Project Title:	**A Peer Navigator Model to Improve Quit Attempts and Smoking Cessation Rates among HIV-positive smokers**
Principal Investigator:	**Patricia A. Cioe, PhD**
Co-Investigators:	**Christopher Kahler, PhD; Karen Tashima, MD; Megan Pinkston-Camp, MD**

Description and Purpose of the Project

Current smoking prevalence among persons living with HIV (PLWH), is high (40%) compared to the general U.S. population, where smoking prevalence is approximately 15%. Several studies have suggested that PLWH lose more years due to smoking than to HIV infection itself. However, smoking cessation studies in PLWH to date have demonstrated disappointing outcomes, with low quit rates, poor adherence to therapy, and a lack of sustained abstinence. While most HIV-positive smokers report a strong desire to quit, many are unable to do so, and low cessation rates are reported. Considering their high levels of nicotine dependence and low quit rates, HIV-positive smokers may require additional support for quitting compared with the general population of smokers, as they may not only have more smokers in their social network but also may smoke to cope with social isolation related to living with HIV. Peer navigators (PNs) have been used for many years in the field of HIV to support entry and retention in care, and adherence to ART. Linking HIV-positive smokers with PNs—who are already embedded within most HIV community care settings—to support access to and utilization of existing smoking cessation resources represents a novel and sustainable approach to encouraging smoking cessation and providing the additional support these smokers may need to make a quit attempt and achieve and sustain abstinence. For example, a PN may encourage the smoker to set a quit date, adhere to smoking cessation medication therapy, utilize the many available smoking cessation resources (e.g., Quitline's, web-based smoking cessation, text messaging support, and local group counseling), and achieve, maintain, or regain abstinence after a smoking lapse. Applying this approach to smoking cessation within the HIV clinic seems to be an untapped resource for improving smoking cessation rates in HIV-positive smokers.

The primary objective of this project is to examine the feasibility, acceptability and initial efficacy of a peer navigation social support for smoking cessation (PNSS-S) intervention for HIV-positive smokers. We will enroll 78 HIV-positive smokers, regardless of their readiness to quit, into a 24-week randomized pilot study to determine whether enhanced treatment (using a PN to navigate smoking cessation, help obtain medication and treatment, improve adherence to treatment, and provide social support for quitting) will increase quit attempts and smoking cessation rates (measured by 7-day point prevalence) compared with standard care (SC; provider recommendation to quit and quit line referral using the 5A's).

Aims

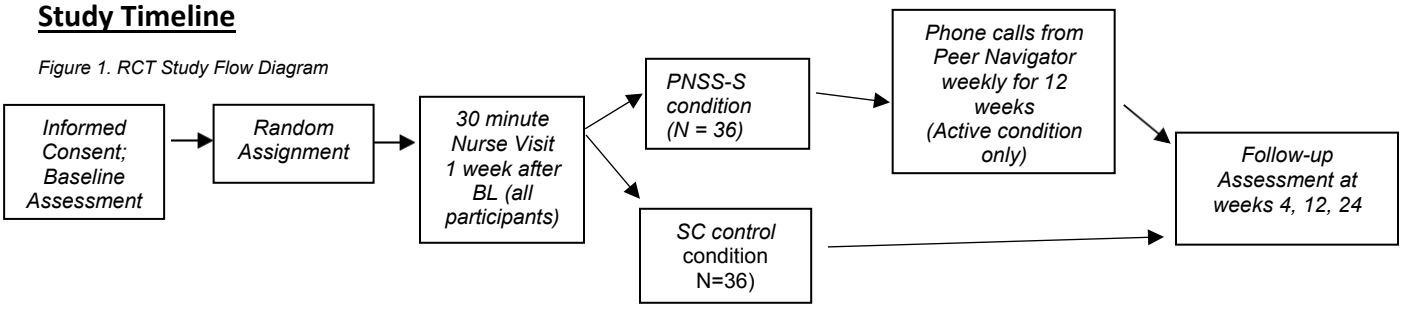
Our specific aims are to examine: (1) the feasibility, acceptability, and initial efficacy of PNSS-S in a 24-week randomized pilot study; (2) to compare the effect of PNSS-S, relative to SC, on mechanisms thought to underlie smoking abstinence in HIV-positive smokers.

Methodology

We will adapt an existing, highly effective PN training program that was developed by Co-I Dr. Pinkston-Camp to increase engagement in care within the HIV clinic. The PNs for smoking cessation will be former daily smokers who quit smoking and have remained smoke-free for at least two years. We will train the two PNs, enroll 6 HIV-positive smokers to test the intervention, and finalize our protocol. We will refine the PNSS-S based on feedback from the PNs, the 6 participants, and the study nurse. Next, we will conduct a pilot RCT (N = 72) to test the feasibility, acceptability, and initial efficacy of PNSS-S in a randomized, 2-group, repeated measures design. We will randomize 36 HIV-positive smokers to each condition: PNSS-S or standard care (SC). Assessments will be collected at baseline (BL), and at 4-, 12-, and 24-weeks following BL. We will examine the effect of PN on Quitline contact, quit attempts, adherence to pharmacotherapy, smoking cessation rates, 7-day point prevalence abstinence (with biochemical verification), sustained abstinence, self-efficacy for quitting, social support for smoking cessation, study retention and satisfaction. We will calculate a preliminary effect size estimate of PNSS-S on smoking and other secondary outcomes and mechanisms of change. Data will be used to plan a future full-scale RCT.

Study Timeline

Figure 1. RCT Study Flow Diagram



Participant Population

Participants for this study will include 78 participants (N = 6 for Stage 1a; N = 72 for Stage 1b) recruited from the Miriam Hospital Immunology Center and Providence, RI. They will be adult smokers, diagnosed and living with HIV. This study is designed to address the barriers and challenges to successful smoking cessation in PLWH, thus our population will include only PLWH.

For inclusion, participants have to (1) be diagnosed with HIV; (2) be at least 18 years of age; (3) smoke at least 5 cigarettes per day for longer than one year; and, (4) have an exhaled carbon monoxide (CO) level greater than 5 at BL.

Participants will be excluded if they (1) are currently using pharmacotherapy for smoking cessation; (2) have an unstable medical or psychiatric condition (defined as a medical or psychiatric hospitalization in the 30 days prior to enrollment); (3) Are experiencing psychotic symptoms; (5) Have past-month suicidal ideation or past-year suicide attempt; (6) Are pregnant or nursing; (7) Blood pressure reading greater than 160/100 or Heart Rate less than 45 or greater than 115; (8) have a family/household member already enrolled.

Inclusion of Women, Minorities, and Children

Participants will be recruited without regard to gender or ethnic background. We hope to recruit equal numbers of males and females so that gender differences can be examined in a preliminary manner. No one will be excluded from participation in this study on the basis of gender.

The sample for this study will not include children (child being defined as individuals under 18 years old; Notice Number: NOT-OD-16-010). Participants in this study will be ages 18 or greater. The HIV clinic serves individuals living with HIV that are over age 18.

Recruitment Procedures

The PN program is currently underway at the MIC and two PNs will be recruited for this study based on the recommendations provided by Dr. Pinkston-Camp. Study PNs will: have a history of smoking at least 5 cigarettes per day for longer than one year; have quit smoking and remained smoke-free for at least two years; and have an exhaled carbon monoxide (CO) level less than 5 at time of study. Each PN will spend approximately 4 hours per week on study activities. They will be responsible for maintaining phone contact (once weekly through week 12 of the study with each participant in the PNSS-S condition). Additionally, the PNs will be responsible for accepting phone calls (during business hours) initiated by their assigned participants during the first 12 weeks of the study. The PNs will be required to maintain phone call/contact logs consistent with current PN practice. PNs complete HIPAA training, as required by all clinic staff at Lifespan. Following training, Dr. Pinkston will monitor the PNs throughout the study period, including weekly team meetings to assure the continued quality of PNSS-S study procedures.

We will recruit participants from the Miriam Immunology Center and the Providence vicinity. Recruitment will be conducted at the Miriam Hospital Immunology center with flyer postings. Study flyers (See Appendix) will be posted on research study bulletin boards in the clinic and placed in the Providence vicinity. When patients call in response to the ad, the research assistant (RA) at the Center for Alcohol & Addiction Studies will describe the study (using a Phone Screen - See Appendix) and ask questions pertinent to inclusion and exclusion criteria. Those who indicate that they would like to participate and are eligible based on the initial phone screen will be scheduled for a baseline (BL) study appointment at the Miriam Immunology Center(MIC) or at the Center for Alcohol & Addiction Studies (CAAS) lab (based on participant preference and convenience). When screening a person, the RA will record all appropriate information on a hard-copy of the phone screen. The phone screen will be shredded after the baseline visit, once the participant is enrolled or once they are deemed ineligible.

Informed Consent

During the in-person, baseline session (conducted at the MIC or at CAAS), the RA will explain details of the study and participants will complete a written informed consent in a private room. This RA will have extensive experience with the process of informed consent and will have conducted informed consents for multiple research studies previously. S/he will have been fully trained to complete IC's for this study.

All participants will be fully informed about the purpose and procedures of the study. The RA will describe the screening and the study to potential participants, including that, if they are eligible and then agree to participate, they are paid for completing the BL session, and the follow-up interviews, that the information they provide is kept confidential, and that they may withdraw at any time without penalty. Time will be allowed for participants to ask all questions. If an individual wishes to participate, s/he will be asked to sign an informed consent form prior to completing the baseline

assessment. Participants are provided with a copy of the consent form, and the originals are kept in a locked file at the Center for Alcohol and Addiction Studies. Potential participants have the option of refusing to participate in the study, withdrawing their participation at any time, and/or refusing to answer any questions that they feel uncomfortable responding to.

To ensure voluntary participation and to minimize the possibility of coercion or undue influence, we will use flyers to recruit subjects, which will allow participants to call us, by their own choosing, with interest in the study. We will make sure participants are aware that the study is voluntary and that they can withdraw if they choose to at any time and with no penalty to them and no effect to their clinical care.

Baseline Assessment

Following informed consent, the baseline assessment will be administered. Participants will then complete written questionnaires and interviews to determine eligibility for the study, including a medical history screen. For those with reading difficulties, assessments will be administered by the RA. Women will be administered a pregnancy test to ensure non- pregnancy status.

Participant Locator

Contact information will be recorded at baseline for all participants for the purposes of collecting follow-up data. The RA will record the participant's email address and telephone number. In addition, participants will be asked to provide the name of a friend or relative who can act as a locator in the event that the participant moves.

Enrollment

Once the BL interview is complete, the PI, who is not involved in conducting assessments, will randomize eligible participants to one of two study conditions (PNSS-S or SC). The RA will not be informed of treatment condition assignment. All participants will be scheduled for a week 1 session with an MIC study nurse within one week of the BL appointment. The nurse will use a detailed counseling manual to ensure standardization of treatment delivery.

Nurse Visit

All participants regardless of condition will meet with a MIC registered nurse at the clinic. The session will last for 30 minutes. See description of condition content in the following paragraphs.

Standard Care Condition (SC)

Participants in the SC condition will meet for a 30-minute session with a study nurse. This session will be consistent with standard guidelines for brief advice for smoking cessation based on the 5A's. The nurse will ask about current smoking habits, advise the participant to quit, assess readiness to quit, assist by providing resources (community programs, Quitline phone number), and arrange follow-up. The nurse will calculate and provide personalized feedback about the participants' Lung Age, which provides an estimate of the age at which the FEV1 would be considered normal. This will serve as a motivation tool to encourage smokers to quit and has been shown to increase the odds of quitting. Those willing to set a quit date will be instructed to call their physician for cessation medication and will be provided with the National Cancer Institute (NCI) self-help pamphlet entitled *Clearing the Air* and the *smokefree.gov* website address. Brief treatment is consistent with the

minimum standard of care recommended by the Agency for Health Research and Quality (AHRQ) panel to address smoking cessation treatment. Those participants not willing to set a quit date will be instructed to contact their MD when they are ready.

Peer Navigation Social Support for Smoking Cessation Condition (PNSS-S)

Participants in the PNSS-S condition will also meet for a 30-minute session with the study nurse. The nurse will discuss the same content that was provided in the SC condition. In addition (for the PNSS-S condition participants only), the nurse will discuss the importance of social support for quitting and will explain the role of a Peer Navigator (PN). The nurse will then introduce the participant to his/her assigned PN. Finally, the nurse will ask if the participant is ready to set a quit date. Participants who set a quit date will choose the appropriate medication in collaboration with their clinic physician. PNs and nurses will reinforce adherence to the chosen medication. Participants will be informed of the efficacy of pharmacotherapy for smoking cessation. The PN will act as an intermediary between the patient and physician - facilitating the acquisition of the medication by coordinating with the participant's MD for a prescription, reviewing the formulary for medication coverage, ensuring that the prescription is picked up at the pharmacy, and managing any side effects via MD/nurse consultation (similar to their role in improving ART adherence). The PN will also assume the role of providing social support for quitting via weekly phone calls with the participant for 12 weeks. The PN will be well versed with local groups and resources, so that they can direct their participants to the most appropriate services/resources, if the participant is interested. Participants not willing to set a quit date at the time of the nurse visit will be engaged in a discussion of "quitting as a process" and will be encouraged to discuss barriers to quitting. This discussion will continue in contacts with the PN over the coming weeks.

In total, participants randomized to PNSS-S will receive a 30-minute session with the nurse, a quit-day counseling call from the PN (as appropriate), and weekly calls from the PN to address issues based on stage of quit attempt for 12 weeks.

Pharmacotherapy

Participants who set a quit date during the study period will be prescribed one of four FDA-approved options by their treating MD and medication will be provided through their insurance plan and usual pharmacy: 1) Nicotine replacement therapy (NRT) prescribed as an 8-week course of treatment with transdermal nicotine patch - initial dose starting at 21 mg for 4 weeks (14 mg for those smoking 5-10 cigarettes per day); 2) combination NRT in the form of patch/lozenge or patch/gum; 3) varenicline; or 4) bupropion.

Participants will select treatment, based on the advice of their physician. Dose and duration of the oral medications will be at the discretion of the physician (consistent with clinical care).

See Appendix for medication coverage list by insurance plan in RI.

Weekly Phone Call from Peer Navigator

Only applies to those in active condition. The PN will call the participant once each week (preferably on Mondays but may be on another day if there is difficulty reaching the participant or if the participant and PN agree on a more convenient day). See description of PNSS-S condition in preceding paragraph for detail about phone call content. (See Attachments for PN script).

Follow-up Visits (weeks 4, 12, and 24)

Participants will have vital signs checked. FEV1 will be assessed. Exhaled breath for carbon monoxide (CO) analysis will be obtained. Participants will then complete a series of paper/pencil assessments (See Attachments for Schedule of Assessments). A saliva sample will be obtained for cotinine analysis from any participant who reports that they have quit smoking (defined as no cigarette smoking for at least the past 24 hours).

Assessments

All measures will be completed by paper and pencil at the study session. The measures have a participant ID and a study session number as the only identifiers (See Attachments).

Measures

Phone Screen- The phone screen will include age, HIV status, current smoking behavior, current use of pharmacotherapy for cessation, and unstable medical conditions (recent opportunistic infection or hospitalization). Women will be asked if they are pregnant, intend to become pregnant in the next six months, are using a reliable means of birth control, or are nursing.

Baseline Visit- Subjects will complete a medical screening questionnaire (self-report) to assess medical and psychiatric histories, medication use, current use of antiretroviral therapy (ART), and contraindications for using pharmacotherapy (unstable angina, pregnancy). A Tobacco Use Questionnaire will assess all forms of tobacco use (past and present), including the use of electronic cigarettes. Alcohol and drug use disorders will be assessed using the Short Michigan Alcoholism Screening Test (SMAST) and the Drug Abuse Screening Test (DAST-10), brief measures used in primary care. The suicide subscale from the Mini International Neuropsychiatric Interview (MINI) will be used to evaluate suicide risk. Vital signs will be obtained and subjects who have elevated blood pressure (>160/100) or an abnormal heart rate (<45 or >115) will be excluded and referred to their physician for evaluation. All women will complete a urine pregnancy test.

Baseline Measures of Individual Differences

Demographics will include age, sex, gender, race, ethnicity, marital status, employment status, income, education level, number of years living with HIV, and history of opportunistic infections. We will obtain most recent CD4 T-cell value and HIV viral load from the MIC medical record (commonly measured in the clinic every 3-6 months). The Fagerström Test for Cigarette Dependence (FTCD) will be administered to evaluate severity of cigarette dependence. An exhaled carbon monoxide (CO) level will be obtained (using a Smokerlyzer ED50 CO meter [Bedfont Scientific, Haddonfield, NJ]), a valid assessment of recent smoking. Participants will provide breath samples for CO at baseline, and each study interview; values of 5 ppm or higher will be considered indicative of smoking. Intention to quit smoking will be assessed using the Smoking Stage of Change questionnaire. Depressive symptoms will be assessed with the Center for Epidemiologic Studies –Depression scale (CES-D).

Feasibility and Acceptability Measures

Feasibility and acceptability will be assessed using session attendance (recorded as a continuous variable ranging from 1 to 4 study sessions) and retention (coded as a dichotomous

variable with participants who complete the 24-week session characterized as completers and those not attending the final session as non-completers). The Helping Relationships subscale of the Processes of Change Questionnaire will be used to examine satisfaction with PNs in the active condition. CSQ-8 will be used to compare treatment satisfaction by condition.

Efficacy Measures: The main outcome analyses and effect size estimates will be based upon biochemically verified 7-day point-prevalence abstinence at 4-, 12-, and 24-week follow-ups. Point-prevalence abstinence will be verified by saliva cotinine radioimmune assay analysis (cutoff value of < 15 ng/ml) for stated abstinence of 7 days or longer in those not currently using NRT or other nicotine-containing products. Self-report will always be overridden by objective verification of abstinence in the final analyses. Timeline Followback (TLFB) will be used to assess Quitline contact, enrollment in smokefree.gov, prescription receipt for cessation pharmacotherapy, quit attempts (defined as a 24-hour period of no smoking), and continuous abstinence. Breath samples for CO will be obtained at each study visit.

Mechanisms of PNSS-S Effect

Social support for quitting will be assessed using the Partner Interaction Questionnaire, which assesses negative and positive support for quitting. Participants will be instructed to include all forms of support for quitting (including PN support if assigned to the PNSS-S condition). Self-efficacy for smoking cessation will be measured using the Contemplation Ladder, a one-item Likert-type scale (rating 1-10). In participants who set a quit date, adherence to pharmacotherapy will be measured via participant self-report and pharmacy refill report at each study session.

Confidentiality

Confidentiality will be maintained as follows: Data files are recorded with an identification number, are stored at the Center for Alcohol and Addiction Studies, and are accessed only by project staff. All project staff are knowledgeable about confidentiality and human subjects' protection. Follow-up contact forms that require identifying information are stored separately from data files and are accessed only by those staff conducting follow-up interviews. During follow-up telephone calls to the participants' homes, no information is provided to others in the household.

Potential Research Risks / Discomforts to Participants

The following risks would need to be considered for this study -

- Legal risks (e.g., mandatory reporting).
  a) Information would only be released to the appropriate authorities to the extent of the laws of Rhode Island.
- Psychological or emotional risks (e.g., fear, stress, confusion, guilt, loss of self-esteem, depression, triggering of past emotional experiences).
  a. Potential Discomfort Relate to Questionnaires: Some questionnaires ask about sensitive information such as psychological and alcohol/drug problems. The questionnaires and interviews are commonly used in research and clinical practice; however, some questions may be of an embarrassing or sensitive nature. Some participants may experience discomfort in disclosing or discussing HIV status. To minimize this potential discomfort, questionnaires will be completed in a private study room. Also, a participant may refuse to answer or skip any question asked of him. They

do not have to answer any questions that they choose not to answer.

b. Potential Discomfort in Quitting Smoking: Quitting smoking can result in uncomfortable withdrawal symptoms including mood changes, irritability, and changes in sleep. The nurse will discuss quitting smoking with each participant and will recommend actions they can take to reduce any symptoms related to nicotine withdrawal. The use of smoking cessation medications may also reduce these symptoms.

- Information risks (e.g., loss of privacy and/or breach of confidentiality) -
    a. Potential Breach of Confidentiality and/or Privacy: There is always a risk of loss of confidentiality. This risk will be minimized by conducting study interviews in a private room, assigning participants a study number and identifying this information only by this number, storing all study documents in a locked file cabinet in a locked office, and only using a password protected computer. Also, (if assigned to a peer navigator), it is important for a participant to know that the peer navigator is an employee of the clinic and is trained in maintaining confidentiality, similar to their doctor and nurse.

All of these risks are minimal and have a low magnitude effect. Currently MIC staff are HIPAA trained and they know confidentiality protocol after receiving extensive clinical training in order to work in this clinic setting.

In an effort to meet the NIH policy for Data and Safety Monitoring, we have created a system for oversight of the project. Oversight of internal monitoring of the participants' safety will be conducted by the PI, Dr. Patricia Cioe. The internal Data Safety and Monitoring Board at the Center for Alcohol & Addiction Studies (CAAS) will participate in the oversight of this study. Investigators in the application have extensive experience with clinical trials for substance use disorders, tobacco dependence, and smoking cessation.

The PI and co-investigators will meet bi-weekly on the project, at which time they will evaluate the progress of the trial, review data quality, recruitment, and study retention, and examine other factors that may affect outcome. They will review the rates of adverse events to determine any changes in participant risk. A report will be generated semi-annually for the study record. It will also be forwarded to Brown University's Institutional Review Board. The Investigators will be available to meet outside of the weekly meetings, if necessary, due to concerns regarding a particular participant or any problems that may arise for participants. If necessary, they will make appropriate recommendations for changes in protocol. Dr. Cioe will conduct daily oversight of participant safety. She will meet weekly with staff to review participant progress and their experience with the procedures, including adverse events. Any adverse events that are observed and/or reported will be immediately reported to Dr. Cioe. Serious adverse events (SAEs) will be reported to the Brown University IRB immediately by telephone and by written report within 24 hours of our receipt of information regarding the event; SAEs will also be reported in writing to NCI. Adverse events will be reported to the Brown University IRBs and NCI semi-annually.

Compensation / Reimbursement

Total possible compensation is $180, according to the following schedule: $40 for the BL assessment; $25 for the nurse visit; $25 for the week 4 assessment, $40 for the week 12 assessment; and $50 for the week 24 assessment. Participants will receive compensation only for the sessions they complete, and compensation will not be contingent upon smoking status. If a participant is ineligible at Baseline, they will be compensated $10 for their time. This amount is similar to payments made by similar, previous studies. The amount helps to cover transportation costs and compensates the participants for the time spent with the research staff at the visit.

Data Analysis Plan

Assessments will be designed as scannable forms for use with the Cardiff Teleform Scanner System®. Data will be verified, checked, and uploaded to an SPSS file to conduct analyses. Initial data analysis will include studies of randomization effects (group differences), distribution properties of dependent and other variables, and correlations among outcome measures.

Sample Size and Power Considerations. Our primary objective will be to examine preliminary effect sizes for PNSS-S, rather than to determine statistical significance between groups at certain p values. At the same time, we are well aware of the dangers of relying exclusively on small-scale pilots to determine the promise of novel treatment approaches. These effect size estimates have a large standard error, and we primarily will be hoping to find a pattern of results that is supportive of the experimental treatment. Effect size estimates will include odds ratios for smoking abstinence. We believe a sample size of 72 should allow adequate examination of PNSS-S intervention effect sizes while staying within the scope of a developmental project. We recognize that only medium to large effect sizes will be likely to attain statistical significance with a sample of this size. Our data also will allow us to obtain stability estimates for point-prevalence abstinence (i.e., intercorrelations among outcomes at 4, 12, and 24 weeks). Using a program that allows us to specify proportions at each time point and the correlations between time points, we will be able to get a good estimate of the sample size needed to find a significant main effect of treatment in a repeated measures analysis using generalized estimating equations. All analyses will include sex as a covariate and follow-up analyses will test the Sex x Condition interaction to determine whether sex moderates the effects.

Treatment Feasibility, Acceptability, & Efficacy. Individual analyses of variance will be conducted to compare treatments (PNSS-S vs. SC) on the continuous variables of number of sessions attended and client satisfaction scores. For treatment retention rate (dichotomous), a chi-square analysis will be used. Analyses will test the hypothesis that PNSS-S improves point prevalence abstinence relative to SC. Tests of the effect of treatment condition on Quitline usage, quit attempts, and on 7-day point-prevalence abstinence across the 4, 12, and 24 week assessments will be conducted using GEE, which provides appropriate modeling of covariance structures when observations are correlated across time. The primary, between groups, independent variable in the GEE analysis is treatment condition assignment, which will be dummy-coded using SC as the reference group.

Following the intention-to-treat principle, all participants who have been randomized will be included in the analyses.

Potential Mechanisms of PNSS-S Effects. Sample size in this trial precludes formal mediation analysis with adequate power. The analyses are designed to test the plausibility of potential mechanisms of the PNSS-S treatment effect. We will examine change in these variables using multilevel modeling as increased social support and self-efficacy for quitting are important outcomes in and of themselves, which may affect long-term smoking outcomes and will be useful in demonstrating the longer-term effects of PNSS-S. Mediators will be examined separately, rather than simultaneously, given our limited sample size. For each mediator, we will fit a multilevel model to obtain both an initial value (intercept) and rate of change (slope) in each of these variables from baseline to week 4. We will first test whether treatment condition predicts change in these variables. We will then enter the intercept and slope parameters from these models into the main GEE model of smoking outcome to determine whether change in these variables predicts smoking outcomes. We will be able to examine whether the effect of treatment is reduced when the mediator is added to the model and can test for significance (not expected given the sample size) using the products of coefficients method. Social support in the 4 weeks after quitting also will be examined as a potential mediator of PNSS-S effects.

Missing Data

We will explore patterns of missing data to determine possible mechanisms of missingness and will explore different techniques to impute missing data values in different analyses. In the primary analyses using GEE, we will include all participants and will assume that participants with missing data are smoking.