Communication and Activation in Pain to Enhance Relationships and Treat Pain with Equity (COOPERATE)

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Statistical Analysis Plan

D7. STATISTICAL CONSIDERATIONS

D7a. Sample size and power. Our sample size is calculated based on estimated differences of intervention effects between the intervention and control arms on the primary outcome, patient activation (PAM), which is a continuous measure. In Dr. Matthias' pilot study with Veterans with chronic pain,[82] we found a pre-treatment PAM score of 41.22 (std dev = 5.69) and a post-treatment score of 44.0 (std dev = 5.58), which represents a .49 standard deviation change in patient activation (d = .49) in response to a peer intervention for chronic pain. To be conservative, we are powering COOPERATE on a medium effect size of .40. To detect a .40 effect size based on a two-sample independent t-test with type I error =.05 and 80% power, 100 patients per group (N = 200) are required. Although our prior pain studies have had low attrition rates (<15%), we will conservatively plan for an attrition rate of 20%, which requires N = 250 (200/.80), or 125 patients per group. For secondary outcomes of COOPERATE, we estimated standardized effect sizes (difference in mean change from baseline between treatment groups divided by the pooled SD at baseline) for pain (BPI total) and anxiety (GAD-7) to be .69 and .40, respectively – these estimates were based on data from the SCAMP trial which involved phone-delivered pain self-management.[93] In COOPERATE, with a similarly delivered behavioral intervention and a sample size of 100 patients per arm, we will have 98.8% and 59.1% power to detect effect sizes of this magnitude for BPI total and GAD-7 based on a two-sample independent t-test with type I error set at .01 (assuming 5 clinical outcomes adjusted for multiple comparisons with a Šídák adjustment), which provides similar power to our contrast of interest from the linear mixed model. For other secondary outcomes (communication self-efficacy, depression, and pain coping), with a sample size of 200, we have 82.4% power to detect medium effect sizes (.50 SD difference), even after adjusting for multiple comparisons.

D7b. Randomization. Participants will be randomly assigned to one of the two study arms using random numbers generated by our statistician, Dr. Daggy. Randomization with block sizes of 4 and 8 will be executed to ensure balance.

D7c. Data Analysis: Baseline Comparability. Because of the size of this study, we expect randomization will produce intervention and control groups that are comparable and balanced. However, we will tabulate baseline characteristics of participants and assess for potential imbalance in variables such as demographics, patient activation, communication self-efficacy, and pain severity between study arms. Continuous variables will be assessed with summary statistics (means, standard deviation, range, etc.). Frequency distributions will be calculated for categorical data. Appropriate tests, such as t-tests and chi-square, will be performed to determine whether there are differences between the two groups on these potential baseline covariates and, if so, these variables will be included in subsequent analyses. In all statistical analyses described below, we will employ an intent-to-treat (ITT) analysis.

D7d. Missing Data. We conservatively anticipate 20% attrition, which is reflected in our sample size. We will compare patient demographics between those who withdraw and those who participate to determine any discriminating characteristics. The proposed mixed model is appropriate if data are missing completely at random or missing at random. If data are missing not at random, we will use appropriate models (i.e., selection models,[94] pattern mixture models[95]) to account for the missing data mechanism.

D7e. Data Analysis for Aim 1: **Test effects of COOPERATE on key Veteran outcomes:** patient activation (primary outcome), communication self-efficacy, pain intensity/interference, and psychological functioning.

All outcomes will be collected at baseline, 3, 6, and 9 months. A linear mixed-model repeated measures approach will be used to test the hypothesis in Aim 1 that COOPERATE will improve the primary outcome of patient activation (PAM) compared to the control condition at the 3-month time point. Fixed effects will include treatment, time (as categorical), and treatment X time interaction. We will examine the associations among the repeated measures within subjects and determine the appropriate variance-covariance structure. Our primary contrast of interest will be the group difference in change from baseline at the 3-month time point. Group differences in change from baseline at other time points (6-month and 9-month) will also be estimated. Covariates found to significantly differ between treatment and control groups at baseline will be included in the models. All analyses will include checking of assumptions and model fit. Working alliance, which is a key indicator of the quality of the patient-provider relationship, will serve as a baseline covariate in all models. Other potential covariates include physical and psychological comorbidities, patient-provider race and gender concordance, and patient-provider relationship length. Since patient activation and number of provider visits could influence one another, we will use number of visits during the prior year as a baseline covariate (if imbalanced between study arms), and will run a sensitivity analysis in which we re-run the final models for primary and secondary outcomes while adjusting for number of visits during the intervention period. Additionally, adherence to the intervention as measured by the number of sessions attended will be assessed for its dose-response effects on the primary and secondary outcomes.

Secondary outcomes of communication self-efficacy, total BPI (as well as BPI subscales: pain intensity and pain interference), and psychological functioning (depression, anxiety, and coping), will all be analyzed with the same mixed model approach as for the primary outcome. Because there are a number of secondary outcomes in Aim 1, we will use the Šídák method to adjust for multiple comparisons.

Communication and Activation in Pain to Enhance Relationships and Treat Pain with Equity (COOPERATE)

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Table of Contents:

1.0 Background

Chronic pain affects 40-70% of Veterans and amounts to over $600 billion/year in direct medical costs and lost worker productivity. Racial disparities in pain treatment have been extensively documented. Minority patients, including Veterans, are more likely to be undertreated for pain. Minority Veterans have pain documented less frequently, undergo more urine drug tests, and are more likely to be referred for substance abuse evaluation than White Veterans. Compounding these pain care disparities, minority Veterans exhibit lower levels of patient activation than Whites. Patient activation—having knowledge, confidence, and skills to manage health—is associated with better health experiences, self-management, and outcomes. Low activation is frequently manifested in poorer communication among minority patients. Minority patients are less likely to share their concerns with providers, ask questions, and prepare for their clinic visits. This poor communication is associated with lower quality care, poorer patient-provider relationships, and treatment non-adherence. The poorer communication experienced by minorities is exacerbated by the documented difficulties in patient-provider communication about chronic pain and its treatment—particularly where opioids are concerned.

2.0 Rationale and Specific Aims

COOPERATE focuses on two important, yet frequently neglected, areas for improvement in minority health: patient activation and communication. This is especially important in chronic pain care, since numerous treatment options with a wide range of risks and benefits exist, and since minorities are offered fewer of these pain treatment options. Helping minority Veterans to become more active in their care is critical for improving chronic pain care. This is especially important in light of VA efforts such as the Opioid Safety Initiative, designed to improve safety for Veterans, but which also require engaged, active patients as Veterans must explore alternative pain treatments with their providers—treatments that are feasible for Veterans' individual lifestyles and consistent with their symptom priorities and treatment goals.

COOPERATE (Communication and Activation in Pain to Enhance Relationships and Treat Pain with Equity) is a pragmatic randomized controlled trial of an intervention to improve patient activation and communication with providers for Black Veterans with chronic pain. COOPERATE focuses on 2 essential skill sets necessary to facilitate effective patient activation: 1) goal-setting and prioritization, and 2) communication skills. COOPERATE is delivered over the telephone in 6 sessions (4 weekly sessions followed by 2 booster session) over a period of 12 weeks. The primary study outcome is patient activation.

COOPERATE's specific aims are as follows:

Aim 1: (primary aim). Test the effects of COOPERATE on key Veteran outcomes. We hypothesize that at 3 months (primary end point), 6 months, and 9 months (sustained effects) from baseline, Black Veterans randomized to the COOPERATE intervention will report greater:

a) increases in patient activation (primary outcome),

b) increases in communication self-efficacy,
c) improvements in pain intensity and interference,
d) improvements in psychological functioning.

***Aim 2*: Examine mediating and moderating effects in COOPERATE.** *We hypothesize that*
a) patient activation will mediate the effect of COOPERATE on clinical outcomes (pain and psychological functioning), and
b) working alliance will moderate the effect of COOPERATE on patient activation.

Aim 3: (pre-implementation aim). Understand facilitators and barriers to implementing COOPERATE. Using the RE-AIM framework, we will conduct qualitative interviews with a purposefully selected subsample of intervention Veterans and with clinicians to better prepare for implementing COOPERATE.

3.0 Inclusion/Exclusion Criteria

Participants will include 250 Black Veterans who are receiving medical care from the Veterans Health Administration.

Eligible patients must:
1) be Black or African American;
2) have musculoskeletal pain in the low back, cervical spine, or extremities (hip, knee, shoulder) for greater than 3 months.

Patients will be excluded if electronic medical records indicate:
1) a psychotic disorder diagnosis
2) current substance use disorder
3) severe medical conditions precluding participation (e.g., NY Heart Association Class III or IV heart failure), or if the eligibility screener reveals
4) active suicidal ideation
5) severe hearing/speech impairment

4.0 Enrollment/Randomization

Enrollment
Our center's data management group will run a query in CPRS (Computerized Patient Record System) to identify potentially eligible patients, who will be recruited from 9 clinics: Roudebush VAMC's 5 primary care clinics, the Indy West Clinic, and the 3 Community-Based Outpatient Clinics (CBOCs) at Bloomington, Martinsville, and Terre Haute. Black Veterans with musculoskeletal pain will be identified. We will use ICD-10 codes from our prior work to identify these conditions.

Alternatively, using Corporate Data Warehouse (CDW), we will identify potentially eligible patients from the 9 clinics: Roudebush VAMC's 5 primary care clinics, the Indy West Clinic and the 3 Community-Based Outpatient Clinics (CBOCs) at Bloomington, Martinsville, and Terre Haute. Black Veterans with musculoskeletal pain will be

identified. We will use ICD-10 codes from our prior work to identify these conditions. The Corporate Data Warehouse is located on VINCI servers and will accessed using the DART request process.

This list of potential participants will be updated monthly during the enrollment period, and a recruitment letter, describing the study will be mailed to qualifying Veterans. Potential participants will be contacted by phone within a week after mailing the letter to assess eligibility (including confirmation of musculoskeletal pain and race) and determine their interest in participating. If the Veteran is eligible and interested, an appointment will be scheduled at the Roudebush VAMC to obtain a signed informed consent statement and HIPAA authorization or the consent will take place by phone and the consent forms will be mailed. Backup recruitment methods include 1) giving Veterans opportunities to self-refer by responding to study advertisements placed in hospital elevators and clinics, and 2) contacting potential participants in clinics by cross-referencing the CPRS list with the weekly appointment roster for each participating VA provider.

Due to the COVID-19 pandemic, if the Veteran is unable to consent in-person they will be mailed an ICF and allowed time to review it. COOPERATE research staff will follow-up with each Veteran to answer questions about the ICF and get verbal consent to participate in the study. Once the COVID-19 social distancing/quarantine procedures are lifted, we will return to normal in-person consenting procedures with written signatures.

For clinicians, COOPERATE research staff will present the study at regularly scheduled clinic meetings. Clinicians in attendance will be provided an Interest in Participation slip to indicate, via checkbox, whether they are or are not interested in participating. Those not interested in participating will be removed from the recruitment list. The research team will then email the Study Information Sheet to all clinicians interested in participating and those not present at the clinic meeting. The research team will respond to incoming emails and/or follow-up in person accordingly. Clinicians choosing to participate in the study will be scheduled for interviews at the Roudebush VAMC, at which time the research team will review the Study Information Sheet and ask for questions or concerns and offer a paper copy or additional email copy prior to participation.

Randomization

Participants will be randomly assigned to one of the two study arms using random numbers generated by our statistician. Randomization with block sizes of 4 and 8 will be executed to ensure balance.

5.0 Study Procedures

Intervention

Veterans randomized to the intervention will participate in the COOPERATE intervention. The intervention consists of 6 total sessions delivered individually over 12 weeks: 4 sessions focused on teaching skills related to goal clarification/prioritization and

communication (approximately 30-minutes each), delivered weekly for the first 4 weeks, plus 2 booster sessions (approximately 20-25 minutes each) delivered once per month for the next 2 months. All intervention sessions will be delivered by study team "coaches" via phone, audio-recorded, and a random subset reviewed for fidelity and quality. Coaches will be trained and supervised by Dr. Matthias and co-investigators. Coach adherence checklists completed by trained study staff will be used. During regular supervision meetings, adherence and fidelity will be discussed. Role-play will be used to reinforce and correct deviations from study procedures.

Attention Control

Veterans randomized to the control group will receive phone calls on the same schedule as intervention Veterans. During these phone calls, study staff will ask Veterans a series of questions about their pain, self-management activities, and any changes they have experienced since the last call. These phone calls are designed to control for attention only, and Veterans will not be offered specific information or advice about their pain or its management (with the exception of suggesting a doctor visit if warranted).

Qualitative Interviews

Veterans

A subset of intervention patients will be selected for a qualitative interview at 6 months to better understand patient experiences with the intervention, including barriers, facilitators, and other factors that might affect implementation of COOPERATE. Veterans will be purposefully sampled using maximum variation sampling, a qualitative sampling strategy to obtain the broadest range of perspectives, purposefully challenging investigators' preconceived understandings of the phenomenon under study and thus helping to elucidate the diversity of participants' experiences.

Clinicians

Up to 35 clinicians who work with patients with chronic pain (e.g., psychologists, primary care physicians, rehabilitation physicians, nurses, physical therapists) will also participate in interviews. Questions directed toward clinicians will focus on institutional implementation, including facilitators and barriers to adoption of COOPERATE ("adoption"), challenges to delivering this intervention with fidelity ("implementation"), and the ability to sustain such a program within either primary care or the chronic pain clinic ("maintenance"). Interviews will take approximately 30-45 minutes.

All interviews will be one-on-one, face-to-face, and will take place in a private room in RVAMC. They will be conducted by research study staff, who have training and experience conducting qualitative interviews for Dr. Matthias. Interviews will be audio-recorded, transcribed, and checked for accuracy.

During the COVID-19 crisis, qualitative interviews will be conducted over the phone.

Data Collection

The Data Manager will create and maintain all databases. To ensure quality, data will be entered by the RA and checked by another study team member. For qualitative data, transcribed interviews will be checked for accuracy, de-identified, and entered into NVivo. Each patient will be assigned a unique study ID number, and all data will be

entered into a password-protected database behind the VA firewall using these ID numbers.

Participant Payments
Participants will be paid $40 for each assessment completed (baseline, 3 months, 6 months, and 9 months), for a total of $160 per participant. Clinicians will not be compensated.

Due to a policy change in the VA Research and Development department regarding purchasing incentives, we are increasing the incentive from $40 to $50, which is a nominal increase of $10. This is only for 3M, 6M and 9M assessments, as all the BL assessments have been completed as of 10/25/21.

Timeline
The first half of year 1 involves hiring and training personnel, obtaining permission from primary care providers to approach their patients, programming to identify potential study participants from CPRS, and setting up study databases. After startup, we will enroll 250 participants at an average of 7-8/month in years 1-3, who will be randomly assigned to the intervention or the control group. See Section D5a for alternative recruitment methods to be used if recruitment does not meet expectations. Once recruited, intervention Veterans will be scheduled for delivery of the COOPERATE intervention. The intervention will last 12 weeks (3 months) for each Veteran, with outcome assessments at baseline, 3 months, 6 months, and 9 months. Aim 3 qualitative interviews (pre-implementation) for a subset of purposefully-sampled Veterans will take place at the same time as the 6-month assessments; for clinicians, these interviews will occur in years 2-3. The study duration will be 4 years, to allow for peer coach and Veteran recruitment, peer coach training, completion of the 6-month intervention, assessment of outcomes at 6 months, and the pre-implementation interviews.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events and unanticipated problems will be reported per the rules and regulations of the two governing bodies for this study: Indiana University Institutional Review Board and the Office of Research Oversight at the Veterans Affairs Administration.

7.0 Study Withdrawal/Discontinuation

Participants will receive a copy of the informed consent form for their records and will be reminded that their participation is strictly voluntary and that they may choose to withdraw their data from the study at any time by contacting a member of the study team. If at any time, participants wish to skip a question or discontinue an interview or assessment, they will be permitted to do so.

8.0 Statistical Considerations

Sample size and power

Our sample size is calculated based on estimated differences of intervention effects between the intervention and control arms on the primary outcome, patient activation (PAM), which is a continuous measure. Although our prior pain studies have had low attrition rates (less than 15%), we will conservatively plan for an attrition rate of 20%, which requires N = 250, or 125 patients per group.

Analysis

Effects on COOPERATE outcomes (patient activation [primary outcome], communication self-efficacy, pain intensity/interference, and psychological functioning): All outcomes will be collected at baseline, 3, 6, and 9 months. A linear mixed-model repeated measures approach will be used to test the hypothesis in Aim 1 that COOPERATE will improve the primary outcome of patient activation (PAM) compared to the control condition at the 3-month time point. Fixed effects will include treatment, time (as categorical), and treatment X-time interaction. We will examine the associations among the repeated measures within subjects and determine the appropriate variance-covariance structure. Our primary contrast of interest will be the group difference in change from baseline at the 3-month time point. Group differences in change from baseline at other time points (6-month and 9-month) will also be estimated. Covariates found to significantly differ between treatment and control groups at baseline will be included in the models. All analyses will include checking of assumptions and model fit.

Qualitative analysis

Dr. Matthias will lead qualitative analysis, which will occur in 2 phases: open coding and focused coding. Open coding facilitates development of a code list for further analysis. In this phase, the PI and two Co-Is, all of whom are experienced qualitative data analysts, will independently read selected transcripts to gain a general understanding of the data and variation across participants. Then, analysts will independently label each line of data with initial codes that reflect meanings or themes emerging from the text, and meet to discuss these interpretations. This will occur iteratively until analysts agree on emergent thematic categories (i.e., codes). In focused coding, all transcripts will be divided evenly among analysts, who will apply the codes derived in the first phase to assigned transcripts. A subset of transcripts will be coded by all analysts and discussed to ensure consistency in coding, with discrepancies resolved by consensus. NVivo 10, a qualitative data analysis program, will be used to facilitate storage and access of data for coding purposes.

Missing Data

We conservatively anticipate 20% attrition, which is reflected in our sample size. We will compare patient demographics between those who withdraw and those who participate to determine any discriminating characteristics. The proposed mixed model is appropriate if data are missing completely at random or missing at random. If data are missing not at random, we will use appropriate models (i.e., selection models, pattern mixture models) to account for the missing data mechanism.

9.0 Privacy/Confidentiality Issues

Computerized files will be protected by the electronic firewall at the Indianapolis VAMC, will be kept in locked areas accessible only by authorized persons (i.e., locked offices), and will be password protected. All data will only be accessible to the PI and research staff. We have put procedures in place which successfully minimize any risk to privacy or confidentiality:

- All stored electronic data will be de-identified and placed behind the VA firewall.
- All paper forms with participant's demographic information will be locked and secured in file cabinets only accessible by authorized study personnel in locked offices.
- All study assessments will be conducted in private locations.
- All audio recordings will be saved on a secure VA computer and the original file stored on the audio recording device will be deleted immediately.
- Participants' names will not appear on any of the data collected, including audio recordings. All participants' responses will be matched with a code number only. The key to this code number will be stored in a password protected computer file, separate from other data, locked behind closed office doors accessed by the research team for this study only.

10.0 Follow-up and Record Retention

This study will last for approximately 4 years. Records will be retained according to all applicable laws and regulations. VA research records will be archived and stored in accordance with the VHA Records Control Schedule.