Research Protocol

Title
Proactive Tobacco Treatment for Patients with COPD who Smoke: A Pilot

Investigator
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Specific Aims/Purpose
Overview: Many patients with chronic obstructive pulmonary disease (COPD) due to smoking continue to smoke. Proactive tobacco treatment interventions, where individuals who smoke are targeted in a tailored fashion outside of a routine clinic visit are a method of patient engagement that appears to be highly effective in this population. However, proactive tobacco treatment programs are rarely implemented, in part due to high workload associated with phone-based methods. Electronic outreach programs may be effective and cost-effective and allow additional tailoring to the target patient population. We will perform a pilot evaluation of proactive patient engagement for smoking cessation among veterans with COPD, piloting this program to determine feasibility and estimate effectiveness.

Scientific Rationale and Significance
Veterans carry a high burden from chronic obstructive pulmonary disease (COPD), driven by high rates of tobacco use. The majority of Veterans have a history of tobacco use, and one in 10 carries a COPD diagnosis[1] which is higher than the national prevalence.[1] Unfortunately, patients with COPD smoke at rates nearly double the national and VA averages,[5] with rates of tobacco use from 30-40%.[2,3] Quitting smoking is beneficial even in cases of advanced disease,[6] leading to improved symptoms[4,5] and decreased risk of death from multiple smoking-related causes.[6-8]

Smokers with COPD have significant barriers to cessation. Though these patients have an urgent need to quit, they have many barriers to successful cessation including: high levels of addiction to nicotine,[9] low socioeconomic status,[10,11] medical and psychiatric comorbidities,[12] and low motivation.[13] However, they are also prompted to quit by the presence of respiratory symptoms, which may increase motivation to participate in treatment.[14,15] Evidence suggests that smokers with COPD can quit successfully at rates similar to their healthy counterparts if they receive the guideline-recommended combination of counseling and medication.[16,17]

In practice, few patients receive any support during a quit attempt,[18] and even fewer use both pharmacologic and behavioral support despite being considered best-practices.[19,20] In a large cohort of Veterans admitted for COPD exacerbations, we found that only 15% had any tobacco cessation medication within 90 days of discharge.[23] The cause of this failure to provide best-practice tobacco treatment is multifactorial, attributable to both patient and provider factors, including patient misconceptions,[21,22] low motivation, lack of time and training for front-line providers,[23,24] and the lack of support for system-wide cessation initiatives.[25,26]

Proactive patient engagement is an effective method of increasing participation in tobacco treatment. Proactive patient engagement involves systematically identifying and contacting a group of smokers, providing a motivational and educational intervention, assessing their interest in quitting, and connecting them with appropriate quit resources. It has been tested to positive effect as a strategy in a number of patient populations including hospitalized smokers,[27,28] low income smokers,[29,30] and Veterans in both primary care[31] and mental health clinic settings.[32]

Despite evidence of effectiveness from several trials, proactive patient engagement is rarely implemented as part of clinical tobacco treatment programs. This is likely due to several barriers including: the perception that these interventions would be burdensome, lack of clarity regard staffing or funding, and concerns around the best target population. Using the principles of implementation science, we can analyze and overcome barriers to the implementation of proactive patient engagement in a way that is tailored to the environment and needs of the patients and staff.

Electronic methods of communication such as text messaging are an attractive option, allowing for broad reach with low cost. Patient engagement interventions through electronic portals have been found to be effective for increasing participation in other health behaviors.[33] Most Veterans are interested in using the internet to receive health information from the VA,[34,35] and have access to cell phones and e-mail[36,37] While limited electronic health literacy[38] is a concern in patients with COPD over the age of 50, use of technology among older adults is rapidly climbing.[36] In addition, the population of smokers with COPD at the VA is slowly shifting, as more smokers from Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) are enrolling. These younger Veterans may be more open to electronic health communication.

We conducted a survey and interview of technology use and communication preferences among Veterans with COPD who smoke and found that most (71%) have text-capable phones, and few (<25%) use the secure patient portal. Therefore, we have elected to use text messaging as the mode of delivery for our intervention. A pilot study will provide essential information about the utility of electronic methods for patient engagement among older, medically-ill Veterans.

Because it is not possible to assess population-level efficacy in the context of a single center pilot, we will instead focus on feasibility, which will be assessed by the number of patients engaged into tobacco treatment through the intervention and their interactions with the texting program. Because we hypothesize that cost and burden on staff will be perceived as significant barriers to implementation of proactive tobacco treatment, we will also estimate the cost and workload associated with the intervention. This will allow us to compare our intervention with other previously studied proactive interventions, and to prepare for a formal cost-effectiveness analysis in the context of a future larger trial.

Study Objectives:

1) **Establish feasibility and estimate effect size for proactive tobacco treatment for patients with COPD who smoke offered a via motivational texting program.**
2) **Assess acceptability of the motivational program to further tailor content for larger scale studies.**

Research Design and Methods:

Design: We will conduct a randomized controlled pilot of proactive tobacco treatment delivered through a motivational texting program.

Population and Setting: We will randomize up to 250 MVAHCS patients in a ratio of 2:1 intervention: control.

Inclusion Criteria (EHR):

1) Adults >=18 participating in care, defined as a primary care or pulmonary visit within the past 2 years.
2) Past-year smoking status in the electronic health record defined by health factors indicating current smoking (Via validated VA algorithm)
3) ICD-10 diagnoses of COPD within the past 2 years
4) Not already enrolled in VA tobacco treatment (pharmacist treatment, tobacco groups, mental health tobacco treatment). Patients taking only tobacco cessation medications without counseling will be included.
5) Not enrolled in hospice
6) No diagnosis of advanced dementia

Exclusions (phone eligibility assessment):

1) Unable to communicate by phone in English
2) No text-capable phone
3) Already quit smoking
4) Already participating in tobacco treatment program (note: if using OTC meds without counseling, will not be excluded)
5) Decline to be in study but would prefer to receive care coordination immediately

Eligibility, Sampling and Recruitment: We will screen and enroll patients who meet the eligibility criteria, applying the above criteria initially using the EHR, confirming criteria during phone contact. Patients will be randomized irrespective of their intention to quit smoking.

Women and Racial Minorities: To increase representation of these groups, we will oversample eligible women and racial/ethnic minority patients with a goal of 14% female patients and 24% minority patients invited to participate.

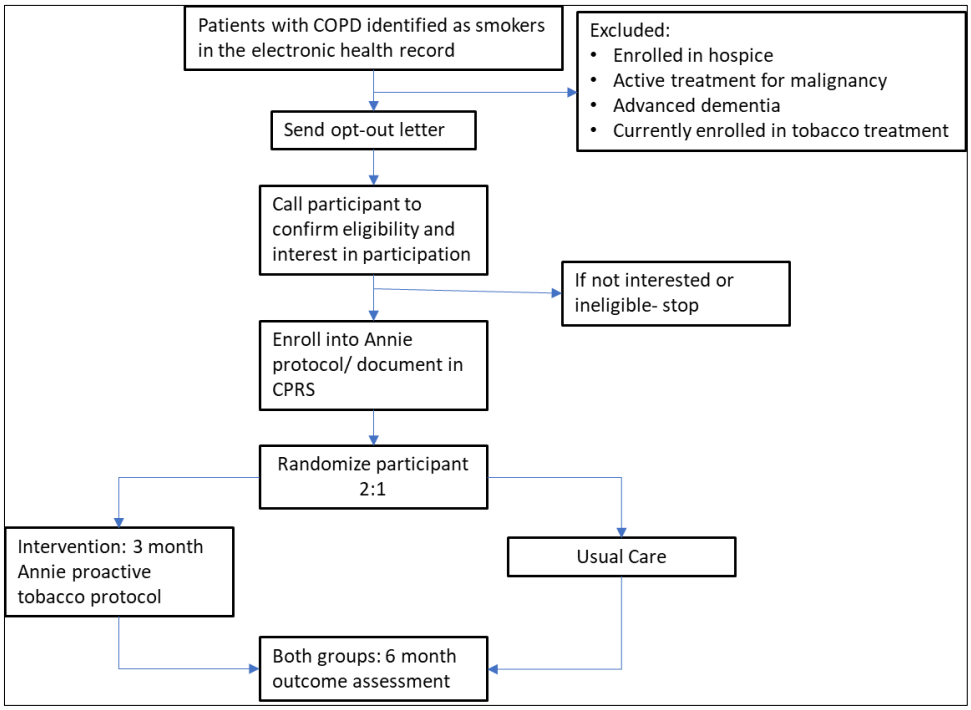
Study Procedures:

Screening: Research coordinator will screen patients for possible eligibility using a secure electronic application located behind the VA firewall.

Invitation: Study is minimal risk and will be conducted under a waiver of HIPPA and documentation of informed consent. Eligible participants will be sent an "opt out" letter that describes the study and contains the necessary elements of informed consent. Eligible patients will have the opportunity to opt out at this time by calling the study team.

Recruitment: Patients will be recruited by phone starting 1 week after letter is mailed. Patients will be called up to 6 times at different times of the day to make contact. Once contacted, research coordinator (RC) will confirm eligibility and obtain verbal consent to study procedures. For consenting patients, RC will administer the baseline survey and verbally consent them to participation in the VA "Annie" program and motivational texting program. Documentation of verbal consent to Annie participation is required by the VA Office of Connected Care. Annie consent language has been approved by MVAHCS representative (Lara Carson, RN, MyHealtheVet coordinator). Verbal consent will be documented in CPRS in a Research Participant Note utilizing the "Annie Consent" template. Patients who decline to complete baseline and immediately have care coordination will be considered ineligible. PCP and PACT pharmacist will be notified by co-signature to a research participant note.

Figure 1: Study flow diagram of the randomized pilot evaluation



Baseline Assessment:

Phone survey will assess: current tobacco use, motivation to quit, prior quit experiences, use of technology, and severity of shortness of breath. See table of measures. Charlson comorbidity index and history of mental health diagnoses will be pulled from the CDW.

Annie Enrollment:

All consenting participants will be enrolled in the VA "Annie App" and will receive an initial text message informing them of this enrollment. The Annie App is the VA's text-message-based health promotion platform used to provide education, self-management and clinical protocols. Participants will need to reply once to this message to confirm enrollment. Participants already enrolled in the Annie App will have this participation confirmed in the Annie portal.

Randomization:

Consenting participants will be randomized 2:1 to the intervention versus usual care using the enrollment application. To maintain balance in race and gender, randomization will be stratified by these characteristics; within strata, randomization will employ randomly permuted balanced blocks of size 2, 4, and 6.

Usual Care:

Participants in the usual care arm will be managed per usual as directed by their medical team.

Intervention:

Participants randomized to the intervention will be enrolled in a longitudinal motivational text-messaging program designed to increase quit attempts and participation in tobacco treatment. In collaboration with the MVAHCS Annie representative, the motivational protocol was adapted from a nationally available protocol available to all clinicians in the Annie App. Tailoring of the content included the addition of COPD-specific motivational quotations and information, inclusion of the local number to contact the study team, as well as the option for a "call back" from the team.

The Annie protocol will deliver approximately 30 motivational messages and a weekly "check in" over a 12 week period. The program will initially text participants once daily for 2 weeks, then approximately once every three days for 4 weeks, then every week until 12 weeks. Participants can opt out at any time from Annie by texting "stop" or by calling the study team to be discharged from the protocol. Protocol will encourage participants to call the study team to connect them to evidence-based tobacco cessation treatments or to call the VA quitline.

Care Coordination:

All treatments offered are standard of care within the VA and are offered in the context of routine clinical care. Study number is a secure VA number with voicemail that will be monitored. Participants who call back or request a call back via the Annie App will receive a return phone call as soon as possible, within a week. Request for callback and date will be logged in study log. For those participants who indicates a readiness to quit but do not call either the study team or their primary care physician, a study team member will call the participant when they are next monitoring participants within the Annie Program.

Both PI and RC are trained in motivational interviewing. At least 6 attempts will be made to return all calls at different times of the day. If participants are unable to be reached after 6 attempts, a letter will be sent encouraging them to call back, to call the quitline, or to contact their primary care provider.

Participants will be encouraged to enroll in an available MVAHCS quit program that provides both counseling and medication management. Phone script will encourage enrollment in more intensive programs first. Offered programs will include:

- Primary Care/Mental Health integration (PMCI) tobacco cessation management (if enrolled in mental health)
- Tobacco cessation class with pharmacist co-management
- Pharmacist tobacco clinic
- Quitline with primary care or pharmacist medication management
- Stay Quit Coach App or SmokeFreeVet texting (VA tobacco treatment programs) and primary care medication management

For participants still unwilling to enroll in treatment, they will be offered a stress relief program and can request a one-time callback in a month.

Once the participant has elected which program they would prefer, study staff will place the appropriate referral within CPRS, addending the research participant note to document the selection and discharging the participant from the Annie protocol.

- Pharmacist: Direct co-signature to PACT pharmacist in CPRS
- Cessation class or PCMI: notification to Dyani Saxby, tobacco lead clinician
- Quitline + primary care medication management: notification to Dyani Saxby (Tobacco Lead Clinician)+ documentation that patient consents to quitline call + co-signature notifying PCP
- Direct enrollment in SmokeFreeVet on smokefree.gov website
- Assistance with downloading of StayQuit Coach

Patients who select to enroll in treatment will be called in approximately a month to ensure they have connected with care and have no further questions.

Final Survey, Biochemical Confirmation of Abstinence, and Qualitative Assessment:

Survey: All participants will be surveyed 6 months after randomization to determine participation in any tobacco treatment (primary outcome), current self-reported tobacco use, quit attempts, and acceptability and feedback of the texting program. Completion via phone will be prioritized but participants will be provided the option to complete the survey via Qualtrics link via email or paper copy. Participants will be contacted 3 times via phone. If they are unable to be reached, they will be sent a letter encouraging them to call the study team to complete the survey.

EHR: Data will be pulled from the CDW supplemented by limited chart review to identify: prescriptions for tobacco-cessation medications, tobacco-treatment-related visits. Tobacco treatment visits will be identified by combining ICD-10 codes for tobacco use and treatment with note titles and visit types for pharmacists, psychologists, and primary care providers.

Biochemical Confirmation of Abstinence: The Society for Research on Nicotine and Tobacco recommends obtaining biochemical confirmation of abstinence whenever possible. We will obtain confirmation of abstinence among participants reporting 7-day abstinence in their follow-up survey using exhaled carbon monoxide (CO) levels. We will utilize the iCO™ Smokerlyzer®. The iCO™ Smokerlyzer® is a handheld device that is FDA approved for clinical and research settings to provide feedback on CO levels as part of a smoking cessation program or for confirmation of abstinence in research. The device connects to the patient's smartphone and uses an interactive smartphone application to collect a breath test to provide instant biofeedback on exhaled carbon monoxide (CO) levels. Exhaled CO is an effective measure of combustible tobacco consumption and is a recommended test for confirming abstinence, particularly among patients who are likely to use nicotine replacement longer term which can lead to misclassification among tests that rely on measuring nicotine metabolites. The protocol for iCO™ Smokerlyzer distribution and collection is in the attached Biochemical Confirmation of Abstinence protocol. All participants who agree to provide biochemical verification via the iCO Smokerlyzer will be compensated with an additional $30.

Interview: Participants will be asked their willingness to participate in a qualitative assessment of their participation in the texting program. Participants will be purposively sampled to ensure variation in characteristics. Participants will complete a brief (<30 minutes) semi-structured interview conducted by PI or RC to obtain feedback on the content, frequency, acceptability and ease of use of the texting program. Interviews will be recorded directly into a VA computer and housed behind the VA firewall and transcribed using the Word automated transcription function. Study staff will also take notes during the interviews.

Cost Analysis: We will prospectively capture information on cost associated with performing the proactive tobacco treatment intervention. To estimate the cost associated with implementation, we will capture time spent building any templates and electronic tools, and training staff. To estimate cost associated with staffing the program once it is created, for one month during the pilot, all study staff will enter daily the time spent in the clinical tasks associated with delivering the intervention into a spreadsheet, excluding activities that are related only to research administration. To estimate cost related to an increase in use of tobacco treatments attributable to the program, we will estimate the difference in use of tobacco treatments in addition to the intervention-related costs.

Measurements and Data Source:

See Table 1 for full list of measurements and data sources.

Table 1: Measures	
Measures	
Baseline Measures	
Survey	Demographics: Age, gender, race, ethnicity, education, income, health literacy Health Measures: Self-reported health, respiratory symptoms questionaire, diagnosis of COPD, Audit-C Access to Technology: Access to devices, access to internet, use of e-mail, use of secure patient portal, frequency of texting, electronic health literacy scale Tobacco Measures: current tobacco product use, heaviness of smoking index, past-year quit attempts and use of cessation resources, ever use of cessation resources, quit confidence scale, motivation to quit, intention to quit

EHR	Charlson comorbidity index, mental health diagnoses
Outcome Measures	
Study Recorded and EHR	Response to the program (via telephone, via Annie App), timing of response to program, Acceptance of referral, choice of referral program, cessation medications (varenicline, bupropion, nicotine replacement single/combination), documented tobacco treatment visits (pharmacist, class, mental health, primary care) or warm handoff to quitline
Survey	Primary outcome: Use of any tobacco treatment Secondary Outcomes: Use of combination treatment (behavioral + pharmacotherapy), individual treatment choice (program, medications), heaviness of smoking, quit attempts (y/n and number), 7 day and 30 day abstinence, Stage of change, quit confidence Additional Outcomes: Acceptability of text messaging program, feedback on messages, agreement to qualitative interview
Annie App	Opted out (y/n), number of messages received, Participant responses received through the app
Cost Measures	
Staff recorded	Program-associated costs: hours/week for patient identification, number of weekly phone calls, average call duration, time spent coordinating care, technology costs (patient identification queries, development of eligibility app) Treatment-associated costs: medication costs, pharmacy processing costs, average number, type and duration of counseling visits (groups, quitline, pharmacist counseling, tobacco-related primary care visits, mental health treatment)

Abbreviations: COPD=chronic obstructive pulmonary disease, EHR: Electronic Health Record

Analysis Plan:

We will perform descriptive analysis of the demographic and health history measures to describe the participants in the study overall, and in each study arm, as well as by outreach contact and receipt of any treatment and combination behavioral and pharmacological treatment. We will also summarize these measures by gender and race. Our primary aim is to assess the feasibility of implementing a larger trial of the electronic patient engagement intervention. Our primary focus then will be estimating rates, along with 95% confidence intervals, of outreach contact and treatment referral in the text outreach arm and of receipt of any and combination behavioral and pharmacological treatment in each study arm; additional analyses will weight observations by sample inclusion probabilities according to gender and race so that sample results are reflective of the overall population. While the study is not powered for detecting differences in cessation, we will explore potential differences in cessation between the two arms using likelihood ratio chi-square tests.

In addition to the descriptive information on the composition of the study population, we will identify the characteristics of those who respond, receive cessation treatment and those who attain abstinence in each arm, again assessing significance of differences in outcomes using logistics regression analyses and likelihood ratio chi-squared tests. This information will be valuable for planning a future study comparing the electronic proactive outreach intervention with previous studies of phone outreach. We will also descriptively analyze the Annie data to further tailor the protocol.

Power and Sample Size:

A sample size of approximately 167 participants in the intervention arm will be sufficient to estimate rates of contact, referral, and enrollment in behavioral and pharmacologic treatment with a precision (standard error) of +/- 3.9% and the control arm of 5.4%, which will be informative for planning future research. However, if feasible we will continue recruitment to attain more precision. Similarly, we will be able to estimate eligible population sizes, outreach connection rates, referral rates, rates of behavioral treatment enrollment and rates of pharmacologic treatment separately, and related facets of the intervention delivery to within similar degrees of precision. We will have enough variation in patient characteristics to stratify uptake on key variables, including age and disease severity. We may not have sufficient power to determine a statistically significant increase in enrollment in behavioral and pharmacologic treatment or smoking cessation, but these will be examined as aims of future research.

Cost Analysis: Estimates of time and workload for each staff member and clinical role involved in implementing and staffing the program will be combined with regional VA salary information to generate total costs for the proactive program. We will combine this also with regional estimates of pharmacy costs and the prevalence of

COPD and tobacco use at the MVAHCS to produce an overall estimate of cost for the program should it be implemented for the total population.

Qualitative Analysis: Transcribed interviews and notes will be analyzed using directed content analysis with NVIVO software, with constructs based on the technology adoption model and the consolidated framework for implementation research.

Expected Outcomes and Deliverables:

We expect that an electronic proactive patient engagement program will be feasible and will result in more patients enrolling in tobacco treatment. We also expect variation in response to the program by age and baseline technology use. We expect to find that the budget impact of the intervention itself is small and that most of the increase in cost will be due to increased utilization of existing quit resources.

Informed Consent

Participation will be performed under a waiver of documentation of informed consent. The opt-out letter will contain all the essential elements of information for informed consent. During the baseline enrollment call, subjects will affirm consent to study procedures and Annie protocol and be given the opportunity to ask questions related to the study. Subjects will have the option to opt out of further contact at any point.

Withdrawal of Subjects: Participation may be ended by the investigator without regard to the subject's consent at the investigators' discretion, or if we cannot contact them. Participants may drop out of this study at any time without prejudice to any future medical care with the institution or with the Department of Veterans Affairs (DVA). The investigator may continue to review the data already collected for the study prior to the participant's withdrawal but cannot collect further information, except from public records data. If at any time a patient wishes to drop out of the study, they may contact the PI or the RC.

Risks and Side Effects

Potential Risks: The risks of the study include possible breach of confidentiality, lost time, and inconvenience associated with participating in a research study, and discomfort with study questions. Veteran subjects may feel uncomfortable completing questionnaires or discussing experiences with smoking cessation or use of technology—experiences which may have been frustrating. There is a risk of breach of confidentiality if information gathered for research purposes is inadvertently shared.

Protection Against Risk

The study will be designed to minimize potential risks to participants, predominantly risk of breach of confidentiality related to research study participation. All study data will be stored on VA servers in restricted access files. Study data will be stored and administered using a VA-created secure research database behind the VA firewall for recruitment and within Qualtrics for survey data. Each study subject will be assigned a unique Study ID. For each study, a single master list ("crosswalk") will contain subject names, last 4-digits of social security number, phone numbers, and unique Study ID. The crosswalk will be stored on a restricted access folder on the Center for Care Delivery and Outcomes Research (CCDOR) server and kept separately from other study data. In all other study data, subjects will be identified by Study ID only. Only trained and approved study personnel will have access to study data. If Veterans experience discomfort while completing study procedures, they may skip uncomfortable questions or procedures. Because patients participating in this study will have COPD, it is possible that they may experience adverse health events related to their disease. It is not expected that participation in the study will lead to any increased risk of adverse health events. We will be including Veterans with all severities of COPD, and some may have severe respiratory impairment. If during study procedures, the study staff identifies concerns related to a patient's mental or physical health, the study staff will notify Dr. Melzer who will determine the need for further evaluation and notify the patient's primary care provider as necessary.

Monitoring Safety

Complications of study procedures will be recorded in study logs. Participants will be asked to report any adverse events that occur during the study, and adverse events will be recorded in study logs.

Benefits

Participation may have significant benefit for the Veterans if they attempt to quit smoking successfully. There is a small stipend for participation in the surveys and or interview.

Protected Health Information
This study will use subjects' Protected Health Information (PHI). PHI collected will be name, address, telephone numbers, e-mail, eligibility, and SSNs (last 4 only), as well as dates of care. These are used to contact the patient and confirm eligibility. The last four of the SSN is used to document eligibility on the EHR.

Costs to Subjects
There is no cost to participate in this study.

Subject Compensation
Participants will be paid $20 per survey for a total of $40 to be paid at the completion of the follow up survey. The subset of participants who participate in the interview following the completion of the intervention will be paid $30 for their time. Subjects will be paid $30 for providing biochemical confirmation. Participants will not be compensated for participation in the text messaging program. Participants will be asked if they already participate in EFT. For those not participating, they will be sent the EFT paperwork in the mail after they consent to be in the study. This will include all EFT paperwork, a letter explaining how to complete the paperwork, and a return address envelop for returning the paperwork to study staff. Study staff will scan and send via an encrypted email the EFT paperwork to the Agent Cashier office. In the 5th month of study, study staff will confirm EFT paperwork have been completed correctly and resend the EFT paperwork if it has not.

Project Management and Research Team Coordination:
As PI, Dr. Melzer will lead all activities related to the study, in collaboration with co-investigators and the research coordinator.

Data and Safety Monitoring Plan
The proposed research will be overseen by the Minneapolis VA IRB. The PI will be responsible for monitoring safety, minimizing risks related to data and safety, protecting the confidentiality of subject data, and reviewing and reporting adverse events and unanticipated problems to the IRB.

The principal investigator will review reports of adverse events and unexpected problems during the conduct of the research. The principal investigator will report all adverse events including breach of confidentiality to the MVAHCS IRB. The principal investigator will ensure that any IRB recommendations and actions related to monitoring are enacted.

Data will be maintained in accordance with MVAHCS protocols. Electronic information will be housed behind the VA firewall and physical files will be kept within locked file cabinets in locked offices. We are applying for a waiver of HIPPA and waiver of documentation of informed consent. Other patient identifiers will be kept in the separate crosswalk.

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