PROACTIVE OUTREACH FOR SMOKERS IN VA MENTAL HEALTH

Protocol Number: IIR 11-291-3

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Principal Investigator/Study Chairs:

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ABSTRACT

Background:

Tobacco use is the leading preventable cause of death in the United States and contributes up to 24% of all VA healthcare costs. Veterans enrolled in the VA healthcare system smoke substantially more than the general population, which is particularly true among Veterans diagnosed with mental illness. Patients with bipolar disorder or schizophrenia have the highest smoking rates (69% and 58-90%, respectively) followed by those with PTSD (45-63%) and depression (31-51%). Numerous barriers exist for tobacco cessation among mental health patients, including high nicotine dependency, low rates of follow through for referrals, and limited availability of tobacco treatment tailored to their needs.

Rationale:

Most medical care providers assess tobacco use and advise smokers to quit, but they have insufficient time to follow up with treatment, leading to low long-term quit rates. Mental health providers who often meet regularly with patients report that they find tobacco cessation outside the scope of their practice and neither assess tobacco use nor refer smokers for treatment. These practice patterns have been very difficult to change even with intensive methods and across various settings and provider types. Therefore, we propose to use the electronic medical record system to identify smokers receiving mental health care and proactively reach out to engage them in treatment in line with the following aims:

Specific Aims:

1. Compare the reach and efficacy of a proactive outreach telephone-based tobacco cessation (PRO) program for patients seen in mental health to usual care (UC) advice and referral to local VA and community tobacco cessation resources.
2. Model longitudinal associations between baseline sociodemographic, medical and mental health characteristics and abstinence at 6 and 12 months in the PRO and UC conditions.

Methods:

We will use the electronic medical record to identify N=20,000patients across 4 VA healthcare facilities who have a clinical reminder code indicating current tobacco use in the past year and who have had a mental health visit in the past 6 months. We will send each patient an introductory letter and baseline survey. Respondents will be randomized in a 1:1 fashion to intervention or control. Control participants will receive VA usual care. Intervention participants will receive proactive telephone counseling and cessation medications. We will survey participants at 2 weeks, 6 months and 12 months from enrollment. The primary outcome is cotinine-validated abstinence at the 12-month follow-up.

LIST OF ABBREVIATIONS

ACOS   Associate Chief of Staff.

COPD   Chronic obstructive pulmonary disease

CPRS   Computerized Patient Record System. The VA's electronic medical record system.

EMR   Electronic medical record.

FAQ   Frequently asked questions.

FDA   U.S. Federal Drug Administration.

HCS   Healthcare system

ICD-9   International classification of diseases – version 9

MH   Mental health

MHC   Mental health clinic

MIRECC   Mental illness research, education, and clinical center.

NRT   Nicotine replacement therapy.

PACT   Patient-aligned care teams. The VA's model for managing panels of patients, rather than individual patients.

PCMH   Patient-centered medical home.

PHS   U.S. Public Health Service.

PRO   Proactive outreach telephone-based tobacco cessation program. This is the name of the study arm that receives our proactive outreach intervention.

PTSD   Post traumatic stress disorder

QUERI   The VA's Quality Enhancement Research Initiative program.

TeleQuitMH Telephone Quality Improvement Trial for Mental Health. This is the name of our previous research study that evaluated a telephone smoking cessation program for smokers using VA mental heath clinics.

UC   Usual care. This is the name of the study arm that receives usual care at each site.

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1.0   STUDY PERSONNEL

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2.0   INTRODUCTION

Tobacco use is the leading preventable cause of death in the United States, responsible for 443,000 deaths per year and 8-24% of all VA healthcare costs.[1,2] Persons with a mental health diagnosis (DSM-IV, Axis I or II), which represent about 25% of VA patients, have particularly high rates of tobacco use and consume over 46% of cigarettes sold in the U.S.[3,4] Patients with bipolar disorder or schizophrenia have the highest smoking rates (69% and 58-90%, respectively) followed by those with PTSD (45-63%) and depression (31-51%).[4-6] Numerous barriers exist for tobacco cessation among mental health patients, including high nicotine dependency, limited support from mental health providers, low follow through by patients with referrals, and limited availability of tobacco treatment targeted to their needs. These barriers suggest a more specialized approach to tobacco cessation with mental health populations is warranted to maximize quit rates in this at-risk population.

The overall objective of the proposed research is to address tobacco use as a chronic health condition and improve tobacco cessation services for Veterans with mental health diagnoses, which is one of the top priorities of the VA Public Health National Prevention Program. While VA primary care providers now consistently assess tobacco use and advise smokers to quit, most have insufficient time to follow up with treatment, leading to low long-term quit rates.[7] Mental health providers often meet regularly with patients, yet report that they find tobacco cessation outside the scope of their practice and neither assess tobacco use nor refer smokers for treatment, often due to a misperception that tobacco cessation treatment would exacerbate patients' conditions.[8] These mental health practice patterns have been very difficult to change. In our team's recently-completed research study, we have been providing telephone-based counseling customized to the needs of mental health patients referred by their mental health provider. While patient participation rates are high (65%) and the long-term abstinence rate is comparable to primary care populations (20%), referrals from mental health providers have remained significantly lower than expected. Despite consistent provider support efforts, our referrals represent only 1.5 - 9% of mental health patients who smoke.

Our central hypothesis is that we can increase the number of Veterans with mental health diagnoses who receive evidence-based tobacco cessation services by proactively enrolling them in treatment. We therefore propose a randomized, controlled trial that will use the electronic medical record system at four VA facilities to identify N=6,400 smokers receiving mental health care and contacting them via letters and telephone to offer cessation treatment. As suggested by our previous experience with this population, the treatment protocol will be targeted to the needs of mental health patients by integrating relapse-sensitive scheduling, stress reduction and problem-solving techniques, educational information, and coordination with patients' mental health providers.

3.0   OBJECTIVES

The Specific Aims of the study are to:

2. Compare the reach and efficacy of a proactive outreach telephone-based tobacco cessation (PRO) program for patients seen in mental health to usual care (UC) advice and referral to local VA and community tobacco cessation resources.
    H1: We hypothesize that compared to the control group, the proactive intervention will increase the smoking abstinence rate at 12 month follow up.

3. Model longitudinal associations between baseline sociodemographic, medical and mental health characteristics and abstinence at 6 and 12 months in the PRO and UC conditions.
    H2: We hypothesize that mental health distress and active substance abuse will be related to treatment uptake and long-term abstinence.[4,9]

4.0   RESOURCES AND PERSONNEL

Resources

The majority of the work for this study will be conducted centrally at our NY Harbor site. Tasks that will be performed at our NY Harbor site include: overall study management and IRB coordination, mailing outreach letters and baseline surveys to potential participants, providing telephone counseling to participants in the Intervention arm, coordinating the mailing of medications to participants in the Intervention arm, completing telephone follow-up surveys, mailing biochemical validation (saliva) kits to participants, and performing all data entry and data quality assurance.

VA programmers and statisticians at our Minneapolis site will be responsible for using VINCI to create our list of potential participants, periodically verifying the list, taking a random sample of the list that will become our pool of patients to whom we will send outreach letters, and conducting all statistical analyses for study reports and publications.

Personnel: Investigators

Scott Sherman, MD, MPH (Principal Investigator) – Dr. Sherman is a Physician at the VA NYHHS and Associate Professor of Medicine and Psychiatry at New York University School of Medicine (NYUSOM). He has 20 years experience in health services research, with particular emphasis on implementation research in smoking cessation and organizational changes to improve tobacco control. He has been Principal Investigator on 10 studies for smoking cessation in the past 10 years, including a six-site VA QUERI implementation study evaluating a telephone program for smokers referred by their mental health provider. Dr. Sherman will work with Dr. Fu to oversee the entire study and serve as site Principal Investigator for the NYHHS site.

Steven Fu, MD, MSCE (Principal Investigator) – Dr. Fu is Co-Associate Director and a Core Investigator of the Center for Chronic Disease Outcomes Research at the Minneapolis VAMC, a Core Investigator at the University of Minnesota Transdisciplinary Tobacco Use Research Center, and an Associate Professor of Medicine at the University of Minnesota. He is nationally recognized as a leader in the treatment of tobacco use among diverse racial/ethnic minority

groups. He has been PI on six tobacco cessation studies in the past seven years. His research is focused on identifying best practices for improving the delivery and utilization of tobacco dependence treatments among diverse populations. Dr. Fu will work with Dr. Sherman to oversee the entire study and serve as site Principal Investigator for the Minneapolis HCS site.

Paul Krebs, PhD (Co-Investigator) – Dr. Krebs is a Clinical Psychologist at the VA NYHHS and an Assistant Professor of Medicine at NYUSoM. Dr. Krebs' research focuses behavioral interventions for cancer risk behaviors and tobacco cessation. He is currently PI on an NIH pilot grant testing an e-health intervention to promote healthy lifestyle behaviors among cancer survivors and a co-investigator on a NIDA-funded study developing and testing a structured gaming environment to promote cessation and prevent relapse in hospitalized smokers. Given Dr. Krebs' background in clinical care for tobacco cessation, he will serve as clinical supervisor to the telephone counselors working on the Intervention arm, which will involve weekly live supervision and fidelity coding of counseling calls.

Radha Rao, MD (Co-Investigator) – Dr. Rao is a staff physician at the Michael E. DeBakey VAMC in Houston, TX. She has facilitated multiple research projects at this site over the past several years. She is currently working on a VA Public Health Strategic Healthcare Group-funded project evaluating inpatient-outpatient transitions in tobacco cessation for surgical patients. On that project she works as the Primary Care Liaison between surgical and primary care staff to ensure appropriate delivery of smoking cessation treatment to recently-discharged surgical patients. She is also currently Principal Investigator on a local project retrospectively examining the side effects of Varenicline in a VA sample. Dr. Rao will serve as site Principal Investigator for the Houston site.

Carolyn Schlede, MD (Co-Investigator) – Dr. Schlede is a staff Physician and the Founder of the Smoking Cessation Clinic at the James A. Haley Veterans' Hospital in Tampa, Florida and has served as Director of the Clinic since 1984. Since 1997 she has also served as Chief of Clinical Champions for Smoking Cessation Clinical Practice Guidelines in VISN 8. Dr. Schlede is currently a Co-Investigator and site Principal Investigator on Dr. Fu's *Proactive Outreach to Smokers in Primary Care* study. Dr. Schlede will serve as site Principal Investigator for the Tampa VAMC site.

Erin Rogers, MPH (Co-Investigator and Project Director) – Ms. Rogers has an MPH in health services management and is currently enrolled in a Doctorate of Public Health program. She is a Health Science Specialist at the VA NYHHS and Project Director of several tobacco cessation studies. Ms. Rogers will coordinate all aspects of the study, including writing the study's IRB applications, coordinating with each site to obtain a list of smokers with a mental health diagnosis, developing the study's data entry program and database, and supervising the study's research assistants and counselors.

Personnel: Study Staff

Telephone Counselors – NY Harbor site
We will have two telephone counselors working at our NY Harbor site who will responsible for calling patients who enroll in the study and providing them with tailored, multi-session telephone counseling session. The counselors will use the study's structured counseling protocol and relapse-sensitive scheduling. Based on previous studies, we expect that each counselor will serve an annual caseload of 250-300 patients. The counselors will have access to PHI stored in password-protected study databases on a VA network server folder designated for this study.

Research Assistants – NY Harbor site

We will have two full-time research assistants and multiple part-time interns who will be responsible for mailing outreach letters and cotinine validation kits to participants, conducting verbal informed consent with participants in the Intervention arm, entering survey data into study databases, conducting telephone follow up calls for 6 and 12 month assessments, and other tasks as needed. The research assistants and interns will have access to PHI stored in password-protected study databases on a VA network server folder designated for this study.

Programmers – Minneapolis site

We will have 1-2 programmers at the Minneapolis site responsible for using VINCI to create our list of potential participants, periodically verifying the smoking status of patients on the list, and selecting a random sample of patients on the list to whom we will send outreach letters each month. The programmers will have access to PHI via VINCI and stored in password-protected study databases on a VA network server folder designated for this study..

Statisticians – Minneapolis site

We will have 1-2 statisticians at the Minneapolis site responsible for designing and conducting all statistical analyses and randomization procedures, and overseeing randomization during the participant enrollment period. The statisticians will have access to PHI stored in password-protected study databases on a VA network server folder designated for this study.
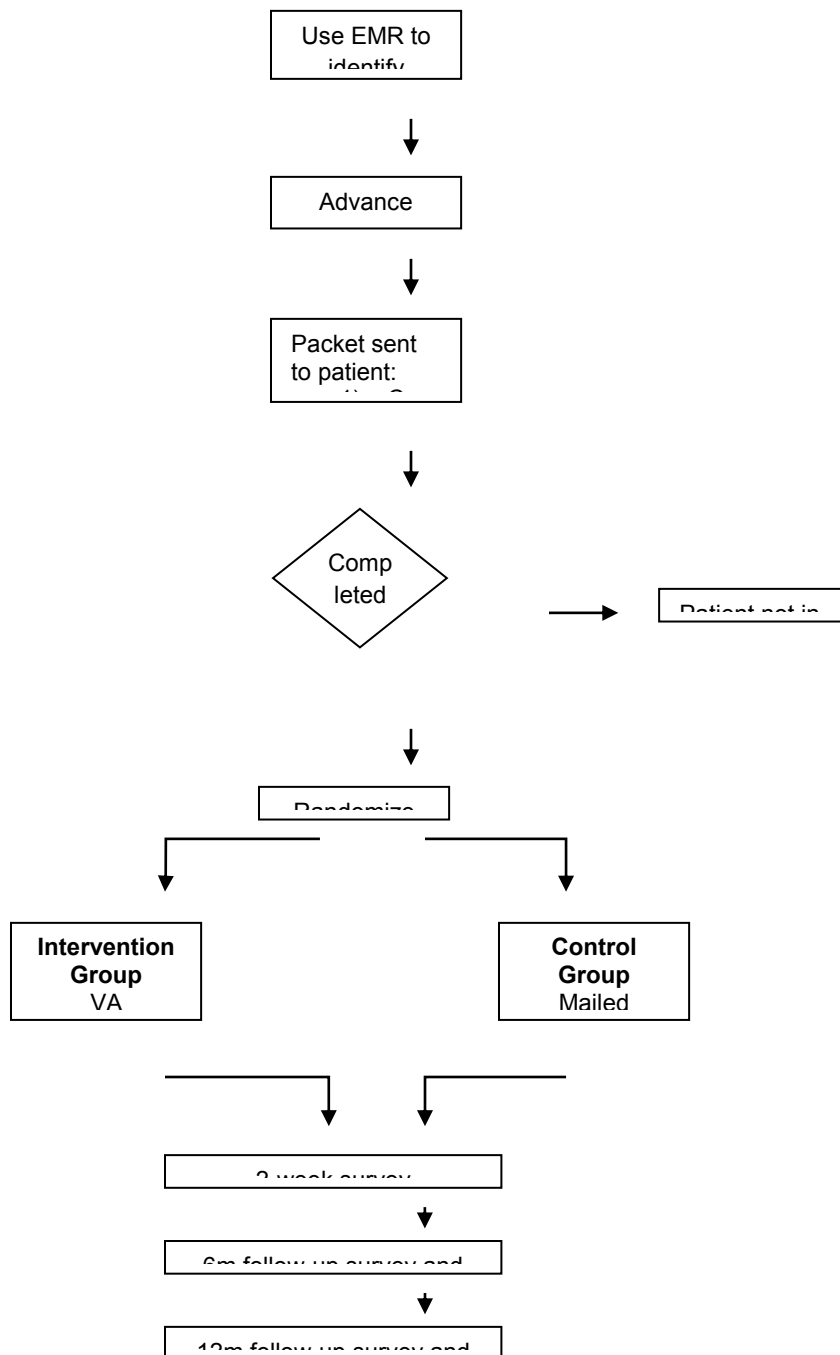
Contracts

We will be contracting with the company Salimetrics. Salimetrics will be analyzing our saliva samples for cotinine (validation of our primary outcome). The study research assistants will send the saliva samples by FedEx to Salimetrics for analysis using FedEx and U.S. government guidelines for shipping biological samples. We will label the samples with a unique barcode only that contains no information that can identify participants as individuals. The VA will maintain ownership over the samples after they are sent to Salimetrics. Salimetrics will send the results of their analyses to the study's PI in an excel report sent via email to the PI's VA email address. A sample report is included in Appendix F. This file will contain no patient identifiers. Results will be labeled with the number on each sample's barcode.

5.0   STUDY PROCEDURES
5.1   OVERVIEW

Figure 1 provides an overview of our study design. We will use the EMR to identify 20,000 patients across four VA health care facilities who have a clinical reminder code indicating tobacco use in the past six months and who have had a mental health visit in the past 12 months. We will send each patient an introductory letter and baseline survey. Respondents will be randomized in a 1:1 fashion to intervention or control. Control participants will receive VA usual care. Intervention participants will receive proactive telephone counseling. For each Intervention participant, study staff will send a medication request via CPRS to the smoking cessation program at their site and primary care provider or psychiatrist as backup. Intervention participants' regular VA mental health providers will be updated on their patients' progress in treatment via CPRS progress notes and be provided with information about the program and with suggestions for how to support their patients. Control participants will receive a mailed list of local VA smoking cessation treatment options that they can access on their own or to which

they can be referred by their regular VA providers (i.e., usual care). We will survey participants at 2 weeks, 6 months and 12 months from enrollment. The primary outcome is cotinine-validated abstinence at the 12-month follow-up.

Figure 1. Overview of Study Design

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5.2   SETTINGS

This study will take place at 4 sites: the VA New York Harbor Healthcare System, VA Minneapolis Healthcare System, Houston VAMC and Tampa VAMC.

5.3   IDENTIFYING POTENTIAL PARTICIPANTS

Using a three-step process, we will work with VA programmers at our Minneapolis site to identify potential participants using specific combinations of administrative data contained in the EMR system.

Selecting current smokers: Current smokers will be identified using the EMR tobacco use clinical reminder codes, where information is stored as a health factor. Patients will be included if they have screened positive for current tobacco use in the previous six months. We selected six months to reduce the false-positive rate of this sampling method (i.e., reduce the number of patients we contact who are no longer smoking). Patients will be excluded if they have an ICD 9 diagnosis of dementia (i.e., 290.XX or 331.XX).

Identifying Mental Health patients: Within the list of all eligible smokers, VA programmers will identify patients treated in the previous 12 months in a VA Mental Health Clinic, using VA clinic stop codes: 502-581.

Selecting the initial sample: After receiving a list for each site of current smokers with a recent Mental Health visit, we will select *all* women and a random sample of men to total 5,000 potential participants from each site (N=20,000) as our initial recruitment pool. We are selecting all women as an initial recruitment pool to increase the representation of women in our final sample.

Verifying the sample: We will verify our list of eligible patients each month, since we will be sending out letters and surveys to patients each month throughout the enrollment phase. If we relied solely on data collected at the beginning, smoking status could be over a year old on some subjects by the time they received their letter. Each patient who is no longer listed as a current smoker will be replaced by another patient from the site prior to mailing out any materials (and thus prior to enrollment and randomization).

Inclusion/exclusion criteria: Using administrative data and data from the baseline survey, we will verify the study's inclusion and exclusion criteria with each potential participant. Anyone who is found to be ineligible will be excluded prior to randomization and replaced with a randomly selected person from the list of current smokers for that particular site. We will thus send recruitment letters to 20,000 patients over five quarters (approximately 1400 patients per month). To maximize reach and impact we have chosen broad inclusion criteria; patients do not have to report being ready to quit within a specific time frame to enroll.

Inclusion criteria:

❑ Current smoker (i.e., any tobacco use in past 30 days)
❑ Mental Health clinic visit in past 12 months (and primary mental health diagnosis at checkout)

Exclusion criteria:

❑ ICD 9 diagnosis of dementia (excluded during data abstraction process)
❑ Does not speak English
❑ Does not have telephone and mailing address (necessary to mail out informed consent materials and to deliver the telephone-based intervention)

5.4 PARTICIPANT RECRUITMENT

Returning a mailed baseline survey will enroll a potential participant in the study. We will use a modified Dillman protocol to maximize recruitment response rates and data quality.[10] First, we will send each patient a letter from the Chief of Staff and facility Behavioral Health Coordinator (or other comparable leader from the facility) stating they will soon be contacted about a smoking cessation research study with the goal of helping Veterans who use VA mental health clinics stop smoking (Appendix A). The letter will also include information on how to contact the project director to opt out of receiving further study materials (flyer and baseline survey described below) or if they feel they have been contacted in error (e.g., not a current smoker). One week later, we will send out a packet of information, including a cover letter (Appendix B), a sheet of Frequently Asked Questions (FAQ; Appendix C), and the self-administered baseline survey. The cover letter and FAQ sheet accompanying the mailed baseline survey will contain all the elements of informed consent and explain the purpose of the study. Patients will have information that will explain the study's risk and benefits, that names are not attached to study documents and that choosing to participate or not to participate in the study will have no effect on their medical care. They will also be informed that they will receive a $10 payment for returning the survey. These documents will contain telephone numbers if participants have further questions about the study. Potential participants can also contact us if they wished to be no longer contacted by the study.

5.5 RANDOMIZATION AND BLINDING

After returning the baseline survey, we will randomize respondents in a 1:1 fashion to intervention or control, stratified by site. To randomize a patient, the Project Director will log onto the study's database system (which will be adapted from the one used in Dr. Sherman's previous studies), enter the subject's unique study ID, confirm eligibility, and confirm that the survey has been received. The database system verifies that all randomization criteria have been satisfied, then assigns a study ID and a group to the subject. The database system will automatically input the date of randomization and the participant's assignment into their study record. The study's Project Director and counselors will have access to treatment assignments. The study's research assistants and our biochemical validation company (Salimetrics, described in section 4.0) will be kept blind to treatment assignments. Intervention participants will be aware of the arm to which they are assigned when they receive the first phone call from a study counselor.

5.6 STUDY GROUPS

INTERVENTION

Telephone Counseling

Within one week of receiving a completed baseline survey, a counselor will phone intervention participants. Up to 6 contact attempts will be made at different times (i.e., morning, afternoon, evening) during the week. The purpose of the outreach call is to: 1) deliver motivational enhancement to quit smoking, 2) promote self-efficacy, and 3) encourage participants to participate in smoking cessation treatment. The full telephone counseling protocol is characterized by:

❏ *Motivational enhancement* – We will include motivational enhancement in each of the first several telephone calls and as-needed during later calls to increase patient motivation to quit and reduce relapse.

- *Multiple sessions* – Participating smokers will receive 8 calls over two months and then, for those who quit in this timeframe, monthly maintenance calls for six months. The initial call will be 30-45 minutes and subsequent calls will be 10-20 minutes.

- *Relapse-sensitive scheduling* – Participants will receive 4 calls to plan a quit date, three calls in the first two weeks after their Quit Date, when the relapse risk is highest, followed by another call in another two weeks. Patients who are quit at the 8 week call will receive monthly maintenance calls to work through any slips or barriers to continued abstinence.[11,12]

- *Problem-solving therapy* – This approach, based on helping the smoker identify and solve expected and actual challenge, is endorsed by the national smoking cessation guidelines.[13]

- *Stress Reduction* – Our previous work providing tobacco cessation counseling to VA mental health patients identified stress and anxiety as a major barrier toward quitting and long-term abstinence among this population. Our counseling protocol includes stress reduction techniques, such as relaxation and mindfulness exercises,[11,12] and the incorporation of smoking schedules to remove the link between smoking and stress responses.[14] We will also send stress reduction self-help materials to intervention participants that the counselors will discuss during the counseling.

Medication Requests

All smokers in the intervention arm will be asked about their NRT preference during their first counseling call. Their counselor will place a View Alert in CPRS for their facility's smoking cessation program or regular primary care provider indicating that the participant expressed interest in receiving NRT and their preference. The View Alert will also contain relevant information from the US Public Health Services guidelines for the treatment of tobacco. The counselors will monitor the participants' EMR for whether a prescription is written. If no prescription is written within 1 week after sending the View Alert, the counselor will place a follow-up View Alert reiterating the participant's expressed interest in NRT. The regular smoking cessation providers will not be required to prescribe or be required to prescribe the patient's preferred NRT. Rather, study staff will simply notify the providers that the patient expressed interest in receiving NRT. The Intervention counselors will also encourage participants to discuss NRT use with their regular providers.

Engaging MH Providers in the Treatment Process

In recognizing that a patient's regular Mental Health providers are an important source of support and treatment encouragement for our patient population, we will engage all intervention patients' primary mental health providers into the treatment process by alerting the providers of their patients' progress via CPRS progress notes and providing them information via email about the program and how they can support their patients. As we have done with Dr. Sherman's prior studies, the study's counselors will place a progress note into CPRS for each patient documenting the first counseling call and the quit plan developed during that call. Additional progress notes will be entered into the medical record when the patient quits smoking, when there is a significant change in the quit plan, and when the patient is discharged from the program. On each note, the patient's primary Mental Health provider (identified on the baseline survey and confirmed with EMR review) and psychiatrist (if different from the primary provider) will be added as an additional signer to the note. This process will also ensure the safety of participants using antipsychotic medications by notifying their psychiatrist of their quitting process.

CONTROL GROUP (USUAL VA CARE)

We will send smokers randomized to the control group a mailed list of local VA and non-VA smoking cessation services that they can access on their own. In addition, patients randomized to the control group may receive treatment or referrals to treatment from their regular VA providers as part of usual care. Pharmacotherapy is available at all sites in the form of nicotine replacement (patches, gum and lozenges) and bupropion.

5.7 DATA COLLECTION

All participants will be surveyed by mail at baseline, by mail 2 weeks after enrollment, and by telephone (or mail for non-respondents) at 6 and 12 months from enrollment. Research assistants will make up to 10 attempts at different days and times to reach participants by phone for the 6 and 12 month surveys. If we cannot reach a participant after 10 attempts, we will mail a paper version of the survey with a cover letter (Appendix K) to participants. Patients will receive a $10 payment as reimbursement for completing each survey.

5.7.1 Baseline Survey

Smoking questions

❑ *Smoking habits and history*. We will use measures adapted from the California Tobacco Survey[15] that we have used in several previous studies to assess the number of cigarettes smoked per day, number of days smoking per week, and nicotine dependence..[16]

❑ *Motivation*. We will assess readiness for change using the Stage of Change scale.[17]

❑ *Tobacco treatment used in prior 12 months*. We will ask participants to indicate whether a VA provider talked to them about smoking in the prior 12 months and which tobacco treatments they used in the prior 12 months.

❑ *Health*. We will ask a single item asking participants to rate their general level of health on a 5-point Likert type scale.

5.7.2 2-Week Survey

Sociodemographics

❑ *Demographics*. Age, sex, marital/partnership status, race/ethnicity, education, and occupation will be assessed, as well as text messaging interest and capabilities.

❑ *Environment.* Using questions from the California Tobacco Survey[15] we will assess household tobacco use and restrictions on smoking at home.

Smoking questions

❑ *Smoking habits and history*. We will use measures adapted from the California Tobacco Survey[15] that we have used in several previous studies.

❑ *Self-Efficacy*. Self-efficacy for smoking cessation will be measured with the 14-item Confidence Questionnaire Form[18] which assesses smoking cessation self-efficacy across 14 different situations or mood states.

❑ *Pros and Cons*. We will use the 6-item decisional balance scale which measures positive and negative attitudes toward quitting.[19]

❑ *Perceptions regarding tobacco use*. We will also assess perceived control over withdrawal symptoms[74] and perceived antismoking norms,[20-24] measures that predict tobacco use.

Health questions

- *Health habits.* We will use the AUDIT-C[24,25] to assess alcohol use and a single item measure developed to assess drug use in primary care.[26] We will measure frequency, type and quantity of exercise using questions from the National Health Interview Survey.

- *Comorbidities.* We will assess baseline comorbid conditions using the survey version of the Charlson index.[27]

- *Mental Health.* We will use the Kessler-6 psychological distress scale, as used by the National Survey on Drug Use and Health to measure general psychological distress.[28] The scale validity discriminates between cases and non-cases of mental illness. In addition we will use 14-item Hospital Anxiety and Depression Scale[29] to assess specific mood symptoms.

- *Mental Health provider.* In order to coordinate care and encourage involvement of the mental health clinicians, we will ask each patient for the name of the person he/she identifies as his/her primary mental health provider. This would be the provider he/she sees the most or feels is the most involved in his/her mental health care.

5.7.3   6- and 12-Month Surveys

All measures assessed at baseline and 2 weeks (except the sociodemographic measures) will be assessed again at 6 and 12 months. In addition, we will assess:

- *Cessation outcomes at 6 and 12 months*: We will follow recommended guidelines for measuring and validating tobacco abstinence in clinical trials.[30,31] Smoking cessation (7-day point prevalence), quit attempts, reduction in smoking, use of cessation pharmacotherapy, and counseling received outside of this study will be collected.

5.7.4   Saliva Sample - Validation of self-reported abstinence

Self-reported smoking abstinence can be verified by assays of cotinine, the principal metabolite of nicotine. Patients with cotinine levels > 15ng/ml will be classified as current smokers.[32] Sample collection will be conducted by mail. Patients will be eligible for verification if they report 7-day abstinence from cigarettes, other tobacco products, e-cigarettes and nicotine replacement therapy (NRT). A research assistant will send a saliva collection kit, collection instructions (Appendix D), a collection date sheet (Appendix E), and a postage-paid return envelope on the day of telephone survey with a postage paid return envelope. Subjects will receive a reminder call 5 and 8 days later. If they do not respond, another kit will be sent at 2 weeks, followed by two more reminder calls. We will mail a $25 payment to participants who return a saliva sample.

5.7.5   Administrative Data – Mental Health Diagnoses and Utilization

Programmers at our Minneapolis site will use the EMR to obtain the number of mental health clinic visits in the 12 months following study enrollment by each participant and to obtain a list of mental health diagnoses in each participant's EMR in the 12 months prior to study enrollment. The programmers will use this list to assign to each patient a primary mental health diagnosis using methods recommended by the MH QUERI. Primary mental health diagnosis will be defined as the most frequently occurring diagnosis at MH encounters during the 12 months prior to enrolling in the trial. For example, if a patient had three schizophrenia diagnoses and two schizoaffective diagnoses, s/he would be assigned the diagnosis of schizophrenia. We will then assign one of six main diagnostic categories to each participant based on their primary diagnosis: affective disorders, substance abuse disorders, non-PTSD anxiety disorders, PTSD, schizophrenia disorders, or other diagnoses.

5.8 OUTCOMES

The primary outcome will be cotinine-validated abstinence from smoking at 12-month follow-up. Secondary outcomes include the following:

1. Self-reported 7-day abstinence (to estimate rates of misreporting) at 6 and 12 month follow-up.

2. Other cessation related outcomes at 6 and 12 months – e.g., quit attempts, cigarettes per day, cessation medication use, motivation, and self-efficacy.

3. Self-reported mental health distress and active substance abuse.

5.9 INFORMED CONSENT PROCEDURES

There are several levels of patient information and consent for this study, which are summarized in the table and discussed below.

Category	Type of data	Approx. n	Authorization	Comments
1. Health system users	Administrative data • Smoking status • Mental Health clinic use • Phone number • Mailing address	40,000	HIPAA waiver	We will randomly select 20,000 from the EMR to contact via mail for possible enrollment
2. All study participants	Survey data • Baseline survey • Follow-up surveys Saliva sample Administrative data • Utilization • Mental health diagnoses	3,840	Waiver of documentation of consent	Completing the baseline survey will serve as implied consent to the telephone follow-up surveys and saliva collection, to be contacted for counseling if in the Intervention arm, and to collect follow-up administrative data from the EMR.
3. Intervention treatment participants	Intervention data • Counseling information • Nicotine replacement preference	384	Verbal consent with a waiver of documentation of consent	Participants will provide verbal informed consent prior to enrolling in counseling

Category 1: Health System Users. The proposed study will include men and women over the age of 18 years old who smoke and have had a Mental Health visit in the past 6 months. We will

request a HIPAA waiver to obtain a limited data set from the EMR to identify eligible subjects, which is necessary to carry out the study.

Category 2: All Study Participants. Patients who complete and return the baseline survey will be participants in the study. As indicated in the cover letter and FAQ sheet, their returning the survey implies they consent to participate and no written documentation of consent will be required. After receiving the baseline survey and verifying that the respondent is still smoking, we will randomize each person to either the intervention or control group.

Category 3: Intervention Arm Participants. Intervention participants will be offered telephone counseling. Prior to starting treatment, the counselors will discuss what each treatment involves and obtain verbal consent to proceed.

6.0   STATISTICS AND DATA ANALYSIS

Analysis

In the data analysis, we will focus on the analysis for inference in the subpopulation of smokers who respond to the baseline survey. The underlying assumption is that respondents to the baseline survey are comparable to non-respondents. With our proposed sample size, random assignment among subjects who returned baseline surveys stratified by hospital site can be expected to create two groups that are balanced with respect to observed and unobserved baseline characteristics. Balance of the two groups will be tested using Mantel-Haenszel χ^2 tests for categorical variables and appropriate parametric tests (e.g., Blocked Anova F-tests) or nonparametric tests (e.g., Wilcoxon rank-sum test). In addition, the data will be summarized numerically using descriptive statistics (means, medians, standard deviations, frequency distributions, and graphical displays including box plots) to characterize study participants in the two groups.

Missing Data

We anticipate low, but potentially important rates of survey non-response to all or part of the 6- and 12-month surveys. We will use the evidence-based recruitment strategies described above (incentives, reminders, mixed mode survey administration) to minimize non-response. A common practice in smoking cessation research is to treat non-respondents at follow-up as continuing smokers (i.e., intent to treat). This practice is perceived to be a conservative approach but does not, in fact, produce valid estimates of quit rates.[33] We will use multiple imputations to fully use available baseline information and partial later surveys. We will use a propensity-based multiple imputation method similar to that discussed by Little[34] using separate imputation procedures within each study group and design stratum combination. Within a given combination, we will estimate the propensity for responding to cotinine validated abstinence for each individual from a logistic regression model for survey response using the characteristics measured at baseline as explanatory measures. Within a combination of intervention and design strata, we will further stratify the sample according to the values for these estimated propensities. Within a propensity substratum, we will impute a value for the outcome measure for each non-respondent by randomly sampling an outcome value from the respondent values in the substratum. Multiple completed datasets will be created and the point estimates and the estimated standard error from each dataset will be combined to arrive at a single point estimate (using the specific method discussed below), its estimated standard error, and the associated confidence interval or significance test. This approach assumes that missing outcome data due to non-response is missing at random.

To assess the impact of non-ignorable survey non-response, or missing not at random non-response, we will implement pattern-mixture analyses. Using content expertise and the observed missing data patterns, we will develop these pattern-mixture models. The nature of these models is difficult to specify in advance of observing the different patterns but we will posit distributions for the missing data. For each set of posited distributions and the observed data, we will calculate revised estimates for the relevant intervention effects. One potential model would be to use the propensity stratum derived in the analysis described above and, within each stratum build a distribution for the outcome of interest by shifting the observed distribution among the responders. Content expertise and empirical results will be used to determine the form and magnitude of shift. These distributions would then be used to impute values for the non-responders to cotinine validation in the imputation process described immediately above. Variations of this approach and other approaches will be used to assess the sensitivity of the analyses above to non-ignorable non-response.

We will be enrolling patients after they complete the baseline survey, which maximizes our internal validity; thus we will have baseline data on all participants. The methods above for imputing missing data address the issue of non-response to all or part of either the 6-month or 12-month survey and cotinine validation. We will have limited data available on those who do not respond to the baseline survey, but we will use what data we have to compare initial responders to non-responders, in order to address external validity.

Specific aim analysis

The data will first be summarized numerically using descriptive statistics and frequency distributions examined for validity. Comparison of the baseline demographic and tobacco use characteristics between the two treatment groups will be performed using chi-square tests for categorical data and t-tests or nonparametric tests for ordinal or continuous data.

Aim 1: Compare the reach and efficacy of a proactive outreach telephone-based tobacco cessation (PRO) program for patients seen in mental health to usual care (UC) advice and referral to local VA and community tobacco cessation resources.

H1: Compared to the control group, the proactive intervention will increase the smoking abstinence rate at 12 month follow up.

Method: The study design is a randomized block design with the blocks comprising combinations of the four hospital sites.

We will address the question of Reach via two indices:
- Proportion of patients who respond to the outreach letters and enroll in the study (i.e., completed the baseline survey). This analysis will help us understand the proportion of smokers in Mental Health who will respond to proactive outreach. Given the innovative nature of the proactive outreach approach, we will examine the acceptability of the intervention to determine which patients are more likely to accept treatment in the PRO and UC conditions. Specifically, we will use multivariable logistic regression to determine which baseline characteristics (e.g., age, race/ethnicity, income, mental health diagnosis, symptom severity) are associated with receipt of cessation counseling (state quitline or VA) or use of cessation medications.
- Proportion of patients who engage in at least one treatment session compared to control patients. Specifically, we will determine how many patients in the intervention arm used treatment (counseling and/or medications) and compare this to the number of patients

enrolled in the control arm who report using existing VA tobacco cessation services on the follow-up surveys, which will provide data regarding acceptability of treatment.

The primary smoking outcome variable that is expected to be affected by treatment is dichotomous cotinine-validated abstinence at 12 months post-enrollment. The comparisons of the abstinence rates across the two groups will be made using exact logistic regression methods, accounting for stratification by site, to model the log odds of use of smoking cessation treatment and log odds of 12-month abstinence. Exact logistic regression employs the non-parametric Chi-square test or Fisher's exact test.[35] These tests are widely applicable in complete randomized experimental designs that yield contingency tables. Fisher's exact test is particularly suitable for contingency tables with small and unbalanced frequency counts, which are to be expected for the population-based outcome we have chosen where our population quit rate in the control condition is expected to be 4%.

Aim 2: Model longitudinal associations between baseline sociodemographic, medical and mental health characteristics and validated abstinence at 6 and 12 months in the PRO and UC conditions.

H2: We hypothesize that mental distress and active substance abuse are the strongest baseline predictors of treatment uptake and long-term abstinence in a mental health population.

Method: We will use a generalized linear mixed model approach[36] to determine smoking outcomes at 6 and 12 months. Following the recommended best practices in longitudinal data analysis,[37] we will use a two-level hierarchical linear model to fit the data. The outcome variable of interest will be the dichotomous cotinine-validated smoking abstinence data. Therefore, a logit model is appropriate at Level 1, where individual outcomes will be fitted for each subject using time as the primary covariate. The parameter estimates from these individual functions will then be entered as dependent variables in Level 2 in which treatment group (PRO vs. UC) is the covariate. This longitudinal analytic approach will help understand to what extent treatment effects differ between 6 and 12 months and whether they show a delayed effect (either increasing or decreasing over time). This will allow us to determine a treatment main effect as well as a treatment by time interaction. Baseline covariates will be included at the patient level (age, sex, race/ethnicity, nicotine dependence, motivation, self-efficacy, mental distress, and current substance use). Inclusion of covariates typically reduces residual errors and thus boosts statistical power as well as allows us to determine factors that affect abstinence to better target intervention design and content.

Power calculations

The power analysis is based on the primary outcome – cotinine-validated abstinence at 12-month follow-up. Our data is stratified on four hospital sites. Considering that a stratified random sample is usually more efficient than a simple random sample, to be conservative, we assume the two groups are two independent simple random samples in the following power analysis. Based on response rates during the first quarter of recruitment, we expect to receive completed surveys from 20-25% of the 20,000 patients receiving the initial mailing and 85% of respondents will be eligible (i.e., report smoking cigarettes in the prior 30 days). We will send initial mailings until we receive completed surveys from 3,840 eligible patients who will be randomly assigned to intervention and control and comprise the study population. We estimate the quit rate in the control group will be 4%. In the intervention group, about 20% of the people will accept our offer of telephone treatment, based on Dr. Fu's data. We anticipate that the quit rate among Veterans

enrolled in counseling will be 16%. We are using a more conservative estimate from what we found in our recently-completed reactive recruitment study (20%) because participants will not have been directly referred from a healthcare provider. When the treatment cessation rate is combined with that from patients who do not accept treatment (assuming also a 4% quit rate), there will be a population-level quit rate of 6.4% in the intervention group, which gives us a 90% chance to detect a difference between the two groups.

The table below shows the detectable increases in anticipated long-term abstinence rate for the intervention group for power = 0.75, 0.80, 0.85, 0.90, based on two sided two independent proportions test with type I error of alpha=0.05, We varied the anticipated long-term abstinence rate in the control group from 3% to 4%. (We used Pass 2008 NCSS software for the calculation.) As an example, the proposed sample size provides 80% power to detect any increase greater than 2.0% in population-level abstinence rate for the intervention group when the abstinence rate in the control group is 4%, a small but clinically-meaningful quit rate that results in overall cost-savings.[38] Reversing the calculation and solving for the quit rate for people who accept counseling, if the underlying quit rate is 4% and we get 20% of intervention patients to enroll in counseling (N=384), we will have 80% power to detect a difference if the success rate at counseling is as low as 14%.

Note that a lower response rate on the baseline survey does not affect our power. Since we randomize after response, we can mail additional surveys until we have 3,840 respondents. A recruitment cohort of 20,000 patients and enrolled sample of 3,840 participants therefore gives us some safety margin, to allow for variability in:

❑ The treatment engagement rate
❑ The rate of success at counseling (i.e., if less than 16%)
❑ If the success rate among intervention patients who do not enroll in counseling is <4% (which is conceivable, since these are the people who declined to enroll in telephone counseling).

Table 1: Statistical Power Analysis (1920 baseline survey respondents per group) for Abstinence Rates

Control group P1	Power	Intervention group P2	Difference P2-P1	Odds Ratio
0.03	0.95	0.053	0.023	1.82
0.03	0.90	0.051	0.021	1.72
0.03	0.85	0.049	0.019	1.66
0.03	0.80	0.047	0.017	1.61
0.03	0.75	0.046	0.016	1.57
0.04	0.95	0.066	0.026	1.70
0.04	0.90	0.063	0.023	1.62
0.04	0.85	0.061	0.021	1.56
0.04	0.80	0.060	0.020	1.52
0.04	0.75	0.058	0.018	1.49

7.0   WITHDRAWAL OF SUBJECTS

Participants can withdraw from the study at any time verbally or in writing by contacting one of the Principal Investigators. Any data collected prior to the participant's withdrawal will still be

used, but no further data collection or contact with the participant will occur after the date of their withdrawal.

8.0   SAFETY MONITORING AND REPORTING

Potential Risks
The intervention treatment being delivered in this study (counseling) is already shown to be effective and approved by the VA for use without informed consent. The main risk in this study is a breach of confidentiality similar to the risk incurred during a normal visit for care.

Surveillance and Reporting Procedures
In order to ensure patient safety, we will use the same approach we are using for our ongoing VA studies. We will monitor the following events:

Adverse events (AEs):
- Violations of confidentiality
- ER visits without hospitalization
- Suicidal ideation not requiring intervention

Serious adverse events (SAEs):
- Death
- Life-threatening event
- Hospitalization
- Suicidal ideation requiring intervention

Any AE that the research staff thinks may be related to study participation will be reported to a PI within 24 hours. If the PI is unavailable, the research staff will report it to the Project Director. The PI or Project Director will determine whether the event is a) serious or non-serious and b) anticipated or unanticipated. The PI or Project Director will ensure that any necessary actions are taken immediately to address the current patient situation, and then will decide if the team needs to make any changes in the protocol and/or consent forms to prevent future occurrences or better inform future participants. We will report the event to the IRB and DSMB as per VHA Handbook 1058.01 requirements.

In the case of suicidal or homicidal ideation, we will follow a protocol used on previous studies. We will train each person who contacts participants (tobacco cessation counselors and research assistants) in appropriate methods for assessing risk, conversing with participants, and completing a 'warm-transfer' to the VA National Suicide Prevention Hotline if a patient reports suicidal or homicidal ideation, plan or intent during counseling or a telephone survey. Clinicians (either Dr Sherman, a VA primary care physician, or the counseling supervisor, Dr. Krebs, a VA clinical psychologist) will also be informed to evaluate cases and provide any further advisement or follow-up with patients' primary mental health providers.

9.0   PRIVACY AND CONFIDENTIALITY

We will obtain a HIPAA waiver for the entire study. This waiver will allow us to access patient PHI using the EMR in order to identify our random sample of potential participants and collect administrative follow-up data on participants enrolled in the study. All study staff who have access to PHI will complete all required VA patient privacy trainings and the Project Director will be responsible for ensuring that each staff member's training is up to date.

Participants' identifiers will be kept in a separate password-protected database from their PHI abstracted from the EMR and other study data. All databases will be stored on VA network servers behind the VA firewall. Only study staff will have access to the password. Paper data will be stored in locked filing cabinets in locked offices at the Manhattan or Brooklyn campuses of the VA NY Harbor Healthcare System.

Electronic and paper data collected by study staff will not be transmitted or shipped outside the VA's protected environment. This study will be collecting saliva samples for cotinine analysis. These samples will be sent by FedEx to Salimetrics for analysis using FedEx and U.S. government guidelines for shipping biological samples. The samples will be labeled with a unique barcode only that contains no information that can identify participants as individuals. Salimetrics will send the results of their analyses to the study's PI in an excel report sent via email to the PI's VA email address. A sample report is included in Appendix F. This file will contain no patient identifiers. Results will be labeled with the number on each sample's barcode.

10.0   COMMUNICATION PLAN

The Project Director will work with the local site coordinators to develop their local IRB applications and ensure that they receive appropriate approvals before beginning research at any site.

Hard copies of all current study materials (e.g., outreach letters, surveys) will be stored on a VA network server to which all study staff will have access to ensure that only the most recent, IRB-approved documents are used. The verbal informed consent process for enrollment in telephone counseling and all telephone surveys will be completed using computer-assisted script and interview programs to ensure that staff are delivering informed consent information and obtaining survey answers in a standardized, IRB-approved methods.

We will have bi-weekly study meetings at our primary site (NY Harbor) and monthly conference calls with all sites to discuss overall study progress, protocols, and updates. When protocol changes, unanticipated problems, and SAEs occur, the Project Director will immediately notify the LSIs and their appropriate staff via phone and schedule a conference call as soon as possible to discuss the events or changes with all sites. Minutes from each meeting and conference call will be emailed to all study staff and stored on a VA server to which all study staff will have access.

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