Title: TIP TOP (Tobacco Intervention in Primary Care Treatment Opportunities for Providers)

Abstract

Most smokers do not make a quit attempt in any given year. For those who do, use of evidence-based treatment, including the use of nicotine replacement therapy (NRT) is modest at best. Brief physician advice to quit, based on the 5As/5Rs model, while offering some efficacy, is inconsistently administered and thus has limited population impact. There is a clear need for more efficacious methods, particularly in the clinical setting, to promote quitting. Our team recently completed a large, nationwide clinical trial of NRT sampling, i.e., testing whether brief provision of NRT promotes further uptake of cessation behavior, higher incidence of quit attempts, and higher rates of abstinence. The results of that trial were promising for all outcomes, and suggested that NRT sampling works by increasing both motivation and confidence to quit and increasing familiarity with NRT products as an option for quitting.

NRT sampling, when added to physician advice to quit, is uniquely suited to busy primary care settings for several reasons. First, primary care represents a prominent point of healthcare contact for a large number of smokers. Second, the sampling intervention is simple, takes only a few minutes to deliver, and requires minimal instructions. Third, unlike other clinic-based strategies such as motivational advice, NRT sampling is behaviorally based, and offers providers and patients, both of whom are often frustrated by persuasive messaging, a concrete experience to catalyze quitting. Fourth, sampling is supported by numerous quitline studies that show that free medications significantly increase call volume and cessation. Finally, sampling has a strong theoretical foundation to suggest that brief exposure to a product promotes wider acceptability of it.

This competing renewal proposes a translational comparative effectiveness trial, testing standard care (Ask, Advise, Refer) vs. standard care + NRT sampling (2wk supply of both nicotine patch and lozenge). Working within an established network (based at our institution) of primary care providers who have all established infrastructure for coordinating clinical research, smokers will be recruited directly within clinic practices. Interventions will be delivered by clinic personnel, and prospective follow-up will be centrally coordinated by our research team, using established procedures that yield high rates of retention. Though we track a number of outcomes, our primary aims are to examine the impact of NRT sampling on smoking behavior: cessation, quit attempts, uptake of additional evidence-based treatment.

Long, intensive treatments that combine behavioral and pharmacologic treatment have strong empirical support. However, they offer only partial utility because they do not readily lend themselves to real world primary care settings, where providers have limited time and expertise to address tobacco dependence. Improving the effectiveness and reach of brief intervention within primary care, as could be accomplished by NRT sampling, could have a major impact on population quit rates.

Project Narrative

The primary care setting offers a powerful opportunity to identify smokers and engage them in the quitting process, with the ultimate goal to lower the burden of preventable disease. Based on significant and promising findings from a recently completed randomized clinical trial, this comparative effectiveness trial will test whether NRT sampling, i.e., provision of starter-kits of nicotine replacement therapy, when combined with standard physician advice to quit, results in significant improvements in smoking-related outcomes (abstinence, quit attempts, use of additional quit resources) as compared to quit advice alone. Positive findings could offer both clinical and policy significance.

Specific Aims:

Smoking cessation rates have stagnated in the past decade. The ratio of ex- to ever-smokers (quit ratio) has plateaued, and smoking prevalence, once on a steady decline, has decreased <5% in the past 10 years. While smokers claim to be motivated to quit, fewer than half make a quit attempt in any given year, a statistic that has not demonstrably changed in over a decade. Cessation medications are significantly underutilized, in large part due to lack of knowledge that products even exist, how they work, and misperceptions about safety and efficacy. New and stronger efforts are need to engage smokers in the quitting process, to increase the incidence of quit attempts, promote wider uptake of evidence-based treatment, and to promote cessation.

The primary care setting offers a powerful opportunity to identify large numbers of smokers and engage them in the quitting process, with the ultimate goal to promote quit attempts and cessation and lower the burden of preventable disease. Most smokers visit a doctor annually, and all practice organizations (e.g., Amer. Academy of Family Physicians) endorse evidence-based guidelines for treatment of tobacco dependence. Yet in the context of a busy and often over-burdened clinical setting, many physicians have limited time and other resources to effectively treat tobacco users. Novel interventions that are both brief and efficacious are needed to engage smokers in the quitting process and enhance quitting behavior.

Our study group has extensive experience developing and testing novel, behavioral-based interventions to prompt quitting. We recently concluded a large (N=849) nationwide, population based randomized clinical trial (RCT) testing the concept of NRT sampling, i.e., providing brief samples of over-the-counter nicotine replacement therapy with minimal behavioral instructions on use. NRT sampling was hypothesized to increase self-efficacy and motivation, and to familiarize smokers with and facilitate positive attitudes toward medication. The study sample consisted exclusively of smokers with no current interest in quitting (i.e., unmotivated smokers). This efficacy trial of cessation induction was powered on quit attempts, with secondary outcomes of abstinence. NRT sampling significantly increased the incidence of quit attempts, and there were strong trends for increased abstinence. NRT sampling worked through hypothesized mediators noted above. Based on these promising findings, we now propose a translational comparative effectiveness study, i.e., to disseminate and test our intervention into real world clinical practice, within the primary care setting to fully test (i.e., powered on abstinence) the concept of NRT sampling as an added component of standard care.

Our **Primary Specific Aim** is to examine cessation outcomes of a large-scale (N=1300; 20 participating clinics) randomized clinical trial of 1) Standard Care, based on established guidelines (Ask, Advise, Refer [quitline referral]) vs. 2) Standard Care + NRT Sampling. Participants will be drawn from a network of primary care settings that has established infrastructure in which to embed clinical research. Randomization will be at the clinic level, but individual participants represent the unit of analysis. Identified smokers who meet eligibility criteria will be consented into a trial. Interventions will be delivered within the primary clinic directly by providers who are trained and monitored on study procedures. All participants will receive advice to quit and referral to state quitlines. Half of the sample will receive a small token bag that includes samples (i.e., 1-2 week starter kit) of both nicotine patch and lozenge. Follow-up assessment (through 6 months) will track both primary (abstinence, quit attempts, use of additional treatment) and secondary (motivation, confidence) outcomes. Our team has strong experience in such trials, including methods to efficiently recruit and effectively retain large numbers of smokers in clinical research. Our principle hypotheses are as follows:

Hypothesis 1a: As compared to Standard Care model of physician-delivered brief advice (Ask, Advise, Refer), provision of brief advice + NRT samples within primary care setting will result in a higher abstinence rates (7-day, point prevalence at 6 month follow-up).

Hypothesis 1b: Brief advice + NRT sampling will result in longer period of abstinence (longest # days non-smoking) across the entire study duration.

Hypothesis 2: NRT sampling will result in higher rates of quit attempts (any self-defined and any 24hr quit attempt).

Hypothesis 3: Brief advice + NRT sampling will result in higher subsequent uptake of evidence-based treatment (behavioral, pharmacological assistance).

NRT sampling represents a brief, concrete, easy to explain strategy that both healthcare providers and smokers readily accept. Thus, it is uniquely suited to the primary care setting, and could be a novel, behaviorally based intervention to promote quitting. If so, NRT sampling holds great significance on both a clinical and policy level.

Human Subjects Research

1. Risks to Human Subjects

1.1 Human Subjects Involvement and Characteristics

General Inclusion / exclusion criteria are as follows:

a) age ≥18
b) daily (25+ days within past 30) cigarette smoker of ≥5 cigs/day
c) English speaking
d) recruited through primary care sites aligned with study
e) no FDA contraindications for use of NRT:
    a. not pregnant, breastfeeding, or planning to become pregnant
    b. no recent (past 3 months) cardiovascular trauma: MI, stroke

1.2 Sources of Materials

Research material obtained from the participants include responses to in-person and telephone-based questionnaires regarding smoking patterns, attitudes, behaviors, etc. Research data will be obtained specifically for research purposes. There will be no use of existing specimens. The consent form will include language to allow access to the participant's Electronic Medical Record (EMR) data, for up to 2 years following date of consent. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA.

1.3 Potential Risks

The research protocol calls for non-treatment seeking smokers, who will vary across the motivational spectrum from wanting to quit vs. not wanting to quit, to receive standard care (Ask, Advise, Refer) or NRT sampling. The sampling intervention consists of a two-week supply of both nicotine patch and lozenge, both over-the-counter products that have received extensive support for their efficacy and safety (19, 97-102). Nonetheless, there are potential for risks for each product alone, as well as when used concurrently. We believe these risks, described below, will be minimal and mild.

1.3.1 Nicotine lozenge In a prior trial of the particular lozenge we will be using, 68% and 71% of 2 and 4 mg users of nicotine lozenge reported an adverse event (AE) vs. 54% of placebo users (103, 104). With both active doses of the lozenge, 7% dropped out due to AEs and 7% dropped out due to AEs on placebo. With both active doses, 1.6% reported a serious AE which was not different than that for placebo. There were no deaths or irreversible injuries deemed possibly due to lozenge. The most common AEs were nausea, flatulence and upper respiratory tract infection (103). The current labeling on OTC lozenge states pregnant and breast feeding women, those less than 18 years of age, those using a prescription medication for depression or asthma or a smoking cessation medication and those with heart disease, recent heart attack, irregular heartbeat, high blood pressure not controlled by medication, stomach ulcers or diabetes should consult a provider before using the lozenge.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation (85), the three most common adverse events within the lozenge group were 1) nausea: 7.8%, compared to 4.4% within placebo group, 2) mouth/throat irritation: 6.7%, compared to 3.3% within placebo group, and 3) hiccups: 6.2%, compared to 0.3% within placebo group. All other adverse events occurred <5%. In our recent trial of sampling nicotine lozenge, which was not placebo-controlled but was based on a similar sampling strategy as proposed here, the most common adverse events were nausea (23% of all adverse events), throat irritation (17%), and hiccups (13%).

Dependence on the lozenge and harm from concurrent use of lozenge and cigarettes has not been reported but has not been studied. The pharmacokinetics of the lozenge most closely matches that of nicotine gum. With gum used for abrupt cessation, the estimated incidence of dependence is 1-3% (105). Although an early anecdotal report suggested concomitant use of NRT and smoking could induce heart attacks, several large empirical studies since then have failed to confirm this observation (106). For example, in the LHS study (107) and in our prior study (45), large numbers of smokers concurrently smoked and used nicotine gum or other NRT products and the incidence of any significant AEs was < 1%.

1.3.2 Nicotine patch The most common side effects from nicotine patch are skin irritation, insomnia, and headache or nausea. In an early but seminal placebo controlled test of patch (108), there were few systemic side effects of patch use: 21% vs. 15% of smokers in the patch and placebo groups respectively reported a side effect during the treatment period. The most frequent symptoms with the patch as compared with the placebo patch were headache (4 vs. 4 percent), nausea (4 vs. 1 percent), and vertigo (4 vs. 0 percent). Transient mild itching was reported by 14% of the subjects in the patch group and 1% in those in the placebo group after the first week ($P<0.001$). At each visit, 4.5% to 7.3% of the remaining subjects in the patch group reported erythema, as compared with 2.3% to 6.7% of those in the placebo group. Acute eczema persisting for several days in the area of the patch caused 1.4% of the subjects in the nicotine group and 0.7% of those in the placebo group to stop using the patch.

In a separate but similar study comparing bupropion vs. patch vs. combined bupropion/patch vs. placebo (109), the most common adverse events reported by patch participants were 1) insomnia (30% in active patch group vs. 20% in placebo), 2) headache (28% in active patch group vs. 33% in placebo), 3) application site reactions (19% in active patch group vs. 7% in placebo), and 4) dream abnormalities (18% in active patch group vs. 3% in placebo).

Finally, in a recent trial of placebo vs. single vs. multiple medications for smoking cessation (85), the two most common adverse events within the patch group were 1) skin irritation: 14.7%, compared to 2.7% within placebo group, and 2) disturbed sleep: 11.3%, compared to 5.6% within placebo group. All other adverse events occurred <5%. Seven percent of patch users vs. 4% of placebo users discontinued medication due to adverse events.

1.3.3 Combined patch & gum Our sampling intervention allows smokers to briefly try evidence-based cessation medications, either singularly or concurrently. We do not explicitly encourage dual use, but we will not discourage it either. We do belief combined medication use is safe. Combination treatments are often suggested for more dependent smokers and/or smokers with chronic medical conditions (110-112). One review in particular (110) provides significant rationale by which combined NRT should not incur significant risks, since NRTs provide lower doses per unit or per hour than are typically obtained by cigarette smoking, and the rate of nicotine administration for all NRT products is substantially slower than that from an inhaled cigarette.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation (85), the four most common adverse events within the combined patch/lozenge group, were 1) disturbed sleep: 9.0%, compared to 5.6% within placebo group, and 2) skin irritation: 8.9%, compared to 2.7% within placebo group, 3) nausea: 7.9%, compared to 4.4% within placebo group, and 4) mouth/throat irritation: 5.7%, compared to 53.3% within placebo group. All other adverse events occurred <5%.

1.3.4 Combined use of any NRT product and smoking Our study allows smokers to sample individual or combined NRT products, but without a requirement of a formal quit attempt. Thus, smokers could be using NRT products concurrently (same day) as smoking. This could result in nicotine intoxication; i.e. nausea, dizziness, headache, stomachache, etc (106). In our prior study, participants completed a nicotine intoxication scale, and we found no evidence of nicotine intoxication when gum and cigarettes were used concurrently. In addition, our review of prior smoking reduction studies found most participants did not have higher than normal cotinine levels with concurrent use of cigs and NRT, and there were few AEs reported (113).

1.3.5 Undermining Cessation Another potential risk is that the sampling intervention will decrease rather than increase future cessation as briefly discussed in Section A.5. However, the limited data available (114) suggest this is unlikely. Our prior work on providing NRT to smokers not yet fully committed to cessation (44, 45, 64), as well the work of many others (115, 116) clearly demonstrate that use of pharmacotherapy among smokers not wanting to quit effectively promotes cessation.

1.3.6 Confidentiality A final risk is breach of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

Study participants will be recruited directly within affiliated primary care clinics by personnel who have been trained on study procedures and who have active CITI Certification for Protection of Human Subjects. Potential study participants will be screened for potential inclusion by nursing/support staff within each clinic, who will then collect informed consent and administer the baseline questionnaire, with instructions to mail the consent back to the central study office using a pre-addressed, pre-stamped envelope. A copy of the informed consent will be given to each study participant. Participants will be given a toll-free number to call for questions. Only individuals who sign and return a legible informed consent will be officially considered consented.

Human Subjects Protection within Clinics

Our trial will enroll smokers in 20 different clinics within the CCI network. Recruitment is staggered, such that 2 clinics will initiate enrollment in Year 1, 5 in Year 2, 6 in Year 3, 4 in Year 4, and 3 in Year 5. We have not determined which clinics will initiate in which years, nor do we believe we can at this early point of planning. We also do not believe it wise to submit 20 separate forms at this early juncture, knowing that so many changes are likely in the coming five years (possible change of clinics, or more likely, change of personnel within clinics).

Thus, we have submitted the initial IRB application with 2 clinics only: McLeod Family Practice and 2) Spartanburg Internal Medicine. Forms and CITI certifications were enclosed.

Our plan going forward is to submit separate IRB amendments 2-3 months prior to each clinic going "live." All such amendments will include appropriate forms, listing of clinic personnel involved, letters of support, and CITI certifications. Most, but not all, of the clinics in the CCI network do NOT have their own IRB, and have agreed to abide MUSC IRB regulations. Of our 20 clinics, a few have their own internal IRB, but they require MUSC approval prior to internal review. Note that under no circumstances will we allow screening/recruiting/assessment/intervention to take place in individual clinics without a) IRB approval of clinic involvement, b) CITI certification of all personnel involved, and c) appropriate training and monitoring as identified in the protocol.

All recruiting personnel and treatment-delivering providers have or will have up to date CITI Certification for Protection of Human Subjects prior to study initiation.

2.2 Protection Against Risk

2.2.1 Nicotine lozenge The primary protection against risk of the nicotine lozenge (an OTC product) is the short duration for which it will be provided– only a 2-week supply. However, because this is a clinical trial, we will have a Safety and Data Monitoring Plan that includes monitoring of Adverse Events (AEs). An added precaution is the actual delivery of the lozenge, provided directly the participant's primary care provider. We will exclude individuals based on standard FDA contraindications for NRT use (pregnancy, recent cardio trauma). We will clearly advise against use of NRT during pregnancy and breast-feeding but we will not require pregnancy tests to be in the study. Through brochures delivered as part of the sampling intervention, participants will be educated about lozenge AEs and nicotine intoxication symptoms. A physician will be on call throughout the study for questions about AEs, etc. Participants will be encouraged to contact the Study PI as soon as possible for serious AEs and for those conditions that OTC labeling suggests seeing a provider. We will withdraw participants who have a serious AE. For other AEs, if the study physician, the participant's physician or the participant wishes it, the participant will be withdrawn from the study. We will also form a Data Safety and Monitoring Board. If the percent of serious or severe AEs appears to be greater than 5% this board will be notified to make a decision on early termination of the study.

2.2.2 Nicotine patch The same precautions as above apply to the use of nicotine patch.

2.2.3 Combined patch & gum We will not explicitly encourage or discourage use of combined medication. The sampling experience is meant to provide smokers with a real-world opportunity to "test drive" different medications. Our accompanying brochures will discuss the anticipated negative consequences of dual use

(nausea, headache) and advise participants to discontinue one or both products should they arise. Given the 2week sampling experience, we expect adverse events to be rare and mild.

2.2.4 Combined use of any NRT product and smoking As above, accompanying brochures will advise smokers not to smoke while using NRT product (even though most studies have demonstrated no significant events for combined use (63).

2.2.5 Undermining Cessation To protect against this outcome, we will form a Data Safety and Monitoring Board (DSMB) and have them conduct an interim analysis after 50% of the sample has completed 6 month follow-up. We chose this number as this is the minimum necessary given our base rate is projected to be 15% and one has to see clear trend toward an even lower rate. To do this, the statistician will provide a copy of the dataset to the board. If this occurs, this board will independently decide on whether to stop the study.

2.2.6 Confidentiality We will use the participant's name only on the screening and informed consent documents and these will be keptin a locked file, to be kept centrally at our study office. The research materials will become part of the modern record keeping facility of the Institute of Psychiatry, which will minimize risks to the privacy of participants. All interviews, records, charts, rating scales, and other patient information will be kept on a secure server or in locked files at the Cancer Control Program, with limited access to the study personnel. All database files will be on a secure server or MUSC network drive only accessible to our research group and include password protection to further ensure confidentiality.

3. Potential Benefits of the Proposed Research to the Participants and Others / Importance of the Knowledge to be Gained

All smokers in this trial will receive at minimum standard care, consisting of brief provider advice to quit and referral to quitting resources. Half of the participants in the trial will receive samples of two products that alone and in combination have shown significant benefits on quitting. Thus, there are direct benefits to all participants. The major benefit to society will be whether a brief samples of evidence-based medication serve as an effective method to catalyze cessation (abstinence, quit attempts, uptake of additional quit resources). The risks of nicotine lozenge and patch are very small, even when used concurrently. The sampling period of our trial consists of two weeks, which further minimizes risk potential. Smoking cessation is the most important activity to improve public health and many smokers are resistant to quitting. Recent trends in smoking cessation are moving towards longer, more intensive treatments that combine behavioral and pharmacologic treatment. While efficacious, such approaches do not lend themselves to clinical practice within primary care settings, where providers have limited resources (time and expertise) to address tobacco dependence. If NRT sampling results in the hypothesized outcomes, it could offer an innovative, easy to implement option that has significant reach. Thus, NRT sampling represents a significant strategy that offers both clinical and policy significance to promote public health.

4. Data and Safety Monitoring Plan

This section is based on the recommendations in NCI's "Guidelines for Developing a Data and Safety Monitoring Plan" (http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1) as well as NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html).

4.1 Summary of the Protocol

The design calls for a 2-group, randomized clinical trial of 1) standard care (Ask, Advise, Refer) vs. 2) standard care + NRT sampling. Randomization will be at the clinic level, but the unit of analysis is the individual smoker. Following consent, baseline assessment, and provider intervention (all done within clinic), follow-up assessment (coordinated centrally through our study team) will continue at +1, +3, and +6 months. The primary outcome will be 7-day point prevalence abstinence at 6-month follow-up, though we track a number of other outcomes as well. A recent trial of comparative effectiveness for single/combined pharmacotherapy (79) provided strong framework for our decisions. As a comparative effectiveness study, our guiding philosophy is to optimize ecological (i.e., external) validity, while at the same time maintaining basic standards of scientific rigor.

4.2 Primary and secondary outcomes

The primary outcome on which our study is powered is 7-day point prevalence at 6 month follow-up, which, unlike continuous abstinence, allows for delayed quitting. Unlike traditional cessation trials, there is no uniform quit date for all participants in the current trial, and thus anchoring abstinence to a designated quit attempt is unrealistic. However, we will track a number of secondary outcomes, including 30-day point prevalence abstinence, and incidence, frequency, latency, and duration of quit attempts (both self-defined and those lasting >24hrs), as well as smoking reduction (% reaching 50% reduction between baseline and end-of-study), provider acceptability and cost-effectiveness.

4.3 Inclusion/exclusion criteria

General Inclusion / exclusion criteria are as follows:

a) age ≥18
b) daily (25+ days within past 30) cigarette smoker of ≥5 cigs/day
c) English speaking
d) recruited through primary care sites aligned with study
e) no FDA contraindications for use of NRT:
    a. not pregnant, breastfeeding, or planning to become pregnant
    b. no recent (past 3 months) cardiovascular trauma: MI, stroke

4.4 Sample Size

The sample size is 1300 participants. Section C.10 of the grant text provides a detailed rationale for why this sample size was chosen.

4.5 List of participating / enrolling clinics

A listing of the 28 possible clinics is below. If hurdles arise with any, the CCI network offers 120 total sites to work with, and we are confident we can enroll the anticipated number of participants. The original grant included letters of support.

	Clinic	**Cities**	**Urban / Rural**	**Miles from MUSC**
1	Aiken	Aiken	R	137
2	AnMed	Anderson	R	238
3	Eau Claire	Columbia	U	120
4	Eau Claire	Batesburg	R	144
5	Eau Claire	Cayce	U	120
6	Family Diagnostics Associates	Holly Hill	R	49
7	Internal Medicine Specialists of Florence	Florence	U	136
8	Lexington Family Practice	Lexington	U	118
9	Lovelace Family Medicine	Prosperity	R	142
10	McLeod Family Practice	Florence	U	136
11	Palmetto Primary Care	Bonneau	R	41
12	Palmetto Primary Care	Charleston	U	18
13	Palmetto Primary Care	Goose Creek	R	20
14	Palmetto Primary Care	Hampton	R	76
15	Palmetto Primary Care	Hanahan	R	12
16	Palmetto Primary Care	Moncks Corner	R	34
17	Palmetto Primary Care	North Charleston	U	18
18	Palmetto Primary Care	Summerville	U	23
19	Spartanburg Internal Medicine (CMA)	Spartanburg	U	204
20	Spartanburg Regional	Boiling Springs	R	211

21	Spartanburg Regional	Duncan	R	203
22	Spartanburg Regional	Gaffney	R	230
23	Spartanburg Regional	Greer	U	212
24	Spartanburg Regional	Inman	R	212
25	Spartanburg Regional	Landrum	R	223
26	Spartanburg Regional	Spartanburg	U	204
27	Spartanburg Regional	Spartanburg	U	204
28	USC (Chillage)	Columbia	U	120
29	Medical Center of Easley	Easley	R	223
30	Mackey Family Practice	Lancaster	R	177
31	Wellspring Family Medicine	Columbia	U	127
32	Mackey Family Practice/Indian Land	Indian Land	R	197
33	Eau Claire/Ridgeway	Ridgeway	R	140
34	Northlake Family Practice	Columbia	U	124
35	Lexington Family Practice/Otarre Pointe	Columbia	U	109
36	Dillon Internal Medicine	Dillon	R	161

In anticipation of potential budget cuts, we will reduce the number of clinics that enroll, and we have in fact identified 8 clinics that could be removed, with offset increases in per-clinic enrollment within remaining 20 clinics. Our minimum number of clinics to participate is 20. Also, as the study progresses, we do expect some changes in clinic involvement, for any number of reasons (e.g., change in clinic staff, change in structure/volume, etc). The table above merely represents the 28 clinics from which we anticipate we will select our 20 final clinics. Appropriate amendments will be obtained in advance of all such changes. Changes in clinic involvement will be noted in all progress reports sent to NIDA. The CCI network currently has 120 sites in South Carolina alone, of which 70 meet our inclusion criteria, and these numbers are increasing regularly, as CCI grows. If any one site is not able/willing to be included, we have ample additional sites to include.

4.6 Projected Timetable

The timetable is as follows:

	Year 1 (months)	**Year 2** (months)	**Year 3** (months)	**Year 4** (months)	**Year 5** (months)
Refine all procedures	1-6				
Procure supplies	1-6				
Refine recruitment methods	1-6				
Hire and train Central Personnel	5-8				
Hire & Train Additional Personnel*		13	25	37	
Pre-trial Focus groups (n=4)	7-8				
Train Clinic Personnel	Rolling, as new sites come on line				
Study Enrollment					
Cumulative Clinics to Begin Enrollment**	(2)	(7)	(13)	(17)	(20)
Cumulative N to start**[a]	(116)	(406)	(754)	(986)	(1300)
First Participant Starts	10				
First Participant Completes		16			
Last Participant Starts					50
Last Participant Completes					56
Data Analysis					56-60
Manuscript Preparation					56-60

* Additional study personnel beyond year one per budget justification; All numbers reflect months within total study duration (**with the exception of cumulative clinics to begin recruitment, and cumulative N); [a] assumes average of 58 participants recruited per clinic

4.7 Target Population

Women will be included in this protocol. Currently, women are about 50% of smokers (slightly less among African American women) and thus it is estimated that 50% of the study sample will be women. If there are discrepancies in terms of gender, efforts will be made to improve recruitment of women into the study through oversampling via online recruitment.

Minorities are also included in this study, and we have increased our estimates of minority enrollment to address reviewer concern from the initial grant submission. All participating sites in the CCI network (network of primary care providers) are based in South Carolina, where approximately 28% of the population is African American (http://quickfacts.census.gov/qfd/states/45000.html). We will aim for 28% enrollment of African Americans (all other minorities collectively comprise <5% of South Carolina population, reflected within target enrollment). We will monitor closely our minority recruitment goals on an ongoing basis and initiate oversampling of African Americans if recruitment rate of minorities drops below 25%.

4.8 Data Acquisition and Transmission

The study will be managed from the Division of Clinical Neuroscience within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC), but physically based within the Cancer Control Program of the Hollings Cancer Center, where the PI is based. Recruitment will be coordinated through a consortium of primary care providers (CCI). Recruitment will be conducted at separate participating clinics, and intervention will be delivered locally at each clinic as well. All recruited participants will locally (within each clinic) sign a consent form and complete a baseline questionnaire. The consent form will be returned in a pre-addressed, pre-stamped envelope that we provide, and the baseline questionnaires will be completed in REDCap and securely transmitted to MUSC study staff electronically. Nothing beyond the baseline visit is conducted at the clinics; all follow-up data collection and management will be centrally managed at our research lab at MUSC.

4.9 Data Analysis Plan

All analyses are based on an intent-to-treat approach, and are nearly identical to analyses from our current and prior studies. Exploratory analysis will be performed on all variables to determine if transformations are needed. Any significant baseline differences between groups will be included in regression analyses described below. All analyses below will be run separately for full intent-to-treat sample (immediately below), per protocol, and, within the NRT group, using those participants who used single vs. combined NRT products.

Examination of Potential Site Differences Outcomes and patient characteristics will be estimated across clinics using summary statistics and confidence intervals. This will be considered an exploratory analysis due to the relatively large number of clinics and, hence, the large number of multiple comparisons that could arise. Grouped logistic regression modeling may be used to describe associations between clinic characteristics and binary clinical outcomes (e.g., quit rate).

Missing Data & Dropout The most conservative approach for handling missing data is to substitute them with baseline values, assuming outcomes have all returned to baseline, with no quit attempts made or abstinence achieved. If this assumption is incorrect, it biases the results towards the null by reducing between group differences. Since we expect few missing data, we will use this approach. If missing data >10%, we will calculate results using this conservative method but also using methods in which missing data are imputed as described in the SRNT guidelines. We will also assess whether dropout is differential by study group. In our current and recent studies of cessation induction, this has not been the case. Abstinence will be reported both with and without (missing samples) cotinine verification.

Hypotheses 1a, 2, & 3 These hypotheses predict that provision of NRT samples will lead to higher abstinence rates (Hyp. 1a), incidence of quit attempts (Hyp. 2), and uptake of additional treatment (Hyp. 3). Logistic regressions will be performed for each outcome with treatment group (standard care vs. NRT sampling)

as the covariate, estimated using generalized estimating equations (GEE) to account for clustering within clinic. Rates for each outcome will be estimated along with its 95% confidence interval. The coefficient on group will be evaluated using a Wald test to determine if the abstinence rates in the two arms are statistically significantly different at the one-sided 0.025 level. Additional regression modeling will be performed where covariates such as age, gender, and race are accounted for. We will also consider interactions between NRT and categorical covariates to determine if there are certain subgroups in which NRT sampling is more or less effective. Though we expect few individuals to make more than one quit attempt over the span of 6 months, and thus examine incidence of quit attempts (Hypothesis 2), we will examine the distribution of quit attempts, and if appropriate, examine number of quit attempts via Poisson regression modeling. In addition to binary outcomes of treatment uptake (Hyp. 3), we will test for continuous outcomes (e.g., treatment intensity, duration) via GEE regressions.
Hypotheses 1b Hypothesis 1b predicts that provision of NRT samples will result in longer period of abstinence (longest # days non-smoking) across the entire study duration, and will be evaluated using regression modeling via GEE accounting for clustering by clinic.

Secondary Analyses
Provider Acceptability We will provide separate, descriptive data on provider acceptance and satisfaction with treatment delivery. We do not plan any formal between group comparisons because of very limited sample size (14 clinics in each site). This study is not powered on provider-level outcomes of our intervention, but such data will useful as we consider expanding our intervention into different venues.

Cost Effectiveness We will track intervention delivery costs (i.e., personnel, materials, NRT itself) per treatment group, though anticipate the only difference to be the cost of NRT. We will analyze and compare costs for intervention and control patients, for quit attempters vs. non-quit attempters, and for quitters vs. non-quitters. We will do this both across and within groups, and our model will adjust for patient characteristics, including demographics and smoking history. Led by our dissemination expert (Dr. Melvin), we will examine differences in direct medical costs (from the EMR) of all medical care post study enrollment for a sample of all study participants, of all participants who quit smoking during the trial, and for all intervention participants. We expect to show that NRT sampling as a strategy is, at least in the short term cost neutral, if not cost saving.

Other We will also examine changes in cigarette smoking, motivation, confidence, attitudes/knowledge of NRT over time, as a function of treatment group. These continuous variables (absolute, and change since baseline) will be examined as per Hypothesis 1b above.

4.10 Quality Assurance Plan

Data will be collected centrally by our research staff rather than locally at each clinic. Computerized data collection methods (Redcap) optimize quality assurance. Redcap system does not accept outliers, illogical response patterns, etc. The PI will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores, comparability of baseline characteristics, follow-up rates and use of extra-study cessation treatment across conditions in case analyses need to be adjusted for these.

4.11 Reporting mechanisms of AEs/SAEs to IRB, FDA, NIDA

Prior to the start of the study, the protocol will be registered on the clinicaltrials.gov registry. In our prior work on smoking reduction, in which smokers were using OTC NRT for non-cessation indications, we three times filed for an IND with FDA. On all three occasions the FDA has stated an IND is not necessary. For this study, we do not believe an IND is necessary, but we will again notify FDA of our intent to conduct a trial with a non-approved indication.

Serious Adverse Events (SAEs) are defined as any even that is fatal or life threatening, is permanently or significantly disabling (physically or psychologically), requires inpatient hospitalization or prolongation of hospitalization, contributes to a congenital anomaly/birth defect or is any medical event that requires treatment to prevent one of the medical outcomes listed above.

For a study of this size (N=1300) and duration (6 months), we do expect some deaths to naturally occur, all of which will be reported to IRB, but given that we are providing a mere 2-week sample of NRT, we do not anticipate any study-related SAEs. In our ongoing trial of now 1200 smokers followed for 1 year, there have been <5 deaths total.

All serious AEs (SAEs), study related or not, will be reported to the MUSC Committee on Human Research within 72 hrs. We will also report SAEs to NIDA within 72hrs of learning of any such occurrence, using the NIDA SAE Report Form. Follow-up of all unexpected and serious AEs will also be reported. All AEs are reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB, protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be 5% or less. If the monthly monitoring indicates the rate is above this, we will convene a special meeting of the DSMB.

4.12 Reporting mechanisms of IRB actions to NIDA & Report of changes or amendments to the protocol

We anticipate numerous amendments to our IRB protocol as new clinics are brought online into recruitment (all new personnel will need IRB approval). We also anticipate minor procedural amendments (e.g., updates of assessment protocol). We will not update NIDA for each individual minor amendment, but we will a) discuss with NIDA in advance any need for major protocol changes (e.g., change in clinics, significant (+/-10%) change in sample size), and b) provide IRB approval to NIDA once these major protocol changes have been local approved. We will report any IRB-actions within 5 business days. Notice of annual continuing approval will be included within each annual progress report to NIDA.

4.13 Trial stopping rules

There are three potential reasons to stop the trial prematurely: a) undermining of cessation, b) higher-than-anticipated quit rates, and c) significant rate of adverse events. Each is addressed below.

a) To protect against undermining of cessation, we will form a Data Safety and Monitoring Board (DSMB) and have them conduct an interim analysis after 50% of the sample has completed 6 month follow-up. We chose this number as this is the minimum necessary given our base rate is projected to be 15% and one has to see clear trend toward an even lower rate. To do this, the statistician will provide a copy of the dataset to the board. If this occurs, this board will independently decide on whether to stop the study.

b) We plan to examine the data halfway through enrollment to determine if observed differences in quit rates are so large that the trial should be stopped early. Using the method of O'Brien and Fleming (129) the significance level for this interim analysis is $\alpha = 0.005$. According to this same reference, conducting this analysis decreases our power for detecting our projected differences only from 0.80 to 0.79.

c) The research staff will report any unexpected AEs or any scores of "severe" on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Since a maximum two week supply of OTC nicotine lozenge and patch will be provided, adverse events will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules (127) and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity, whether they occurred during smoking or abstinence, caused a dropout, required treatment and presumed relation to drug intake. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms of emergence of a mental disorder such as depression or alcohol dependence. Dr. Gray, a board-certified psychiatrist, will be available for on-site medical supervision. Any study-related SAE will be reported to the DSMB immediately, which may convene a special meeting. Aggregate summary of all AEs will be provided at each regularly scheduled DSMB meeting.

4.14 Conflicts of Interest

The Medical University of South Carolina is fully compliant with federal laws in reporting of conflicts of interest. All key personnel listed within this application have complied with this policy. Any conflicts of interest will be acknowledged in any publications or conference proceedings.

4.15 Potential risks and benefits to participants

The research protocol calls for non-treatment seeking smokers, who will vary across the motivational spectrum from wanting to quit vs. not wanting to quit, to receive standard care (Ask, Advise, Refer) or NRT sampling. The sampling intervention consists of a two-week supply of both nicotine patch and lozenge, both over-the-counter products that have received extensive support for their efficacy and safety (22, 107-112). Nonetheless, there are potential for risks for each product alone, as well as when used concurrently. We believe these risks, described below, will be minimal and mild.

4.15.1 Nicotine lozenge In a prior trial of the particular lozenge we will be using, 68% and 71% of 2 and 4 mg users of nicotine lozenge reported an adverse event (AE) vs. 54% of placebo users (113, 114). With both active doses of the lozenge, 7% dropped out due to AEs and 7% dropped out due to AEs on placebo. With both active doses, 1.6% reported a serious AE which was not different than that for placebo. There were no deaths or irreversible injuries deemed possibly due to lozenge. The most common AEs were nausea, flatulence and upper respiratory tract infection (113). The current labeling on OTC lozenge states pregnant and breast feeding women, those less than 18 years of age, those using a prescription medication for depression or asthma or a smoking cessation medication and those with heart disease, recent heart attack, irregular heartbeat, high blood pressure not controlled by medication, stomach ulcers or diabetes should consult a provider before using the lozenge.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation (92), the three most common adverse events within the lozenge group were 1) nausea: 7.8%, compared to 4.4% within placebo group, 2) mouth/throat irritation: 6.7%, compared to 3.3% within placebo group, and 3) hiccups: 6.2%, compared to 0.3% within placebo group. All other adverse events occurred <5%. In our recent trial of sampling nicotine lozenge, which was not placebo-controlled but was based on a similar sampling strategy as proposed here, the most common adverse events were nausea (23% of all adverse events), throat irritation (17%), and hiccups (13%).

Dependence on the lozenge and harm from concurrent use of lozenge and cigarettes has not been reported but has not been studied. The pharmacokinetics of the lozenge most closely matches that of nicotine gum. With gum used for abrupt cessation, the estimated incidence of dependence is 1-3% (115). Although an early anecdotal report suggested concomitant use of NRT and smoking could induce heart attacks, several large empirical studies since then have failed to confirm this observation (116). For example, in the LHS study (117) and in our prior study (48), large numbers of smokers concurrently smoked and used nicotine gum or other NRT products and the incidence of any significant AEs was < 1%.

4.15.2 Nicotine patch The most common side effects from nicotine patch are skin irritation, insomnia, and headache or nausea. In an early but seminal placebo controlled test of patch (118), there were few systemic side effects of patch use: 21% vs. 15% of smokers in the patch and placebo groups respectively reported a side effect during the treatment period. The most frequent symptoms with the patch as compared with the placebo patch were headache (4 vs. 4 percent), nausea (4 vs. 1 percent), and vertigo (4 vs. 0 percent). Transient mild itching was reported by 14% of the subjects in the patch group and 1% in those in the placebo group after the first week ($P<0.001$). At each visit, 4.5% to 7.3% of the remaining subjects in the patch group reported erythema, as compared with 2.3% to 6.7% of those in the placebo group. Acute eczema persisting for several days in the area of the patch caused 1.4% of the subjects in the nicotine group and 0.7% of those in the placebo group to stop using the patch.

In a separate but similar study comparing bupropion vs. patch vs. combined bupropion/patch vs. placebo (119), the most common adverse events reported by patch participants were 1) insomnia (30% in active patch group vs. 20% in placebo), 2) headache (28% in active patch group vs. 33% in placebo), 3) application site reactions (19% in active patch group vs. 7% in placebo), and 4) dream abnormalities (18% in active patch group vs. 3% in placebo).

Finally, in a recent trial of placebo vs. single vs. multiple medications for smoking cessation (92), the two most common adverse events within the patch group were 1) skin irritation: 14.7%, compared to 2.7% within placebo group, and 2) disturbed sleep: 11.3%, compared to 5.6% within placebo group. All other adverse events occurred <5%. Seven percent of patch users vs. 4% of placebo users discontinued medication due to adverse events.

4.15.3 Combined patch & gum Our sampling intervention allows smokers to briefly try evidence-based cessation medications, either singularly or concurrently. We do not explicitly encourage dual use, but we will not discourage it either. We do belief combined medication use is safe. Combination treatments are often suggested for more dependent smokers and/or smokers with chronic medical conditions (120-122). One review in particular (120) provides significant rationale by which combined NRT should not incur significant risks, since NRTs provide lower doses per unit or per hour than are typically obtained by cigarette smoking, and the rate of nicotine administration for all NRT products is substantially slower than that from an inhaled cigarette.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation (92), the four most common adverse events within the combined patch/lozenge group, were 1) disturbed sleep: 9.0%, compared to 5.6% within placebo group, and 2) skin irritation: 8.9%, compared to 2.7% within placebo group, 3) nausea: 7.9%, compared to 4.4% within placebo group, and 4) mouth/throat irritation: 5.7%, compared to 53.3% within placebo group. All other adverse events occurred <5%.

4.15.4 Combined use of any NRT product and smoking Our study allows smokers to sample individual or combined NRT products, but without a requirement of a formal quit attempt. Thus, smokers could be using NRT products concurrently (same day) as smoking. This could result in nicotine intoxication; i.e. nausea, dizziness, headache, stomachache, etc (116). In our prior study, participants completed a nicotine intoxication scale, and we found no evidence of nicotine intoxication when gum and cigarettes were used concurrently. In addition, our review of prior smoking reduction studies found most participants did not have higher than normal cotinine levels with concurrent use of cigs and NRT, and there were few AEs reported (123).

4.15.5 Undermining Cessation Another potential risk is that the sampling intervention will decrease rather than increase future cessation as briefly discussed in Section A.5. However, the limited data available (124) suggest this is unlikely. Our prior work on providing NRT to smokers not yet fully committed to cessation (47, 48, 67), as well the work of many others (125, 126) clearly demonstrate that use of pharmacotherapy among smokers not wanting to quit effectively promotes cessation.

4.15.6 Confidentiality A final risk is breach of confidentiality.

Benefits: All smokers in this trial will receive at minimum standard care, consisting of brief provider advice to quit and referral to quitting resources. Half of the participants in the trial will receive samples of two products that alone and in combination have shown significant benefits on quitting. Thus, there are direct benefits to all participants. The major benefit to society will be whether a brief sample of evidence-based medication serve as an effective method to catalyze cessation (abstinence, quit attempts, uptake of additional quit resources). The risks of nicotine lozenge and patch are very small, even when used concurrently. The sampling period of our trial consists of two weeks, which further minimizes risk potential. Smoking cessation is the most important activity to improve public health and many smokers are resistant to quitting. Recent trends in smoking cessation are moving towards longer, more intensive treatments that combine behavioral and pharmacologic treatment. While efficacious, such approaches do not lend themselves to clinical practice within primary care settings, where providers have limited resources (time and expertise) to address tobacco dependence. If NRT sampling results in the hypothesized outcomes, it could offer an innovative, easy to implement option that has

significant reach. Thus, NRT sampling represents a significant strategy that offers both clinical and policy significance to promote public health.

4.16. Collection, reporting and management of AEs and SAEs

Adverse events will be tracked and rated as mild, moderate or severe by the patient and rated as related to NRT by the research assistant using guidelines. We will determine if any adverse events result in dropouts or are serious according to FDA guidelines (95, 96). A DSMB will assist in determining if the rate or severity of adverse events exceeds expectations (see Protection of Human Subjects).

The research staff will report any unexpected AEs or any scores of "severe" on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Since a maximum two week supply of OTC nicotine lozenge and patch will be provided, adverse events will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity, whether they occurred during smoking or abstinence, caused a dropout, required treatment and presumed relation to drug intake. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms of emergence of a mental disorder such as depression or alcohol dependence. Dr. Gray, a board-certified psychiatrist, will be available for on-site medical supervision.

4.17 Plans for Interim Analyses of efficacy data

We plan to examine the data halfway through enrollment to determine if observed differences in quit rates are so large that the trial should be stopped early. Using the method of O'Brien and Fleming (129) the significance level for this interim analysis is $\alpha = 0.005$. According to this same reference, conducting this analysis decreases our power for detecting our projected differences only from 0.80 to 0.79.

4.18 Responsibility for data and safety monitoring

The PI will be responsible for monitoring the trial. The statistician will monthly examine the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will weekly check the AE database prepared by the research assistants immediately prior to the lab meeting a) to see if any particular COSTART categories are being endorsed more frequently than normal and b) to determine if any side-effect symptom checklist scores are higher than expected. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

4.19 Frequency of DSM reviews

The DSMP will be reviewed annually.

4.20 Content of DSM report

The DSM report, which will be provided to all DSMB members, will include: a) enrollment data, in aggregate and split by gender and race, b) retention (% of all scheduled contacts that are completed), and c) adverse event data. Adverse event data will be presented in aggregate, but will also include a detailed listing of all serious adverse events (SAEs).

4.21 DSMB

We will create a Data Safety and Monitoring Board to monitor both the rate and severity of adverse events, and any decremented rate of quitting in the NRT-group. This panel will include 3 clinicians with expertise in smoking cessation trials, and a statistician. The DSMB will meet annually to review any adverse events related to the study, as well as review any data management related errors. Potential conflicts of interest will be discussed jointly by the PI and the Chair of the DSMB; at least 1 member of the DSMB will be from outside the PI's home

department. The board may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board.

5. Inclusion of Children

Children under 18 will be excluded since this age group does not conform to FDA approved use of NRT. Children ages 18-21 will be eligible for the trial.

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