. 2006;295:2148-2157.
47. Katon WJ, Von Korff M, Lin EH, et al. The pathways study: A randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry. 2004;61:1042-1049.
48. Dobscha SK, Corson K, Perrin NA, et al. Collaborative care for chronic pain in primary care: A cluster randomized trial. JAMA. 2009;301:1242-1252.
49. Morasco BJ, Turk DC, Donovan DM, Dobscha SK. Risk for prescription opioid misuse among patients with a history of substance use disorder. Drug Alcohol Depend. 2013;127:193-199.
50. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA. 2012;307:940-947.
51. Dobscha SK, Corson K, Hickam DH, Perrin NA, Kraemer DF, Gerrity MS. Depression decision support in primary care: A cluster randomized trial. Ann Intern Med. 2006;145:477-487.
52. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. J Pain. 2011;12:964-973.
53. Dobscha SK, Leibowitz RQ, Flores JA, Doak M, Gerrity MS. Primary care provider preferences for working with a collaborative support team. Implement Sci. 2007;2:16.
54. Dobscha SK, Snyder KM, Corson K, Ganzini L. Psychiatry resident graduate comfort with general medical issues: Impact of an integrated psychiatry-primary medical care training track. Acad Psychiatry. 2005;29:448-451.
55. Bergman AA, Matthias MS, Coffing JM, Krebs EE. Contrasting tensions between patients and PCPs in chronic pain management: A qualitative study. Pain Med. 2013;14:1689-1697.
56. Flickinger TE, Saha S, Moore RD, Beach MC. Higher quality communication and relationships are associated with improved patient engagement in HIV care. J Acquir Immune Defic Syndr. 2013;63:362-366.

57. Saha S, Beach MC. The impact of patient-centered communication on patients' decision making and evaluations of physicians: A randomized study using video vignettes. Patient Educ Couns. 2011;84(3):386-392.
58. Hsu I, Saha S, Korthuis PT, et al. Providing support to patients in emotional encounters: A new perspective on missed empathic opportunities. Patient Educ Couns. 2012;88:436-442.
59. Ray MK, Beach MC, Nicolaidis C, Choi D, Saha S, Korthuis PT. Patient and provider comfort discussing substance use. Fam Med. 2013;45:109-117.
60. Corson K, Doak MN, Denneson L, et al. Primary care clinician adherence to guidelines for the management of chronic musculoskeletal pain: Results from the study of the effectiveness of a collaborative approach to pain. Pain Med. 2011;12:1490-1501.
61. Krebs EE, Ramsey DC, Miloshoff JM, Bair MJ. Primary care monitoring of long-term opioid therapy among veterans with chronic pain. Pain Med. 2011;12:740-746.
62. Morasco BJ, Cavanagh R, Gritzner S, Dobscha SK. Care management practices for chronic pain in veterans prescribed high doses of opioid medications. Fam Pract. 2013;30:671-678.
63. Saha S, Jacobs EA, Moore RD, Beach MC. Trust in physicians and racial disparities in HIV care. AIDS Patient Care STDS. 2010;24:415-420.
64. Kumar R, Korthuis PT, Saha S, et al. Decision-making role preferences among patients with HIV: Associations with patient and provider characteristics and communication behaviors. J Gen Intern Med. 2010;25:517-523.
65. Korthuis PT, Saha S, Chander G, et al. Substance use and the quality of patient-provider communication in HIV clinics. AIDS Behav. 2011;15:832-841.
66. Dobscha SK, Corson K, Flores JA, Tansill EC, Gerrity MS. Veterans affairs primary care clinicians' attitudes toward chronic pain and correlates of opioid prescribing rates. Pain Med. 2008;9:564-571.
67. Morasco BJ, Corson K, Turk DC, Dobscha SK. Association between substance use disorder status and pain-related function following 12 months of treatment in primary care patients with musculoskeletal pain. J Pain. 2011;12:352-359.
68. Krebs EE, Lurie JD, Fanciullo G, et al. Predictors of long-term opioid use among patients with painful lumbar spine conditions. J Pain. 2010;11:44-52.
69. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288:1775-1779.
70. Weimer MB, Macey TA, Nicolaidis C, Dobscha SK, Duckart JP, Morasco BJ. Sex differences in the medical care of VA patients with chronic non-cancer pain. Pain Med. 2013;14:1839-1847.
71. Dietrich AJ, Oxman TE, Williams JW, Jr, et al. Re-engineering systems for the treatment of depression in primary care: Cluster randomised controlled trial. BMJ. 2004;329:602.
72. Donner A, Klar N. Statistical considerations in the design and analysis of community intervention trials. J Clin Epidemiol. 1996;49:435-439.
73. Unutzer J, et al. IMPACT: Late Life Depression Treatment Manual for Collaborative Depression Management. UCLA Center for Health Services Research 2004.
74. Sullivan MD, Leigh J, Gaster B. Brief report: Training internists in shared decision making about chronic opioid treatment for noncancer pain. J Gen Intern Med. 2006;21:360-362.
75. Sullivan MD, Gaster B, Russo J, et al. Randomized trial of web-based training about opioid therapy for chronic pain. Clin J Pain. 2010;26:512-517.
76. Nicolaidis C. Police officer, deal-maker, or health care provider? Moving to a patient-centered framework for chronic opioid management. Pain Med. 2011;12:890-897.

77. McKenzie M, Tulsky JP, Long HL, Chesney M, Moss A. Tracking and follow-up of marginalized populations: A review. J Health Care Poor Underserved. 1999;10:409-429.
78. Twitchell GR, Hertzog CA, Klein JL, Schuckit MA. The anatomy of a follow-up. Br J Addict. 1992;87:1327-1333.
79. Hunt JR, White E. Retaining and tracking cohort study members. Epidemiol Rev. 1998;20:57-70.
80. Butler SF, Budman SH, Fernandez Houle B, Benoit C, Katz N, Jamison RN. Development and validation of the Current Opioid Misuse Measure. Pain 2007;130:144-156.
81. Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross-validation of the Current Opioid Misuse Measure to monitor chronic pain patients on opioid therapy. Clin J Pain 2010;26:770-776.
82. Meltzer EC, Rybin D, Saitz R, Samet JH, Schwartz SL, Butler SF, Liebschutz JM. Identifying prescription opioid use disorder in primary care: Diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011;152:397-402.
83. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for the DSM-IV-TR axis I disorders, research version, non-patient edition. (SCID-I/NP).. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
84. Anderson LA, Dedrick RF. Development of the trust in physician scale: A measure to assess interpersonal trust in patient-physician relationships. Psychol Rep. 1990;67:1091-1100.
85. Thom DH, Ribisl KM, Stewart AL, Luke DA. Further validation and reliability testing of the trust in physician scale. the Stanford trust study physicians. Med Care. 1999;37:510-517.
86. Heisler M, Bouknight RR, Hayward RA, Smith DM, Kerr EA. The relative importance of physician communication, participatory decision making, and patient understanding in diabetes self-management. J Gen Intern Med. 2002;17:243-252.
87. Bodenheimer T, Laing BY. The teamlet model of primary care. Annals Fam Med 2007;5:457-461.
88. Smith BH, Penny KI, Purves AM, et al. The chronic pain grade questionnaire: Validation and reliability in postal research. Pain. 1997;71:141-147.
89. Elliott AM, Smith BH, Smith WC, Chambers WA. Changes in chronic pain severity over time: The chronic pain grade as a valid measure. Pain. 2000;88(3):303-308.
90. Selim, A. J., Rogers, W., Fleishman, J. A., Qian, S. X., Fincke, B. G., Rothendler, J. A., & Kazis, L. E. (2009). Updated US population standard for the Veterans RAND 12-item Health Survey (VR-12). *Quality of Life Research*, *18*(1), 43-52.
91. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary care evaluation of mental disorders. Patient Health Questionnaire. JAMA. 1999;282:1737-1744.
92. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-613.
93. Evans CJ, Trudeau E, Mertzanis P, et al. Development and validation of the pain treatment satisfaction scale (PTSS): A patient satisfaction questionnaire for use in patients with chronic or acute pain. Pain. 2004;112:254-266.
94. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of depression collaborative research program dataset. Arch Gen Psychiatry. 1993;50:739-750.
95. Buelow AK, Haggard R, Gatchel RJ. Additional validation of the pain medication questionnaire in a heterogeneous sample of chronic pain patients. Pain Pract.

2009;9(6):428-434.
96. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146:238-244.
97. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care. 2003;41:582-592.

Ehrman RN, Robbins SJ. Reliability and validity of 6-month timeline reports of cocaine and heroin use in a methadone population. Journal of Consulting and Clinical Psychology 1994; 62:843-850.

Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. Journal of Consulting and Clinical Psychology 2000; 68:134-144.

Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Lowe B. Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. Ann Int Med 2007;146:317-325.

Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In RZ Litton, JP Allen (Eds.), *Measuring alcohol consumption: Psychosocial and biochemical methods* (pp. 41-42). New Jersey: Human Press, 1992.

Spitzer RL, Kroenke K, Williams JBW. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA 1999;282:1737-1744.