Published in final edited form as:

Contemp Clin Trials. 2018 May ; 68: 14–22. doi:10.1016/j.cct.2018.03.007.

Planning a Change Easily (PACE): A Randomized Controlled Trial for Smokers Who Are Not Ready to Quit

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Abstract

Smoking cessation programs are efficacious and have been validated to assist the 10% to 30% of smokers who are ready to quit in the next 30 days. While the majority of smokers want to quit smoking in the future, only 69% are planning to quit within the next year. Planning a Change Easily (PACE) is a nation-wide, telephone-based comparative effectiveness, randomized controlled trial for smokers not ready to quit (SNRTQ). This project, as well as its intervention components, outcomes, and hypotheses are discussed. This study will compare the effectiveness of four intervention conditions that could potentially help SNRTQ to quit smoking: Brief Advice, Motivational Interviewing, Rate Reduction, and Motivational Interviewing plus Rate Reduction combined. Rate Reduction conditions will include the provision of nicotine replacement therapy in the form of gum. Approximately 840 participants will be recruited and randomized to the four intervention conditions. The main outcomes for this study include self-report prolonged and point prevalence abstinence with biochemical verification of cessation. Secondary outcomes include quit attempts, cost-per-quit, and cost-effectiveness analyses. Informed by evidenced-based interventions, strong clinical guidelines, and economic analysis, PACE has the potential for significant public health impact. Results could readily be disseminated and translated to tobacco quitlines, which are present in all 50 states and are offered free to the public.

Keywords

Smoking cessation; randomized clinical trial; smokers not ready to quit; motivational interviewing; rate reduction; brief advice; cost-effectiveness

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Competing Interests

All authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Introduction

Cigarette smoking is the single most important preventable cause of morbidity, mortality, and excess health care costs in the US, causing approximately 480,000 premature deaths annually and accounting for 30% of cancer deaths.¹ The 2014 Surgeon General's Report documents that smoking cessation programs are efficacious across a wide variety of settings (e.g., clinics, worksites, the military), populations (e.g., low income, minorities), and venues (e.g. internet, quitlines, media-based programs). However, all these approaches have been validated to assist the 10% to 30% of smokers who are ready to make a serious quit attempt in the next 30 days.^{1,2} While the majority of smokers want to quit smoking in the future, only 69% are planning to quit within the next year.^{1,3}

The Planning a Change Easily (PACE) project will address the underserved population of smokers not ready to quit (SNRTQ) through the examination of two different counseling strategies shown to be effective in smokers ready to quit: Motivational interviewing (MI)^{4,5} and rate reduction (RR).⁶⁻⁸ Cognitive behavioral theorists would argue that behavioral acquisition of skills, such as those provided in RR, is the key to behavior change.^{9,10} In strong contrast, MI theorists would argue that, through the guided resolution of the individual's ambivalence of behavior change and promotion of self-efficacy (i.e., feeling confident about behavior change) using a conversational style that elicits "change talk," the individual would need remarkably little additional assistance to change their behavior.⁴ Therefore, testing differences between MI and RR, as well as a combination of both (i.e., MI + RR), is necessary to better understand what effective treatment will look like for SNRTQ.

While there is clear support for RR and MI, no study has evaluated their independent and combined effects for smoking cessation in SNRTQ.⁷ Thus, we propose to conduct a comparative effectiveness trial in a time- and intensity-controlled format. This design is essential to the evaluation of the independent and additive effects of MI and RR on abstinence rates while comparing them to Brief Advice (BA), a standard of care condition. In addition, a time- and intensity- controlled format could strengthen our confidence that our outcomes are attributable to intervention differences and not to amount of exposure to the intervention. Results could be easily disseminated and translated to tobacco quitlines, which are present in all 50 states and are offered free to the public. While traditionally used to target smokers ready to quit, tobacco quitlines may also be an appropriate venue for SNRTQ. This study could expand quitlines by treating the vast majority of smokers—those who are not ready to quit at the present time. Informed by evidenced-based interventions, using strong clinical guidelines, conducting economic analysis, and targeting an underserved population of smokers, PACE has the potential for significant public health impact.

Hypotheses

Based on previous research, we hypothesize that RR and MI will have better abstinence rates compared to BA.^{6-8,11} When treatment components are added, superior cessation occurs,¹² especially when MI is added to an efficacious smoking cessation intervention.⁵ Thus, we hypothesize the effects of combining MI and RR will be additive and superior to MI or RR alone. The combined treatment would enhance motivation to quit, provide participants with the techniques necessary to develop confidence to quit and maintain gains, remove the

proscriptive nature of a skills-based intervention, and decrease defensive responses to the use of effective skills strategies. Even though there are no studies comparing smoking abstinence rates between an MI and a combined MI + RR intervention, previous research on marijuana dependency found that a combined MI + skills intervention was almost twice as effective as MI alone in achieving abstinence rates 15 months post-randomization.¹³

Materials and Methods

Study Design

The Institutional Review Board provided approval to conduct this study. We based our design on the Society for Research in Nicotine and Tobacco definition of a “cessation induction trial,” which is a treatment that promotes cessation among all smokers, including those not ready to quit.¹⁴ One implication of this design is that success is based on percent abstinent at a given point in time that is not based on a determined quit date, as smokers not ready to quit often do not typically set formal quit dates.

This research will include a four-condition treatment design as the main independent variable. Participants will be randomized (1:2:2:2) to the four treatment conditions: (1) Brief Advice (BA); (2) Motivational Interviewing (MI); (3) Rate Reduction (RR); and (4) Motivational Interviewing and Rate Reduction combined (MI + RR). The RR and MI + RR conditions will include the provision of Nicotine Replacement Therapy (NRT) in the form of 4 mg nicotine gum.

We applied this type of uneven randomization of participants for three reasons: (1) Ethically, we will randomize half as many participants to a brief advice standard of care group with minimal intensity and allow a majority of participants (6 out of 7) to engage in more intensive interventions; (2) Power was not significantly affected (i.e., we found no measurable drop for effect sizes compared to even randomization and the exact *p*-values remained significant); and (3) Given that this is the first study to compare these interventions individually and in combination for SNRTQ, our estimated outcome measures will have higher precision with larger samples in active intervention arms.

Upon randomization, participants will be assigned to an interventionist who will remain in contact with them throughout all sessions, when possible. All four intervention conditions will include three over-the-phone intervention sessions, each approximately 30 minutes in length. These three treatment sessions will be provided over a period of 3 to 6 weeks, depending on the participant’s availability. Upon the completion of the main intervention components, three booster sessions will be administered in 2-month increments throughout the intervention period (2, 4, and 6 months from randomization) in conjunction with study assessments. Twelve months after randomization, prolonged and point prevalence abstinence (7 days) will be measured through self-report and biochemical verification (i.e., saliva cotinine).^{14,15} The 12-month assessment will be conducted by a research staff member blind to treatment condition.

Participants

We will operationally define a SRNTQ based on the classifications of *contemplation* and *precontemplation* stages in the Transtheoretical Model of Change.¹⁶ Thus, a SNRTQ would be anyone who is either: (1) interested in quitting smoking in the next 6 months but not the next 30 days (i.e., contemplation stage), or (2) not interested in quitting smoking in the next 6 months but at some point (i.e., precontemplation stage).

Based on inclusion criteria, recruitment will target adults in the U.S. who have smoked at least an average of five cigarettes a day for the past year, match the definition of SNRTQ, have access to a telephone, and understand the consent process in English. Exclusion criteria will include having a known contraindication, allergy or hypersensitivity to nicotine gum; being unable to chew gum; using other behavioral or pharmacologic tobacco cessation programs in the past 30 days; current pregnancy or lactation, or planning to become pregnant in the next 12 months; describing a medical history of unstable angina, myocardial infarction within the past 3 months, cardiac dysrhythmia other than medication-controlled atrial fibrillation or paroxysmal supraventricular tachycardia, or medically uncontrolled or untreated hypertension.

Sample Size, Power Analysis, and Detectable Effect Sizes—All power and sample size calculations were done with PASS12.¹⁷ Our power analyses were based on cotinine verified point prevalence. We based our power calculations assumptions on two recent studies to compare BA vs. MI, RR, and MI + RR combination.^{7,18} One of these was a meta-analysis that reported the odds of the outcome in the range of 2.0 to 2.6 for the mentioned treatments.⁷ Based on this research, we would expect MI and RR to at least double the odds of the outcome compared to the control condition (i.e., BA), and the combination therapy (i.e., MI + RR) to have even larger, additive effect. Based on calculations from a previous study, we expect for MI + RR to more than double the odds of smoking abstinence compared to BA alone and increase the odds by at least 50% compared to MI and/or RR alone.¹³ We plan to recruit 840 participants. Based on previous research, control group success rates should not exceed 9% cessation, therefore we assumed a 9%-point prevalence rate in the BA control group.¹⁸ Power calculations showed that group sample sizes of 240 in any of the active intervention arms (i.e., RR, MI, and MI + RR) and 120 in the control arm (i.e., BA) would achieve 80% power to detect a difference in a continuous abstinence rate of 10%. Therefore, cessation in treatment arms was assumed to be 9% under the null hypothesis (i.e., no difference between conditions) and 19% under the alternative hypothesis, which is equivalent to a minimal detectable odds ratio of 2.1. This odds ratio is supported by previous work; earlier research has shown effect sizes comparing control to monotherapy (RR or MI alone) that were much larger than a doubling of effect size.^{5,19} All of the effects potentially larger than 19% (perhaps additive effect of MI and RR) had power in excess of 80%, allowing us to claim those differences as significant if they are truly observed. Furthermore, we have 80% power to detect an increase from 19% to 29% as a result of MI + RR compared to MI and/or RR alone, equivalent to an odds ratio of 1.5. The test statistic used was the two-sided chi-square test. Similarly, a logistic regression model of a binary outcome variable on a nominal covariate (i.e., a binary comparison of control vs. treatment arms coded as dummy variables) with a sample size of 840, achieves 80% power at $\alpha = .05$

to detect a change in probability from the null baseline value (BA group) of 9% to a treatment effect of 11% change (20% prevalence under the alternative hypothesis), which corresponds to a detectable odds ratio of 2.5. Logistic regression model power was calculated under the assumption that the main independent variable had an $R^2 = .1$ with other independent variables in the model. The assumed significance level for all tests was .05.

Recruitment, Screening, and Randomization

Recruitment will be multi-faceted, including local and regional strategies. These strategies will be both traditional (e.g., flyers, business cards, and medical referrals) and electronic (e.g., Facebook, Pandora Radio). We will also incorporate a “refer-a-friend” program where participants will receive an extra \$20 gift card for referring a person who is eligible and enrolls in the study.

Potential participants will learn more about the study by calling a toll-free line, messaging a staff member through our Facebook page, or viewing information on the study website. If the person continues to be interested in the study, he or she will complete a screening visit over the phone. If the person is eligible, the participant will provide verbal consent to continue with baseline data collection. Upon verbal consent, participants will be asked to provide contact information, demographic characteristics, smoking history, current cigarette use, other tobacco and nicotine use, and will be classified as either a contemplator or precontemplator based on the Transtheoretical Model of Change.¹⁶

Once the baseline data is collected, participants will complete the informed consent electronically or via paper form, depending on participant’s computer access and preference. For those who prefer immediate electronic consent, the electronic consent will be sent to the participant’s email via DocuSign and explained during the phone call. For those without computer access, study staff will mail the participant a hard copy of the consent form with a return envelope and will schedule a phone appointment 3 days after the screening call to review the consent with the participant. All participants who consent will receive a blank copy of the consent form for their records after randomization.

Ideally, participants will complete screening, baseline, and randomization in the same phone call, though this can be altered if the participant has extenuating circumstances. Randomization will occur once study staff has received the participant’s signed informed consent document. Each participant will be randomized to treatment group using computerized block design. Once the random assignment is completed, study staff will implement the appropriate treatment for that intervention condition.

Retention Plan for Enrolled Participants

Intensive efforts will be in place to assist interventionists in the retention of participants. These will include incentives for attended sessions (\$20 Amazon gift card), as well a t-shirt that will be provided at enrollment and another t-shirt that will be mailed to the participant one month before their 12-month follow-up. Also, participants will receive birthday cards, holiday cards, and session reminders sent 24 hours in advance.

If participants do not answer the phone for their scheduled session, interventionists will first call or text participants at 15 minutes past their appointment time to complete or reschedule the session. If there is no answer, interventionists will attempt to contact participants at later times through different modalities (e.g., text, phone call, alternative phone number, e-mail) and at different times of the day at least 3 times a week until participant intervention window closes. Interventionists will resume participant contact at the beginning of the next intervention window. If unresponsive participants are reached at some point, interventionist will attempt to re-engage them into treatment by addressing barriers (e.g., changing sessions to later times in the day, less frequent sessions, resuming sessions at a later date, participating only at the 12-month follow-up). Participants will be allowed unlimited opportunities to reschedule until the study team agrees to discontinue contact.

At 12-month follow-up, a staff member blinded to treatment condition will first contact participants by phone to complete the follow-up questionnaire. If there is no response to calls, then an email will be sent to the participant with the follow-up questionnaire to complete via Qualtrics. If there is still no response, a the 12-month follow-up questionnaire and a reminder of their compensation will be sent through regular mail. We chose these strategies because they have yielded 90% retention rates in previous research with similar samples.²⁰

Intervention Conditions

Participants in all conditions (i.e., BA, MI, RR, and MI + RR) will receive the same amount of intervention time (approximately 30 minutes). However, the four interventions will vary in style of counseling (i.e., directive psychoeducation, guided resolution of smoking abstinence ambivalence, behavioral skills with NRT, and a combination of guided resolution of ambivalence and behavioral skills with NRT, respectively). All treatment sessions will begin with 2 to 4 minutes of assessment questions. Then, interventionists will cover the material assigned for the arm and session. Toward the end of each session, interventionists will ask participants if they are ready to set a quit date and will specify that setting a quit date is not required. Participants will be informed that setting a quit date has been recommended in smoking cessation interventions and that participants are more likely to quit in the future to increase motivation to set one.^{12,21} If participants report abstinence at any phone call, the interventionists will provide the same information as planned on each arm, but will focus their efforts on relapse prevention or reviewing how the information presented is pertinent to the participant's recent quit attempt and current goals.

Brief Advice—The state-of-the-science strongly makes the case to document the efficacy of active treatments relative to brief advice or a “standard of care” condition.^{5,22} Previous research has traditionally and extensively compared direct advice using smoking psychoeducation with more intense interventions in randomized controlled trials with smokers ready to quit and SNRTQ.^{5,22–24} Participants randomized to this condition will receive psychoeducation citing health consequences and the impact on mortality and morbidity of smoking, based on information provided by the Centers for Disease Control and Prevention.²⁵ Session 1 will orient the participant about the purpose of this intervention arm: education about the health risks of smoking. The interventionist will educate

participants about the chemicals and toxins in cigarettes and their general use (e.g., arsenic is used in pesticides). Next, the interventionist will educate about the addictive component of cigarettes (nicotine) and withdrawal symptoms. Session 2 will start with the interventionist asking participants about any thoughts from the previous session. Then, the interventionist will educate participants on the increased risk for cancer in people who smoke cigarettes and the benefits of quitting smoking (e.g., decreased risk of lung cancer). In addition, the interventionist will educate participants on how cigarettes damage the circulatory and respiratory systems. Session 3 will, first, provide information about how smoking affects blood sugar and diabetes. Then, the interventionist will educate participants on fertility issues related to smoking, consequences of smoking during pregnancy, and secondhand smoke. To make these initial sessions interactive, the interventionists will ask participants about their existing knowledge prior to presenting the information (e.g., “what do you know about smoking and fertility issues?”). During all booster sessions, the interventionist will briefly review all topics discussed from sessions 1 through 3 and discuss how the information affects participants’ smoking behaviors or thoughts about smoking. To make these booster sessions interactive, the interventionists will ask participants what they remember about each health consequence from previous sessions (e.g., “what do you remember about the toxins in cigarettes?”). Moreover, at any session, participants will be provided with the phone number of the national tobacco quitline (1-800-QUITNOW) and will be encouraged to call when they are ready to quit or when they request cessation resources.

Motivational Interviewing—MI is a collaborative conversation style for strengthening a person’s own motivation and commitment to change.⁴ MI avoids a confrontational style and, instead, collaboration between the interventionist and the participant guides participants to change their behavior. MI is an evidence-based treatment that is effective in the promotion of health behavior.^{26,27} The Cochrane Collaboration conducted a meta-analysis to determine if MI was effective in promoting smoking cessation for smokers ready to quit.⁵ This review analyzed 28 studies conducted between 1997 and 2010 that included a total of 16,000 smokers. Results demonstrated that MI was more effective than brief advice or usual care (Effect Size = 1.26, 95% confidence interval [CI] 1.16 to 1.36, using the longest follow-up period and strictest definition of abstinence).

Basic MI principles will be used for each call with the intention of eliciting language that indicates behavioral change (i.e., “change talk”) using open-ended questions, affirmations, reflections, and summaries.⁴ First, each telephone call will include an initial period of engagement. Then, motivation and confidence to change smoking behavior will be assessed separately using scales from 1 (*not at all motivated/confident*) to 10 (*extremely motivated/confident*). Next, the counselor will focus the discussion using the “5Rs” to increase the participants’ motivation for change and eventual odds of cessation.¹² The 5Rs will provide opportunities to elicit information from participants as follows: (1) Relevance: The interventionist will elicit why quitting is personally relevant to the participant, guiding the participant to be as specific as possible. (2) Risks: The interventionist will ask the participant to identify potential negative consequences of tobacco use, highlighting those that seem most relevant to the patient. Both short-term (e.g., shortness of breath, risk of respiratory

infections) and long-term risks elicited from the participant (e.g., heart attacks and strokes, lung and other cancers) will be emphasized. (3) Rewards: The interventionist will ask the participant to identify potential benefits of stopping tobacco use, highlighting those that seem most relevant to the patient (e.g., improved health, saving money, improved sense of smell). (4) Roadblocks: The interventionist will ask the participants to identify barriers to quitting. Barriers (e.g., enjoyment of smoking, withdrawal symptoms, weight gain, reliance upon smoking to curb emotional distress, and urges to smoke) will be validated and the interventionist will reflect and emphasize the participant's desire, need, and willingness to quit smoking.²⁸ (5) Repetition: The interventionist will elicit differences between previous and a current or future quit attempts and emphasize change talk. The interventionist will use this format for the initial three sessions and the following booster sessions. During booster sessions, the interventionist will attend to, and reflect on, changes in the 5Rs (e.g., "your health has become a higher priority since we started this program") from session to session. In addition, the interventionist will have the opportunity to reinforce (repeat) the participant's decision to stop smoking. At the end of each session, a summary of the discussion will be provided, and motivation and confidence to change smoking behavior will, again, be assessed.

While similar in basic content across initial and booster sessions, each additional session will address new personal or situational changes that the participant has experienced and will focus on having the participant describe how these changes have altered his or her motivation to quit. Counselor-initiated summaries of the participant's current motivation will highlight Relevance and Rewards to ensure the participant continues to focus on their personal reasons for moving toward change. In all booster sessions, we will provide information to normalize experiences during quit attempts. For instance, we will inform that most tobacco users experience relapses and that the best predictor of sustained cessation is the number of participant quit attempts.¹² Should the participant wish to quit at any point during the sessions, the interventionist may assist in creating a participant-centered cessation plan, but no specific skills will be provided in this condition (e.g., "it seems like distraction and exercise could help you quit"). At the end of each session, the interventionist will ask the participant about their willingness to set a quit date using the elicit-provide-elicited approach,⁴(p139) where the interventionist will elicit permission to provide information, will provide the information (e.g., higher likelihood of quitting if setting a quit date), and will elicit the participant's thoughts about setting a quit date.

Rate Reduction—RR has demonstrated to be an effective intervention specifically for SNRTQ.⁷ Throughout RR, the interventionist will inform participants about the strong medical evidence that systematic smoking reductions can lead to long-term smoking cessation.⁶ Also, the interventionist will describe the rate reduction intervention, with both behavioral and pharmacologic aspects, as a "springboard for cessation." In addition, reduction will be described as "taking them down the path of cessation" or "preparing them to quit." The interventionist will emphasize that behavioral and pharmacologic rate reduction is not viewed as an end (e.g., smoking less) but a means to an end (i.e., smoking cessation).

Session 1 will provide information on the first skill, *breaking brand loyalty*. Given the fierce brand loyalty that smokers have for their own cigarettes,²⁹ “breaking” the brand loyalty and having smokers switch to another brand should facilitate behavior change, as smokers who change their preferred brand of cigarette decrease their smoking and feel more confident about having a successful quit attempt in the future.³⁰ Participants will also be encouraged to utilize the second skill, *self-monitoring of smoking* (e.g., amount/frequency, and temporal and situational correlates) using a daily diary to identify personal, automatic triggers to smoke. Appropriate use of NRT (i.e., nicotine gum) will be introduced to enhance usage and adherence. Participants will be encouraged to reduce their smoking rates before the next session. A traditional reduction goal (e.g., 50% reduction) will not be set for participants as we intended to tailor this intervention to SNRTQ, who may not be ready to achieve specific reduction goals. Session 2 will assess change and provide information on the third skill, *disrupting automatic triggers to smoke*. During this session, the interventionist will elicit ideas about how to change each automatic process identified through the use of the daily diary (e.g., delay the first cigarette of the day, eliminating situations where smoking was formerly acceptable, or placing the cigarettes in another room or in the garage). Appropriate use of NRT will be discussed again. Participants will be encouraged to reduce their smoking rates before the next session. Session 3 will assess change and address the fourth skill, *smoking less of each cigarette*. Interventionists will encourage participants to mark their goal amount on the cigarette with a non-toxic pen (e.g., Sharpie or Pentel pens) and to smoke until the marked line is reached. By smoking less of each cigarette, participants will be reducing their overall “dose” of tobacco. Further, issues associated with quit attempts will be discussed, including nicotine withdrawal, symptoms, making a commitment, failed attempts, and reducing vs. quitting (i.e., rate reduction is not associated with maximal health benefits). Appropriate use of NRT will be discussed again. The booster sessions will assess skill practice, provide a review of all skills, review appropriate use of NRT, and problem-solve remaining barriers to skill use and cessation.

Motivational Interviewing and Rate Reduction—MI + RR combines elements of MI and RR conditions. Participants in MI + RR will receive NRT in the same way as participants in RR condition. Session 1 will begin with a discussion of motivation and confidence to change. Interventionists will address the 5Rs in the same way as in the MI condition. Next, participants will be offered information on rate reduction skills. The skills content will be the same as that in the RR condition, but in an abbreviated format. Skills offered in Session 1 will include the first skill, *breaking brand loyalty*, and the second skill, *self-monitoring smoking*. Appropriate use of NRT will be introduced afterward to enhance its use and adherence. Information from 5Rs discussion will be summarized with an emphasis on change talk. Then, participants will be encouraged to set their own reduction goals before the next session and will also be encouraged to think about skills that could help them achieve their goal. Motivation and confidence to change will be assessed again toward the end of the session. Last, participants will be asked to set a quit date if they are ready. Session 2 will begin with a review of the previous session. Motivation and confidence to change will be assessed. Interventionists will address the 5Rs, identifying any new content the participant identifies. Interventionists will focus on the relevance and rewards specific to the participant. Next, participants will be offered information on the third skill, *disrupting*

automatic triggers to smoke. Appropriate use of NRT will again be discussed. A summary of the 5Rs will be provided with an emphasis on change talk. Participants will be encouraged to set their own reduction goals before the next session and will be asked about skills that can help them achieve their reduction goal. Then, motivation and confidence to change will, again, be assessed. Last, participants will be encouraged to consider the importance of setting a quit date. Session 3 will begin with a review of the previous session. Motivation and confidence to change will be assessed. Interventionists will address the 5Rs identifying any new content and will focus on the Relevance and Rewards specific to the participant. Next, participants will be offered information on the fourth skill, *smoking less of each cigarette*, and will engage in a discussion about issues that arise during quit attempts. Appropriate use of NRT will be discussed. A summary of the 5Rs will be provided with an emphasis on change talk. Participants will be encouraged to set their own reduction goals before the next session and will be asked about skills that can help them achieve their reduction goal. Motivation and confidence to change, again, will be assessed. Last, participants will be encouraged to consider the importance of setting a quit date.

The booster sessions will be a continuation of previous discussions. Interventionists will begin each booster session with a broad discussion of the participant's current smoking status. Motivation and confidence to change will be assessed. Interventionists will address the 5Rs identifying and reflecting on any new content the participant describes. Next, participants will be offered a review of all RR skills and will be offered assistance in problem-solving any remaining barriers to skill use and smoking cessation. Then, effective NRT use will be reviewed. A summary of the 5Rs will be provided with a focus on change talk. Participants will be encouraged to continue toward setting goals and elicit skills to help them achieve their goal. Motivation and confidence to change, again, will be assessed. Last, participants will be encouraged to set a quit date using the elicit-provide-elicitation approach.

Due to the strong impact that combined behavioral and pharmacologic rate reduction have on future smoking cessation,^{6–8} participants in the RR and MI + RR arm will receive NRT. Participants will receive 26 weeks' worth of 4 mg nicotine gum. Gum will be dispensed at the baseline call and every two weeks at the participant's request. This is consistent with the nicotine gum usage provided in the most successful trials of pharmacologic rate reduction.³¹ We have elected to use nicotine gum, instead of nicotine patch because participants can dose NRT during high-risk situations with the gum. Moreover, we chose to use nicotine gum instead of lozenges because, even though both methods are equally effective,³² distribution of nicotine gum poses a lower cost.³³ Identical to other protocols in the literature, we will instruct participants to use the gum, instead of smoking, whenever they have a craving for a cigarette. Interventionists will provide instructions directly (RR) and through the elicit-provide-elicitation approach (MI + RR) regarding NRT use. For instance, interventionists will teach participants to make nicotine gum highly accessible (e.g., shirt pocket, purse) while making cigarettes inaccessible. In every session, participants will be instructed to not chew nicotine gum like chewing gum, but instead, to chew for 10 to 15 times and park it between their cheek and gums. This is particularly important, as it reduces side effects (particularly nausea) associated with the use of nicotine gum. We will track the number of pieces of gum used throughout the intervention. NRT will continue to be dispensed upon participant's

request until the 6-months post randomization mark. We will remind participants about this deadline 2 weeks prior to the 6-month mark.

Assessment Components

Baseline Measures—Prior to intervention, we will assess previous quit attempts, previous use of cessation programs, and tobacco use history. Assessment of tobacco use will include cigarettes, smokeless tobacco, Snus, cigars, little cigars, pipe (with tobacco), e-cigarettes, hookah, and rolling your own cigarettes.

Self-Reported Tobacco Use and Dependence—At each phone call, we will collect information about tobacco use amount and frequency of use since the last study contact. We will use the Fagerström Test for Nicotine Dependence (FTND), a widely-used instrument in nicotine and tobacco research.³⁴

Use of Other Cessation Aids—At each phone call, we will assess the use of other smoking cessation aids and any other smoking cessation program or product used by the participants during the trial.

Primary Outcomes

Point Prevalence and Prolonged Abstinence—For individuals who report that they are not smoking, we will assess 7-day point prevalence (i.e., 7 days without a cigarette, “not even a puff”) and prolonged abstinence (i.e., length of time since the quit date with a two-week grace period around the quit date) at each study contact. The Society for Research in Nicotine and Tobacco consensus paper concluded that both point prevalence and prolonged abstinence are appropriate measures in measuring long term outcome and both outcomes have shown to be highly correlated.^{14,35}

Biochemical Verification of Smoking Status—Biochemical verification of smoking cessation is an objective assessment commonly used in clinical trial settings, and generally includes cotinine (a metabolite of nicotine) assessment from saliva.³⁶ While self-reported smoking cessation is often assessed in clinical trials, it is subject to misreporting by participants. A systematic review showed that self-report underestimates smoking prevalence compared to biochemical verification. In addition, recent studies using 7-day point prevalence criteria of those who provided biochemical samples have shown that discordance between self-reports and biochemical verification of cessation (i.e., salivary and urinary cotinine) ranges from 21 to 56%.^{37–39} For this study, we will ask participants who self-report as having quit smoking at their final assessment to submit a saliva sample to confirm their non-smoking status. Participants who have quit but are using nicotine products (i.e. nicotine gum or patch) at the time of their 12-month assessment will not be asked to submit a sample, as these products create a false positive.³⁶ To facilitate the acquisition of saliva samples, participants will be sent an easy-to-use saliva collection kit (Salimetrics SalivaBio Oral Swab) with instructions and pre-paid postage to minimize return barriers. In addition, we will incentivize the return of the kit containing the specimen with a \$20 gift card.

Secondary Outcomes

Quit Attempts—We will assess quit attempts (periods of at least 24 hours of intentional cessation) since the last study contact at all study contacts. For SNRTQ, we believe that quit attempts may be a good indication of whether interventions are eliciting a positive response, even if the 12-month outcomes do not support prolonged abstinence.

Program Costs—We will track the costs associated with the intervention including personnel and facility costs containing those indirectly associated with program management. Personnel costs will be calculated based on the training and average hourly wage (with benefits) of the interventionists. We will also track cost of materials including NRT (based upon actual uptake of NRT which is tracked for each participant in RR and MI + RR conditions), postage used to mail NRT, and any other direct program activities that might contribute toward costs, such as toll-free numbers.

Program Evaluation—At the 12-month follow up visit, participants will complete quantitative and qualitative questions developed for this trial regarding their perspectives on the helpfulness of various program components (e.g. skill and helpfulness of counselor, relevance and effectiveness of treatment, parts of intervention that were most effective) as well as recommendations for program modifications.

Treatment Adherence—We will ask participants in RR and MI + RR conditions to self-report use of NRT, the number of gum pieces used per day, and percentage of time that nicotine gum was used (instead of smoking a cigarette) at each study contact during active intervention. For all participants, we will track the number of sessions completed (1 to 6 possible sessions).

Study Informatics

All data collection (including eligibility, baseline, session, and follow-up), processing, and management will occur via a relational database using FileMaker Pro 14.⁴⁰ All of the informatics structures within this system will operate in a client/server network environment and will provide methods to secure data.⁴¹ Only study personnel with appropriate access privileges will have access to informatics system via a secured virtual private network (VPN) connection by authenticating to the institution's network through the University Active Directory. All assessment data will be entered in real-time while the interventionist is completing the session with the participant.

Interventionist Training and Treatment Fidelity

The interventionists will be recruited based on educational background and past experience with counseling or delivering behavioral interventions. All interventionists will be required to have at least master's degrees in diverse areas of study (e.g., social work, public health, counseling, and psychology). Interventionists will be trained to ensure proper knowledge and skill of interventions and research procedures. The interventionists will be expected to read and become familiar with detailed manuals and guides developed for this study as well as the intervention content for each session type. A decision was made to train interventionists to deliver all of the treatment methods to control for specific interventionist

characteristics. If we dedicated individual interventionists to a specific treatment condition, it would not be possible to evaluate whether the treatment effect was based upon the intervention content or the interventionist.

Interventionists will be trained in MI through a structured process of reading background materials, attending trainings with faculty-level clinical supervisors, and conducting practice sessions with other faculty and staff members. Interventionists will also practice scoring their own sessions to clarify expectations. All interventionists will meet standard proficiency level in MI before working with participants. Audio from all study sessions will be recorded, and approximately one out of every ten sessions will be reviewed and scored for fidelity and MI adherence (when applicable) by doctoral-level clinical supervisors. Interventionists will receive weekly clinical supervision from doctoral-level supervisors for feedback on scored sessions and further training when needed. MI training by local and national experts will be provided periodically throughout the study period.

Statistical Analysis

Primary and Secondary Outcomes—Analyses will be carried out using SAS/STATv14.1. Due to the nature of data capture and inbuilt quality control measures, erroneous values are expected to be minimal; however, all data will be inspected for outliers and out-of-range values. Any inconsistencies will be corrected and examination of distributions may prompt transformations. Justifiable transformations will be applied based on the best available analysis strategy. Our follow-up rates have consistently been at, or above, 90% so we will perform analyses to determine whether differential attrition occurred by subject baseline characteristics.

Analysis will be intent-to-treat.^{14,42} To deal with missing data we will use multiple imputations (model based via MCMC algorithm).⁴³ We will create a monotone missing data pattern, then impute the missing data at least 5 times, analyze each data set with methods proposed below, and finally combine the results to produce inferences.

Given that our primary outcomes and treatment conditions are discrete, we will use categorical analytical methods; however, we will describe baseline characteristics using proportions, means with standard deviations, and medians with interquartile ranges as appropriate and apply comparisons using chi-square test for categorical variables, *t*-tests and/or ANOVA for normally distributed continuous variables, and appropriate non-parametric tests for non-normally distributed continuous variables. We will evaluate the efficacy of interventions and test differences in point prevalence at 6 months post-intervention (i.e., 12-month follow-up) among conditions using a two-step approach. First, we will conduct a chi-square test to compare the equality of outcome proportions between four levels of treatment at the 6-month post-intervention follow-up. Second, we are going to expand these into multivariate logistic regression models, with BA selected as the default comparison group compared to other treatments. We will estimate the relative odds of a treatment effect on smoking cessation point prevalence and prolonged abstinence, while adjusting for baseline demographics, socioeconomic status, smoking history, process measures, and other potential covariates. As such, we will test the associations and estimate effects of additional variables (as listed) besides treatment effect. A secondary outcome in

this study is the number of quit attempts (continuous variable). We will apply multiple linear regression model with repeated measures to test the equality of mean quit attempts among the four intervention arms across time, along with intervention by time interactions. We will control for multiple comparisons of treatment effects using a Bonferroni correction for p -values. Similar to the primary outcome model, we will adjust for baseline demographics, socioeconomic status, smoking history, process measures, and other potential covariates. Associations will be considered significant at $\alpha = .05$.

Moderators and Mediators of Treatment Outcome—We will test moderation and mediation effects of the variables listed below. Moderation will be examined by testing the confounding effects of a given potential moderator. We will formally test mediation by specifying the model of a mediator as a function of intervention assignment, and the model of the primary outcome as a function of intervention and a given mediator. If the effect of intervention in the first model and a mediator in the second model are both significant there would be evidence of nonzero indirect effect.⁴⁴ Given the measurement scale of the outcome(s) and mediator(s) this will be done with models similar to ones proposed for the primary and secondary outcomes. Inferences will be made based on the Sobel test at $\alpha = .05$.

Several demographic (e.g., socioeconomic status) and smoking (e.g., years smoked; previous quit attempts) variables are baseline moderators (predictors) of tobacco outcome studies and will be assessed at baseline.⁴⁵ To understand the effects of treatment on cessation, we will assess several mediators of treatment: (1) adherence to treatment regimen—defined as the percentage of sessions completed in the behavioral intervention and percent of nicotine replacement therapy used in the pharmacologic intervention—; (2) confidence in one's ability to abstain from smoking in high risk situations (self-efficacy); (3) level of smoking at the 2-, 4- and 6-month follow-up assessments (i.e., booster sessions) and the 12-month follow-up in terms of percent reduction relative to baseline use; (4) intentions to quit will be assessed at baseline and for those still smoking at the follow-up assessments, we will assess intentions to quit at the 2-, 4-, and 6-month follow-ups and the 12-month follow-up; (5) tobacco dependence (FTND) at baseline and at the 2-, 4- and 6-month follow-up assessments and the 12-month follow-up; (6) other tobacco and nicotine-containing product use at the 2-, 4- and 6-month follow-up assessments and the 12-month follow-up; (7) use of additional cessation methods; and (8) participants' program satisfaction and how well participants liked intervention components and their therapist. We hypothesize that, although all conditions may evidence varying degrees of cessation, the 12 months follow-up outcomes will be a function of (a) adherence to the intervention (MI, RR, or MI + RR); and (b) pharmacologic adherence to the NRT. Thus, "a" and "b" will be treatment mediators that we will also specifically measure.

Cost-Per-Quit Analysis—Our cost-per-quit analysis will aggregate costs for each study arm and divide by the number of documented quit attempts in the past 12 months. We will also assess cost-per-quit-attempt as a secondary analysis, as each quit attempt increases the likelihood of success and, therefore, is an important intermediate outcome.¹² Cost-per-quit will be compared across study arms using univariate (e.g., Wilcoxon rank sum with

Bonferroni corrections) and multivariate methods (e.g., least squares or lognormal regression if costs are skewed).

Cost Effectiveness Analysis—We will compare cost per quality-adjusted life year saved associated with each study arm.⁴⁶ Like previous cost-effectiveness studies in this area, our analysis will take the provider or payer perspective.^{47–49} Patient time costs will not be assessed to minimize response burden. Quality-adjusted life years allow researchers to consider both quality and quantity of years of life associated with each treatment option, assigning lower weights to years in poor health and higher weights to years in better or perfect health. Because direct calculation of quality-adjusted life year weights imposes significant response burden, we will combine results of our randomized controlled trial (i.e., quit rates, quit odds ratios), with publicly available information on mortality rates, future smoking relapse and quit rates, and nationally representative quality-adjusted life year weights developed for smokers and quitters (by years since quitting)⁴⁷ to calculate quality-adjusted life years. Prominent researchers have advocated the use of standardized, nationally representative quality-adjusted life years to minimize response burden and enhance comparability of cost-effectiveness analyses.⁵⁰ We will use decision analysis to assess how uncertainty affects selection of the most cost-effective treatment option. For example, if our analysis finds that MI + RR is the most cost-effective with an average treatment cost of \$1,000 but $SD = \$800$, we can model the impact of uncertainty with Monte Carlo replications to determine the percent of cases that would still identify this treatment option as most cost-effective. This analysis also allows us to determine when a treatment option would no longer be the most cost-effective option (i.e., parameter values).

Discussion

Previous smoking cessation interventions have been effective with smokers who are in the preparation stage to quit smoking, but most smokers are in earlier stages of change.^{1,3} PACE, the project presented here, is a nation-wide, telephone-based randomized controlled trial designed to evaluate the effectiveness of four cessation interventions for SNRTQ. Upon completion of this study, results could inform current tobacco quitlines and interventions could be readily disseminated; thus, expanding the reach of quitlines to smokers who are not yet ready to quit and improving cessation rates.

We based our four intervention conditions on standard of care (i.e., BA) and evidence-based interventions that have been effective in smoking reduction and cessation (i.e., MI and RR).^{5,7,26} These four intervention conditions could provide exciting results. For instance, this study will not only allow the evaluation of two distinct interventions (MI and RR), but to also compare them to their combined effectiveness (MI + RR). Consequently, PACE results could elucidate if a conversation about quitting smoking, developing reduction skills, or both interventions combined are better at promoting long-lasting cessation. Researchers have found that interventions similar to BA have been more effective than MI in minority light smokers.⁵¹ Considering that almost 50% of smokers are light smokers,⁵² there is a remote possibility we may find two active conditions (MI and RR) to be as efficacious as BA. Even if these two conditions do not demonstrate better outcomes than BA, this minimal

intervention could be more cost-effective than MI and RR due to its low cost in training, aid materials, and delivery.

Besides intervention design, we have generated a strong study based on respectable guidelines in the field of smoking cessation treatment. We will use an intent-to-treat approach, such that all randomized participants will be included in the calculation of abstinence rates. This approach is considered a gold standard in randomized clinical trials and prevents attrition bias and overestimation of cessation rates.⁵³ Nevertheless, it is also important to balance a conservative intent-to-treat approach with less conservative, yet standardized and adequate definitions of abstinence. Thus, we are assessing point prevalence abstinence as the strictest definition of abstinence.

In addition, we are assessing prolonged abstinence to capture quitters who may have smoked a few cigarettes after a set quit date or lapsed, but successfully remained abstinent afterward. In addition, a strength in this study is the inclusion of self-report as well as salivary biochemical verification of cessation.^{36,42} Specifically, salivary cotinine verification is a biochemical marker specific to nicotine with a long enough half-life that will allow us to analyze the saliva sample. Last, we will assess cost-per-quit and cost-effectiveness analyses. These two indices could indicate the comparative economic impact of the four intervention conditions and, together with all aforementioned strengths, provide a holistic rationale for the dissemination of the best intervention for SNRTQ.

Acknowledgments

The authors of this work would like to thank the staff in charge of managing discrete aspects of the study and providing participants with materials and interventions: Cyril Patra, Beverly Word, Robin Hardin, Susan Dalton, Janet Elam, Filoteia Popescu, and John Boatner.

Funding

This work was supported by the National Institutes of Health [grant number 1R01CA193245-01A1]. The National Institutes of Health had no involvement in the study design, collection and analysis of data, interpretation of results, or writing of this report.

References

1. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services; 2014. <http://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html> [Accessed February 6, 2014]
2. Joseph AM, Fu SS, Lindgren B, et al. Chronic disease management for tobacco dependence: a randomized, controlled trial. *Arch Intern Med*. 2011; 171(21):1894–1900. DOI: 10.1001/archinternmed.2011.500 [PubMed: 22123795]
3. Fjalldal SB, Janson C, Benediktsdóttir B, et al. Smoking, stages of change and decisional balance in Iceland and Sweden. *Clin Respir J*. 2011; 5(2):76–83. DOI: 10.1111/j.1752-699X.2010.00201.x [PubMed: 21410899]
4. Miller, WR., Rollnick, S. *Motivational Interviewing: Helping People Change*. 3. New York, NY: Guilford Press; 2013.
5. Lai DT, Cahill K, Qin Y, Tang J-L. The Cochrane Collaboration, editor. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. Jan.2010 doi: 10.1002/14651858.CD006936.pub2

6. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res.* 2006; 8(6):739–749. DOI: 10.1080/14622200600789726 [PubMed: 17132521]
7. Asfar T, Ebbert JO, Klesges RC, Relyea GE. Do smoking reduction interventions promote cessation in smokers not ready to quit? *Addict Behav.* 2011; 36(7):764–768. DOI: 10.1016/j.addbeh.2011.02.003 [PubMed: 21420791]
8. Stead, LF., Lancaster, T. The Cochrane Collaboration. *Cochrane Database of Systematic Reviews.* Chichester, UK: John Wiley & Sons, Ltd; 2007. Interventions to reduce harm from continued tobacco use.
9. Piasecki TM, Baker TB. Any further progress in smoking cessation treatment? *Nicotine Tob Res.* 2001; 3(4):311–323. DOI: 10.1080/14622200110050484 [PubMed: 11694198]
10. Marlatt, GA., Gordon, JR., editors. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors.* 1. New York: The Guilford Press; 1985.
11. Chan SSC, Leung DYP, Abdullah ASM, Wong VT, Hedley AJ, Lam T-H. A randomized controlled trial of a smoking reduction plus nicotine replacement therapy intervention for smokers not willing to quit smoking. *Addiction.* 2011; 106(6):1155–1163. DOI: 10.1111/j.1360-0443.2011.03363.x [PubMed: 21226883]
12. Fiore, MC., Jaén, CR., Baker, TB., et al. *Treating Tobacco Use and Dependence 2008 Update - Clinical Practice Guideline.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2009. <https://www.ncbi.nlm.nih.gov/books/NBK63952/> [Accessed June 14, 2013]
13. Marijuana Treatment Project Research Group. Brief treatments for cannabis dependence: findings from a randomized multisite trial. *J Consult Clin Psychol.* 2004; 72(3):455–466. DOI: 10.1037/0022-006X.72.3.455 [PubMed: 15279529]
14. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res.* 2003; 5(1):13–25. DOI: 10.1093/ntr/5.1.13 [PubMed: 12745503]
15. Aveyard P, Wang D, Connock M, Fry-Smith A, Barton P, Moore D. Assessing the outcomes of prolonged cessation-induction and aid-to-cessation trials: Floating prolonged abstinence. *Nicotine Tob Res.* 2009; 11(5):475–480. DOI: 10.1093/ntr/ntp035 [PubMed: 19346506]
16. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: Toward an integrative model of change. *J Consult Clin Psychol.* 1983; 51(3):390–395. DOI: 10.1037/0022-006X.51.3.390 [PubMed: 6863699]
17. Hintze, J. PASS. Kaysville, UT: NCSS, LLC; 2013.
18. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. *J Consult Clin Psychol.* 2004; 72(3):371–381. DOI: 10.1037/0022-006X.72.3.371 [PubMed: 15279521]
19. Lim KH, Ibrahim N, Ghazali SM, et al. Stages of smoking cessation among Malaysian adults—findings from national health morbidity survey 2006. *Asian Pac J Cancer Prev.* 2013; 14(2):805–810. DOI: 10.7314/APJCP.2013.14.2.805 [PubMed: 23621242]
20. Klesges RC, Ebbert JO, Talcott GW, et al. Efficacy of a tobacco quitline in active duty military and TRICARE beneficiaries: a randomized trial. *Mil Med.* 2015; 180(8):917–925. DOI: 10.7205/MILMED-D-14-00513 [PubMed: 26226536]
21. Gollwitzer, PM., Sheeran, P. *Advances in Experimental Social Psychology.* Vol. 38. Academic Press; 2006. Implementation intentions and goal achievement: a meta-analysis of effects and processes; p. 69-119.
22. Stead, LF., Buitrago, D., Preciado, N., Sanchez, G., Hartmann-Boyce, J., Lancaster, T. *Cochrane Database of Systematic Reviews.* John Wiley & Sons, Ltd; 2013. Physician advice for smoking cessation.
23. Klemperer EM, Hughes JR, Solomon LJ, Callas PW, Fingar JR. Motivational, reduction, and usual care interventions for smokers who are not ready to quit: A randomized controlled trial. *Addiction.* 2017; 112(1):146–155. DOI: 10.1111/add.13594 [PubMed: 27566993]

24. Lindson-Hawley, N., Thompson, TP., Begh, R. The Cochrane Collaboration, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2015. Motivational interviewing for smoking cessation.
25. Centers for Disease Control and Prevention. [Accessed November 30, 2017] Smoking and tobacco use: health effects of cigarette smoking. Smoking and Tobacco Use. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/. Published August 28, 2017
26. Martins RK, McNeil DW. Review of motivational interviewing in promoting health behaviors. Clin Psychol Rev. 2009; 29(4):283–293. DOI: 10.1016/j.cpr.2009.02.001 [PubMed: 19328605]
27. VanBuskirk K, Wetherell J. Motivational interviewing with primary care populations: a systematic review and meta-analysis. J Behav Med. 2014; 37(4):768–780. DOI: 10.1007/s10865-013-9527-4 [PubMed: 23934180]
28. Villanti AC, Bover Manderski MT, Gundersen DA, Steinberg MB, Delnevo CD. Reasons to quit and barriers to quitting smoking in US young adults. Fam Pract. 2016; 33(2):133–139. DOI: 10.1093/fampra/cmz103 [PubMed: 26733658]
29. Dawes J. Cigarette brand loyalty and purchase patterns: An examination using US consumer panel data. J Bus Res. 2014; 67(9):1933–1943. DOI: 10.1016/j.jbusres.2013.11.014
30. Haddock CK, Talcott GW, Klesges RC, Lando H. An examination of cigarette brand switching to reduce health risks. Ann Behav Med. 1999; 21(2):128. doi: 10.1007/BF02908293 [PubMed: 10499133]
31. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ. 2009; 338:b1024. doi: 10.1136/bmj.b1024 [PubMed: 19342408]
32. Pack QR, Jorenby DE, Fiore MC, et al. A comparison of the nicotine lozenge and nicotine gum an effectiveness randomized controlled trial. WMJ. 2008; 107(5):237–243. [PubMed: 18777992]
33. Krupski L, Cummings KM, Hyland A, Carlin-Menter S, Toll BA, Mahoney MC. Nicotine replacement therapy distribution to light daily smokers calling a quitline. Nicotine Tob Res. 2013; 15(9):1572–1577. DOI: 10.1093/ntr/ntt021 [PubMed: 23482718]
34. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström K-O. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991; 86(9): 1119–1127. DOI: 10.1111/j.1360-0443.1991.tb01879.x [PubMed: 1932883]
35. Hughes JR, Carpenter MJ, Naud S. Do point prevalence and prolonged abstinence measures produce similar results in smoking cessation studies? A systematic review. Nicotine Tob Res. 2010; 12(7):756–762. DOI: 10.1093/ntr/ntq078 [PubMed: 20504946]
36. Benowitz NL, PJ, Ahijevych K, et al. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4(2):149–159. DOI: 10.1080/14622200210123581 [PubMed: 12028847]
37. Cha S, Ganz O, Cohn AM, Ehlke SJ, Graham AL. Feasibility of biochemical verification in a web-based smoking cessation study. Addict Behav. 2017; 73(Supplement C):204–208. DOI: 10.1016/j.addbeh.2017.05.020 [PubMed: 28551588]
38. Noonan D, Jiang Y, Duffy SA. Utility of biochemical verification of tobacco cessation in the Department of Veterans Affairs. Addict Behav. 2013; 38(3):1792–1795. DOI: 10.1016/j.addbeh.2012.11.006 [PubMed: 23261494]
39. Abroms LC, Johnson PR, Leavitt LE, et al. A randomized trial of text messaging for smoking cessation in pregnant women. Am J Prev Med. 2017; 53(6):781–790. DOI: 10.1016/j.amepre.2017.08.002 [PubMed: 28982527]
40. FileMaker, Inc. FileMaker Pro. Santa Clara, CA: FileMaker, Inc; 1984. <http://www.filemaker.com/>
41. FileMaker, Inc. FileMaker security guide: in depth security. 2015. https://help.filemaker.com/ci/fattach/get/161164/0/filename/security_guide_en_14.pdf
42. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005; 100(3):299–303. DOI: 10.1111/j.1360-0443.2004.00995.x [PubMed: 15733243]
43. Geyer, CJ. Introduction to Markov Chain Monte Carlo. In: Brooks, S.Gelman, A.Jones, GL., Meng, X-L., editors. Handbook of Markov Chain Monte Carlo. Boca Raton, FL: CRC Press; 2011. p. 3-48. Chapman & Hall/CRC Handbooks of Modern Statistical Methods

44. Kenny, DA., Kashy, DA., Bolger, N. The Handbook of Social Psychology. 4. New York, NY, US: McGraw-Hill; 1998. Data analysis in social psychology; p. 233-265.
45. International Agency for Research on Cancer. Handbooks on Cancer Prevention, Tobacco Control, Volume 12: Methods for Evaluating Tobacco Control Policies. Lyon, France: International Agency for Research on Cancer; 2008. General mediators and moderators of tobacco use behaviours; p. 107-122.http://www.iarc.fr/en/publications/pdfs-online/prev/handbook12/Tobacco_vol12_3B.pdf
46. Wagner TH, Goldstein MK. Behavioral interventions and cost-effectiveness analysis. *Prev Med.* 2004; 39(6):1208–1214. DOI: 10.1016/j.ypmed.2004.04.052 [PubMed: 15539057]
47. Fiscella K. Cost-effectiveness of the Transdermal Nicotine Patch as an Adjunct to Physicians' Smoking Cessation Counseling. *JAMA J Am Med Assoc.* 1996; 275(16):1247.doi: 10.1001/jama.1996.03530400035035
48. Graham AL, Chang Y, Fang Y, et al. Cost-effectiveness of internet and telephone treatment for smoking cessation: an economic evaluation of The iQUITTT Study. *Tob Control.* 2013; 22(6):e11.doi: 10.1136/tobaccocontrol-2012-050465 [PubMed: 23010696]
49. Shireman T, Emchi K, Spaulding R, et al. Comparative and cost effectiveness of telemedicine versus telephone counseling for smoking cessation. *J Med Internet Res.* 2015; 17(5):e113.doi: 10.2196/jmir.3975 [PubMed: 25956257]
50. Dolan P, Lee H, King D, Metcalfe R. Valuing health directly. *BMJ.* 2009; 339:b2577.doi: 10.1136/bmj.b2577
51. Ahluwalia JS, Okuyemi K, Nollen N, et al. The effects of nicotine gum and counseling among African American light smokers: a 2 × 2 factorial design. *Addiction.* 2006; 101(6):883–891. DOI: 10.1111/j.1360-0443.2006.01461.x [PubMed: 16696632]
52. Trinidad DR, Pérez-Stable EJ, Emery SL, White MM, Grana RA, Messer KS. Intermittent and light daily smoking across racial/ethnic groups in the United States. *Nicotine Tob Res.* 2009; 11(2):203–210. DOI: 10.1093/ntr/ntn018 [PubMed: 19246433]
53. Brody, T. Clinical Trials: Study Design, Endpoints and Biomarkers, Drug Safety, and FDA and ICH Guidelines. 2. Boston, MA: Academic Press; 2016.