PROACT Statistical Analysis Plan (SAP)

Project Title: Promoting Smoking Cessation in Lung Cancer Screening Through Proactive Treatment (PROACT)

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1. Study Summary and Aims

Study purpose:

Investigate an intervention designed to help Veterans stop smoking.

Study design:

Parallel two-arm cluster randomized clinical trial.

Primary Aim: Conduct a pragmatic randomized trial among smokers participating in lung cancer screening comparing proactive smoking cessation care with unstructured care. We will assess the differences between the two care approaches on 7-day smoking abstinence 12 months after receipt of screening. Assignment of providers to the two care arms will continue until the study is on track to have 540 patients responding (270 responders per arm) to the 12-month survey. Based on our preliminary findings in a pilot study of proactive care, and related trials in other populations of smokers, we hypothesize that smoking abstinence 12 months after screening will be twice as high (18%) in the proactive group compared to expected abstinence rates in the unstructured group (9%).

2. Data Sources

Data Source	Time Period	Description	Analytic variables of Interest
CDW	Data Collection	Electronic health record for Dept. Of Veteran Affairs	Smoking status and patient characteristics
Surveys	Data Collection	Surveys conducted at 3 and 12 months post LCS	Smoking status, quit attempts, and other patient reported outcomes

3. Study Population

Veterans who smoke being screened for lung cancer at the VA Providence or VA New York Harbor.

Inclusion Criteria	Exclusion Criteria
• Current smoker • Participant in lung cancer screening	• Patients with urgent findings requiring biopsy/immediate attention on the screening CT • Patients with a prior diagnosis of lung cancer or who are receiving active therapy for any cancer other than skin cancer • Patients previously diagnosed with cognitive impairment, dementia, or severe behavioral disorders • Patients who have an indication in chart review of difficulty communicating or participating in telephone counseling sessions

4. Sampling and Randomization

This is a cluster randomized two-arm parallel group trial. Randomization occurred at the provider-level. Lists of providers referring patients to lung cancer screening at Study Site A & Study Site B were

prepared. Providers at each site were pair-matched on patient volume and then randomized to either the intervention arm or the control arm. Randomization was performed using random numbers generated with the R programming language.

Following randomization, all patients of enrolled providers who attended lung cancer screening and met eligibility criteria were considered enrolled in the study, with treatment arm corresponding to the randomized treatment arm of their provider.

5. Study Outcome Measures

			Assessment Timepoint		
Measure (Units)	**Comments**	**Data Type**	**BL**	**3M[1]**	**12M[1]**
Primary Outcome (1)					
Self-reported smoking cessation at 12 months	Constructed from 12-month survey and EMR data	Binary			✓
Secondary Outcomes (3)					
Experience with Telephone Counseling	Survey only	Binary		✓	
Self-efficacy to quit	Survey only	Likert scale (0-10)		✓	✓
Motivational Assessment	Survey only	Likert scale (0-10)		✓	✓
Perception of susceptibility to harm	Survey only	Summary Score		✓	
[1]Months post-LCS					

6. Study Covariates

			Assessment Timepoint		
Measure (Units)	**Comments**	**Data Type**	**BL**	**3M[1]**	**12M[1]**
Treatment Assignment	Intervention or Control	Binary	✓		
Covariates for primary and secondary models (2)					
Site		Binary			
Additional covariates for primary and secondary sensitivity models (4)					
Additional variables collected[2]					
Gender	Self-report from screening and baseline questionnaires	Binary	✓		
Marital/partner status	Self-report from screening and baseline questionnaires	Categorical	✓		
Age	Self-report from screening and baseline questionnaires	Continuous	✓		
Highest level of education	Self-report from screening and baseline questionnaires	Ordinal	✓		
Current employment status	Self-report from screening and baseline questionnaires	Categorical	✓		
Service connection	EHR	Binary	✓		

[1]Months post-LCS

			Assessment Timepoint		
Measure (Units)	**Comments**	**Data Type**	**BL**	**3M[1]**	**12M[1]**

7. Statistical Analyses and Description of Main Tables

Aim 1 statistical analyses

The primary analysis will be an intent-to-treat based comparison of the two intervention arms. The analysis will be performed at the level of the individual. Clustering of patients within providers will be accounted for in the analysis by the inclusion of a random intercept for provider. The primary analysis will be based on the following random intercept logistic regression model

$$logit^{-1}\left(P\left(Y_{ij}\middle|Treatment, Site\right)\right) = \beta_0 + \alpha_j + \beta_1 Treatment + \beta_2 Site$$

Where Y_{ij} is an indicator variable for whether the i^{th} patient of the j^{th} provider had quit smoking at 12 months, *Treatment* is a binary indicator for assigned treatment arm, and *Site* is a binary indicator for VA medical center (New York Harbor or Providence). The α_j represent random intercepts for each provider and are assumed to follow a common N(0, σ^2) distribution. We will report point estimates and 95% confidence intervals for the odds ratio exp(β_1). Confidence intervals will be computed using bootstrap methods. A test of the hull hypothesis of no association ($\beta_1 = 0$) will be performed using a likelihood ratio test. A p-value of less than 0.05 will be taken as sufficient evidence to reject the null hypothesis of no association.

Analyses for secondary outcomes will use models with similar predictor terms but with different link functions depending on the outcome. The table below describes model types in more detail for each outcome.

Analysis	Description	Outcome	Independent Variable(s)	Model type	Statistical Test
Primary outcome	Smoking cessation at 12 months	Indicator of smoking abstinence at 12 months	Binary treatment indicator; Binary site indicator; Categorical provider	Logistic regression with random intercept for provider	

Analysis	Description	Outcome	Independent Variable(s)	Model type	Statistical Test
			(clustering variable)		
Secondary outcome	Use of smoking cessation support within 3 months of LCS	Indicator for receipt of medication or behavioral counseling	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Logistic regression with random intercept for provider	
Secondary outcome	Use of smoking cessation support within 12 months of LCS	Indicator for receipt of medication or behavioral counseling	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Logistic regression with random intercept for provider	
Secondary outcome	Smoked in the last 7 days (3 month survey)	Indicator for smoking	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Logistic regression with random intercept for provider	
Secondary outcome	Smoked in the last 7 days (12 month survey)	Indicator for smoking	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Logistic regression with random intercept for provider	
Secondary outcome	Quit attempts since LCS (3 months)				
Secondary outcome	Tried to reduce or cutdown	Indicator for Yes	Binary treatment indicator;	Logistic regression with	

Analysis	Description	Outcome	Independent Variable(s)	Model type	Statistical Test
	since LCS (3 3 months		Binary site indicator; Categorical provider (clustering variable)	random intercept for provider	
Secondary outcome	Quit attempts since LCS (12 months)				
Secondary outcome	Tried to reduce or cutdown since LCS (12 months	Indicator for Yes	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Logistic regression with random intercept for provider	
Secondary outcome	Support Satisfaction	Ordered categorical (A little/not at all satisfied, somewhat satisfied, very satisfied)	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Ordered logistic regression with random intercept for provider	
Secondary outcome	Motivation to quit	Score on motivation to quit scale	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Linear regression with random intercept for provider	
Secondary outcome	Self-efficacy for quitting	Score on self-efficacy scale	Binary treatment indicator; Binary site indicator; Categorical provider	Linear regression with random intercept for provider	

Analysis	Description	Outcome	Independent Variable(s)	Model type	Statistical Test
			(clustering variable)		
Secondary outcome	Perceived susceptibility to lung cancer	Score on susceptibility scale	Binary treatment indicator; Binary site indicator; Categorical provider (clustering variable)	Linear regression with random intercept for provider	

8. Handling of Missing Data

In descriptive statistics, we will describe the extent of missing data. We will examine whether there is differential missingness in outcomes across treatment arms and sites. We will assess the extent to which the distributions of patient characteristics differ between those with the primary outcome and those without the primary outcome.

Patients may have missing data due to survey non-response or missing EHR data. The primary analysis will be a complete-case analysis among those who have a smoking status at 12 months. In sensitivity analyses, we will adapt a method to examine the impact of non-ignorable missingness on the study's primary conclusions. We will use the following model, which incorporates a Missing Not at Random (MNAR) missingness mechanism through a sensitivity parameter representing the odds ratio of smoking cessation between people with missing outcomes and people without missing outcomes.

$$logit^{-1}\big(P(Smoking)\big) = \beta_0 + \beta_1 Tx + \beta_2 Site + \beta_3 Missing$$

9. Project Links

Clinical Trials Website:

https://clinicaltrials.gov/ct2/show/NCT03612804