STUDY PROTOCOL:
NCT02971137

I. PRINCIPAL INVESTIGATOR:

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II. PROJECT TITLE

Pain-related Anxiety Intervention for Smokers with Chronic Pain: A Comparative Effectiveness Trial of Smoking Cessation Counseling for Veterans

III. Submission Date

1/31/2022

IV. Protocol

Among Veteran smokers with chronic moderate to severe pain, a pain intensity ≥4 for 3 or more months, we are proposing a randomized comparative effectiveness trial to compare the effectiveness of a telephone-based smoking cessation intervention including CBI for pain to a standard telephone-based smoking cessation intervention. The goals of the study are: **1)** Evaluate the impact of **smoking cessation plus CBI (SMK-CBI)** on cigarette abstinence rates among Veterans with chronic pain at 6 and 12-months compared to **standard smoking cessation counseling (SMK-STD);** 2**)** Evaluate the impact of **SMK-CBI** on pain intensity and pain interference among Veterans at 6- and12-months compared to **SMK-STD**; 3) Assess whether change in self-efficacy and pain-related anxiety mediate the impact of **SMK-CBI** on smoking cessation in Veterans with pain at 6- and 12-months compared to **SMK-STD**.

6. Research Plan:

Study methods with proactive recruitment: Potentially eligible patients will be identified by administrative data pull of pain scores equal to or greater than 4 and current tobacco use. We will oversample women Veterans to increase the diversity. Eligible patients will be sent the following components: Introductory letter: A letter from Dr. Bastian to introduce the study, make an appeal to the patient to quit smoking, and informs them that they will be called to complete a telephone survey unless they call a toll-free number to refuse participation; Informational Consent Document: A document providing all the information for informed consent into the study and will be sent along with introductory letter and that describes the study.

Other recruitment methods: Recruitment will also occur via flyers posted in patient care areas, referrals by providers, and self-referrals from Clinicaltrials.gov at VACHS and VA Central Western Massachusetts Healthcare System (VACWM), and with the monthly pain recruitment table at West Haven and Newington. The anticipated goal for this VACHS study is to recruit 371 veterans, and VACWM will look to recruit 100 Veterans.

Approximately seven days after the mailing, Veterans who have not opted out will receive a phone call from a research assistant (RA) to further assess inclusion criteria, obtain informed consent (if interested), and conduct the baseline survey. Eligible patients must be Veterans enrolled at VACHS or VACWM with current tobacco use, willingness to make a quit attempt in the next 30 days, significant pain defined as ≥4 on the pain intensity portion of the BPI, and report that their current pain has been present for 3 months or more. Veterans with any of the following will be excluded: active diagnosis of psychosis or dementia in their medical records, Non-english speaking, refusal to provide informed consent, severely impaired hearing or speech, lack of telephone access, enrollment in another research study that might affect the main outcomes of this study, or terminal illness. Participants enrolled into PASS will have a research alert noted in their medical record.

In this comparative effectiveness trial, both groups will receive 5 sessions of telephone counseling. Five counseling sessions will be completed over 10-12 weeks on an approximately bi-weekly schedule that will be tailored to the individual Veteran's needs. Veterans will be mailed a reminder letter about their 6 month and 12

month follow-up surveys in order to improve retention. Both VA sites will utilize the same counselor for the telephone sessions.

Data sharing plan: Electronic data will be stored on a VA protected SharePoint site or local network, both of which are secure systems that exists behind the VA firewall and access is granted by an administrator only to authorized users. A SharePoint website is established only for the purposes of this project and will serve as a repository for study documents, communication, and other important information to be shared between VA CT and VACWM. The site is private and can only be accessed by approved study personnel with permissions granted by the PI or Project Director.

Smoking cessation counseling: Both groups will receive smoking telephone counseling and smoking cessation content delivered at parallel times. The protocol included in this application is based on standard techniques shown to be efficacious for smoking cessation and is informed by behavioral treatment principles,[45] Social Cognitive Theory,[46] and Motivational Interviewing.[47] The treatment protocol is consistent with the Public Health Service Clinical Practice Guide and was tailored to the Veteran population based on principles of evidence and consensus-based clinical practices.[48]

Cognitive behavioral intervention: In the SMK-CBI arm, behavioral stress reduction pain management approaches will be integrated into the evidence-based smoking cessation counseling. The adjunctive cognitive behavioral intervention emphasizes psycho-educational and skills-based approaches and is informed by VHAs existing pain self-management program. Specifically, the CBI developed for the study includes a focus on increasing physical activity, identifying pleasurable activities, relaxation practices, and thought monitoring/restructuring. The CBI participant manual will also include PASS activity booklet. The main objective of the PASS activity booklet will be to provide Veterans with an opportunity to practice selected behavioral and cognitive skills of relevance for both smoking cessation and pain self-management. Participants in the SMK-CBI arm will be given pedometers. This group will be instructed to track and record their weekly steps in the PASS activity booklet, and will be asked to report their weekly steps to the PASS counselor during each of the 5 telephone counseling sessions.

Counselor education: The PASS study counselor will be trained by a doctoral-level clinician on both SMK-STD and SMK-CBI counseling sessions, will be provided with videos and readings on CBI, smoking-cessation, and pain, and will be audio-recorded using a mock patient. The PASS study counselor will be given the opportunity to ask questions about trainings, and will then be tested and rated by a doctoral-level clinician using the Fidelity Scale to establish proficiency.

Standard of Care:
At VA specialty-based smoking clinics, counseling sessions with NRT are standard care for assisting Veterans to quit smoking. At the first telephone counseling session, counselors will ask potential participants if they are interested in using NRT. Dr. Bastian will contact the patient's PCP to facilitate a NRT prescription if the PCP agrees for those participants who are interested in using NRT.

Table 1: Outline of Counseling Sessions

	Smoking Cessation Counseling SMK-STD	***Smoking Cessation Counseling plus Cognitive Behavioral Intervention SMK-CBI***
#1	✓ Introduce counselor and study ✓ Check in ✓ Explore motivation to quit ✓ Set quit date if appropriate	✓ *All components of SMK-STD Session 1 (to the left, less the quit date discussion), plus the following:* ✓ *Introduce physical activity* ✓ *Use pedometer to record weekly step count* ✓ *Assign homework*

#2	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss ways to manage cravings	✓ *All components of SMK-STD Session 2 (to the left), plus the following:* ✓ *Pleasant activities* ✓ *Set quit date* ✓ *Record weekly step count* ✓ *Assign homework*
#3	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss how to handle slips	✓ *All components of SMK-STD Session 3 (to the left), plus the following:* ✓ *Introduce and practice progressive muscle relaxation* ✓ *Record weekly step count* ✓ *Assign homework*
#4	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss rewards	✓ *All components of SMK-STD Session 4 (to the left), plus the following:* ✓ *Introduce Unhelpful Thoughts* ✓ *Introduce Mini Practices* ✓ *Record weekly step count* ✓ *Assign homework*
#5	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Develop a post-counseling action plan	✓ *All components of SMK-STD Session 5 (to the left), plus the following:* ✓ *Review skills learned in previous sessions* ✓ *Record weekly step count*

V. Outcomes:

Participants will be surveyed three times: enrollment, 6-months post-intervention and 12-months post-intervention using VA RED Cap to collect these data. Baseline survey will assess demographics, smoking history, nicotine dependence, global self-efficacy to quit smoking, depression, pain intensity and other covariates related to pain and smoking, via telephone. Follow-up surveys will be administered at 6-months and 12 months post-intervention. The follow-up surveys will assess smoking status, pain intensity, use of intervention materials (e.g., NRT, PASS activity booklet), and intervention acceptability (e.g., intervention appropriateness, suitability, effectiveness, and convenience). Participants will be compensated $25 per completed follow-up survey. We will abide by the patient's preference since many patients may be reluctant to send their sensitive bank information or provide it over the phone for this telephone-based study.

Saliva samples will be collected from participants who report not smoking in the last 7 days (7-day point prevalence) in order to biochemically validate their self-reported smoking status. This process has been shown to improve the validity of self-reported smoking cessation. Samples will be collected at next clinic visit following the telephone interview.[49] Saliva samples will measure cotinine levels using NicAlert dipsticks with a standard cut point of 16 ng/ml to determine abstinence. Participants will receive $10 incentive for providing each saliva sample.

Counseling session fidelity will be assessed using audio-taped recordings of sessions. We aim to record approximately 20% of sessions (all sessions in the first 3 months of the study and then one week every 2 months for the remainder of the study). Investigators will rate 10% of the sessions to ensure protocol fidelity and lack of drift of information from the SMK-CBI to SMK-STD over time.

Outcome 1: Prolonged abstinence: In keeping with the SNRT recommendations for measuring abstinence, we will use prolonged abstinence as our main outcome and allow for a grace period around quit date. During the 6- and 12-month follow-ups, patients will be asked about prolonged abstinence, "In the past 6 months, have

you smoked at least a part of a cigarette on each of 7 consecutive days?" and "In the past 6 months, have you smoked any cigarettes in each of 2 consecutive weeks?"[50]

Outcome 2: Point prevalent abstinence: At each follow-up (6-and 12-month), patients will be asked whether they have smoked a cigarette, even a puff, in the past 7 days and, if no, will be asked whether they have smoked a cigarette, even a puff, in the past 30 days.

Outcome 3: Pain intensity (usual) and pain related functional interference: Participants will complete the BPI, which includes 2 multi-item scales measuring pain intensity and pain-related functional interference. Pain intensity in the past 24 hours is measured in 4 items—worst, least, current and usual-- each using a validated 11-point *numerical rating* scale (0-10). A rating of 0 indicates no pain while 10 indicates the worst pain imaginable. A score of 4 or above is considered a clinically significant pain level according to VHA treatment guidelines.[51] The functional interference subscale consists of 7 items measuring self-rated pain interference related to general activity, mood, walking ability, normal work (inside or outside the home), relations with other people, sleep and enjoyment of life. Respondents rate how much pain has interfered with these aspects of their lives in the past 24 hours on a 0 (does not interfere) to 10 (completely interferes) point scale.

VI. Statstical Protocol:

Data Summary. Descriptive statistics, including graphical displays, will be used to summarize all study variables, both overall and by intervention group. Evidence of imbalance in baseline characteristics will be noted and discussed as to whether they are clinically significant. As recommended by Committee for Proprietary Medicinal Products (CPMP) guidelines, we will consider sensitivity analyses adjusting for these baseline characteristics to ensure that an observed intervention effect is not due to this baseline imbalance. We will construct individual and mean trajectory plots of the longitudinal outcome variables (e.g., BPI) to understand their general trends over the study period. In addition, we will explore the variability and correlation structure of the longitudinal outcome variables. All statistical analyses will be performed using the SAS software package; the VACHS Center of Innovation maintains the current SAS release on our system.

Intent-to-Treat Analysis. All primary and secondary analyses focus on the effect of SMK-CBI as compared to SMK-STD. We, therefore, plan to use the intent-to-treat assumption for all analyses; participants will be analyzed as part of the group to which they are randomized, regardless of intervention adherence.

Analyses
Hypothesis 1.1: Prolonged abstinence rates will be significantly higher among Veterans in the SMK-CBI group compared to those in the SMK-STD group.
Hypothesis 1.2: The 7-day point prevalence abstinence rates will be significantly higher among Veterans in the SMK-CBI group compared to those in the SMK-STD group.

Rates of cigarette abstinence (prolonged abstinence) will be assessed at 6- and 12-month follow-up. Abstinence will be measured as a dichotomous variable that indicates whether patients have been abstinent or not. The same analysis approach will be used to test both prolonged and 7-day point prevalence abstinence rates. Self-report of abstinence will be validated with cotinine saliva testing.

We will use logistic regression to test for a between-group difference in abstinence rates at 6 months. This logistic regression model can be written as: $\text{Logit}(pi) = \beta 0 + \text{SMK-CBIi} * \beta 1$, where pi represents the probability that patient i has abstained from smoking at the 6-month follow-up. In this model, SMK-CBIi is the intervention group indicator; therefore, $\beta 1$ represents the log-odds ratio of smoking abstinence in the SMK-CBI group as compared to the SMK-STD group. For each of the abstinence outcomes, we will formally evaluate the intervention effect by testing that $\beta 1$ differs from zero and report the odds ratio ($\exp(\beta 1)$) and 95% CI of the odds ratio. An odds ratio significantly greater than 1.0 provides evidence that SMK-CBI group patients have higher prolonged abstinence rates. The model will also include stratification variables (gender) as recommended in the CPMP guidelines.

Sustainability, or longer term effects of the intervention, will be examined by comparing abstinence rates between groups at 12 months. We will model change in abstinence rates at baseline, 6, and 12 months using generalized linear models with a logit link fit with generalized estimating equations. The regression coefficients from this model have essentially the same interpretation as those from a cross-sectional regression analysis (e.g. logistic regression) but are more appropriate as they properly incorporate the within-subject correlation that is inherent in the longitudinal structure of the data. The model will be fit using the SAS procedure GENMOD (SAS Institute, Cary, NC).

Hypothesis 2.1: Veterans in the SMK-CBI will report significantly lower usual pain intensity and pain interference compared to the SMK-STD group.

We will use linear mixed effects models procedure for analyzing repeated measures data with fixed and random effects to evaluate study group assignment effects on our continuous and repeated outcomes (pain intensity and pain interference). The Mixed Models procedure is designed for unbalanced repeated measures with missing data, allowing for intra-participant serial correlation and unequal variance and covariance structure across time. It provides tests of the overall between-participant effects, repeated measures (time) effects, tests of fixed and random effects, and analysis of reduced models that can provide detailed tests of specific pattern of results. A repeated measures analysis of variance in the Mixed Models procedure takes into consideration differences that may emerge over time; we will use this procedure to test for a significant effect of the two treatments on the primary outcome measure, time, and the interactions between time and each of the two treatments. Random effects will also be included to account for intra-participant correlation of repeated measures. Additionally, the model will include the stratification variables. We plan to estimate the parameters in the model using the SAS procedure MIXED (SAS Version 9.2, Cary, NC).

Hypothesis 3.1: The relationship between pain-related anxiety intervention and smoking cessation will be mediated by self-efficacy and pain-related anxiety.

If there is a significant intervention effect on smoking cessation (i.e., if $\beta 1$ is significantly different from zero in the first model above in Hypothesis 1.1), then we also plan to examine whether change in self-efficacy and pain-related anxiety mediate the impact of the intervention. This aim can be addressed under the general framework of mediation. We propose to conduct this mediation analysis using the MacArthur approach, a modification of the traditional Baron & Kenny criteria, developed for use specifically in randomized clinical trials.[90,91] By the MacArthur definition, the potential mediator must be evident during or post-treatment; therefore, for example, the change in patient self-efficacy measures between baseline and 6-months will be considered as potential mediators. The outcome will be patients' abstinence at 12-months. We will first fit a model to examine the correlation between the mediator (C) and the SMK-CBI group: $C = \gamma 0 + \gamma 1$*SMK-CBI. We also fit a model that examines the relationship between the mediator and the probability of abstinence (p): $\text{logit}(p) = \beta 0 + \text{SMK-CBI}*\beta 1 + C*\beta 2 + C*\text{SMK-CBI}*\beta 3$. Improvements in patient self-efficacy or pain-related anxiety will be considered to account for improvements in abstinence rates if there is evidence that $\gamma 1$ is not equal to zero, and if either $\beta 2$ or $\beta 3$ are not equal to zero.

E.12.4. Missing Data. Because the main predictors of interest are collected at baseline, we do not anticipate much missing data in these variables. We do, however, anticipate missing values in the longitudinal outcomes owing to dropout, death, an inability to reach the patient by phone, or item non-response. If the missing values are related to other measured patient factors, such as age, gender, or employment status, then multiple imputation (MI) provides a framework for incorporating information from these auxiliary variables while still preserving a parsimonious main treatment effect mode: this framework is described as a significant advantage in recommendations from the Panel on Handling Missing Data in Clinical Trials. We will follow multiple imputation methods presented in Hedeker et al for missing abstinence outcomes. Depending on the type and scope of missing data for other longitudinal variables, MI will be conducted via the SAS procedure PROC MI or the SAS macro IVEware (http://www.isr.umich.edu/src/smp/ive/).