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Working Title:

A Pilot Translational Study of Varenicline Sampling to Promote Treatment Engagement and Smoking Cessation

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Specific Aims

Smoking cessation remains the primary goal for population-based tobacco control. Many smokers lack intrapersonal resources to initiate and succeed in a sustained quit attempt. Whether lacking in motivation or confidence, or holding misbeliefs that undermine use of evidence-based medications, or through lack of decisional autonomy, many smokers show "cessation fatigue" after repeated failures and remain simply unable or unwilling to quit. Our research program has been addressing these barriers for the past 10 years, focusing on concrete, behavioral tools to overcome each. A number of cessation treatments (both pharmacologic & behavioral) have been available to smokers for some time, but their access and reach are often restricted, and consequently are under-used. We believe that new methods are needed to not only develop new cessation treatments (not our focus here), but also to innovate new methods for how existing treatments get disseminated into the real world for a larger, deeper penetrance. This is our focus herein.

Guided by recommendations for pragmatic interventions (i.e., brief, readily acceptable, easily disseminated), our team has developed and tested interventions that are face valid, easily delivered, practical, and broadly applicable. This work began 10 years ago with a large (N=849) nationwide, population based randomized clinical trial testing the concept of nicotine replacement therapy (NRT) sampling. As applied to a broad population of smokers, inclusive of those wanting and not wanting to quit, sampling provides a concrete, behavioral catalyst to induce quit attempts and quitting. NRT sampling was hypothesized to increase self-efficacy and motivation, and to familiarize smokers with and facilitate positive attitudes toward medication. Our prior trial consisted exclusively of smokers unmotivated to quit, who were given (or not) samples of NRT with minimal adjunctive support. Our positive results received widespread prominence, including high tier publication (*Archives of Internal Medicine*). In separate trials, we further developed the concepts and delivery of medication sampling. This included a small pilot trial (N=157) to isolate the importance of smoker motivation to quit, within a sample of smokers across South Carolina, which demonstrated the beneficial effects of sampling across the motivational spectrum. Finally, we have an ongoing trial to examine NRT sampling in primary care settings across South Carolina (20 clinics; N=1243 participants), our most applied and real-world test of sampling to date. Recruitment and follow-up will conclude in summer 2018, and we look forward to forthcoming results.

Our prior work on NRT sampling creates a compelling question as to whether varenicline sampling would have similar, or better, effects. Varenicline is inarguably the strongest single cessation medication available, superior to other single options. As a prescription medication, whether varenicline is suitable for sampling is unclear. On one hand, haphazard use, over a brief time, may not deliver sufficient pharmacologic benefit. Prescription delivery incurs its own barriers to widespread delivery (which can be overcome). On the other hand, much like NRT sampling, it could provide a tangible cue to action that provides psychological engagement (motivation, confidence, autonomy) to sustain subsequent use and ultimately enhance cessation. Whereas many smokers have negative reactions against NRT, varenicline might be a suitable alternative. Indeed, we ourselves are a bit mixed as to whether varenicline sampling has any clinical potential, but either way, we think it is an interesting and compelling question that offers both clinical and regulatory implications, and thus deserves further testing.

A large-scale trial of varenicline sampling is premature, largely because we do not know if this is even viable. We therefore propose a pilot clinical trial with **primary aims** to: 1) determine feasibility (recruitment, compliance, retention), 2) further evaluate our hypothesized mechanisms (some from our NRT work but others new), and 3) assess preliminary effect sizes, all of which would guide a subsequent trial. We will recruit 100 smokers across our state and randomize them to receive a 4-week sample of varenicline, or not, and will follow all for 3 months. Our statewide focus derives from our hands-off (i.e., translatable) intent, such as would be eventually implemented in busy real world clinical practice (eg. primary care), yet our methods include daily diary assessment to enhance rigor. We are mindful of requirements for physician oversight, and embed full precautions for safety. Our study sample will include smokers both wanting to quit and not (purposeful recruitment of each, with stratified randomization), which will allow for exploratory sensitivity analyses to assess the role of smoker motivation on outcomes. We hypothesize that: 1) varenicline sampling will be feasible to deliver (efficient recruitment among all-comer smokers) with reasonable compliance (>80% of study sample using meds on at least 50% of sampling period), with 2) greater relative increases in all hypothesized mediators, and 3) greater increases in a range of cessation-related behavior: a) further treatment engagement (i.e., further medication use, calls to quitline), b) quit attempts, c) cessation. We are underpowered for tests of mediation and for cessation outcomes. Nonetheless, these effect sizes, as well as the larger lessons learned from this pilot RCT, will guide a larger trial. If varenicline sampling were to show promise through this and future trials, this would offer great dissemination appeal to physicians, quitlines, etc. in that, much like our NRT work, varenicline sampling could be a **pragmatic strategy to engage more smokers in better treatments, sooner**.

Human Subjects Research

1. Risks to Human Subjects

1.1 Human Subjects Involvement and Characteristics

Eligibility criteria include:
1) age 18+;
2) daily smoker (25+ days per previous month);
3) smoking 5+ cigarettes/day;
4) smoking ≥ 1yr;
5) some interest in eventual quitting (>2 on 10-point scale);
6) has a primary care doctor and has seen that doctor at least once in past year;
7) not currently pregnant, breastfeeding, or planning to become pregnant;
8) no suicidal ideation in past month, nor any lifetime suicide attempt;
9) no reports of hallucinations;
10) no reports of history of seizures; and
11) own a smartphone or have regular (daily) access/use of email.
12) if female, willing to take a pregnancy test
13) not currently taking any medications to help quit smoking
14) no diagnosis of schizophrenia or bipolar disorder
15) no members of the same household currently enrolled in the study

Participants will be recruited from the general community, across South Carolina, using print/online advertising, including social medial. We intend to enroll an Intent-to-Treat sample of 100 participants, comprised of 50% female, and at least 30% African American smokers. However, a number of consented participants will not necessarily enroll in the trial (defined as completing initial/Week 0 phone call) and thus we plan for 120 consented participants. No more than 100 will enroll.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Racial Categories	Females	Males	Total
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	20	20	40
White	40	40	80
Racial Categories: Total of All Subjects*	60	60	120

1.2 Sources of Materials

Research material obtained from the participants include responses to phone and online surveys, collected directly by our research team and entered directly within secure databases. Participants will also complete daily diaries, entered directly in to secure REDCap survey database. Research data will be obtained specifically for research purposes. 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 to be supplied with 4-week sample of varenicline, or not. Varenicline is an FDA-approved medication for smoking cessation, and all black-box warnings have been removed. Use of varenicline is entirely self-chosen, since this is one outcome, rather than prescribed. Varenicline is inarguably the strongest single-agent medication to facilitate smoking cessation. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants. Potential risks are as follows:

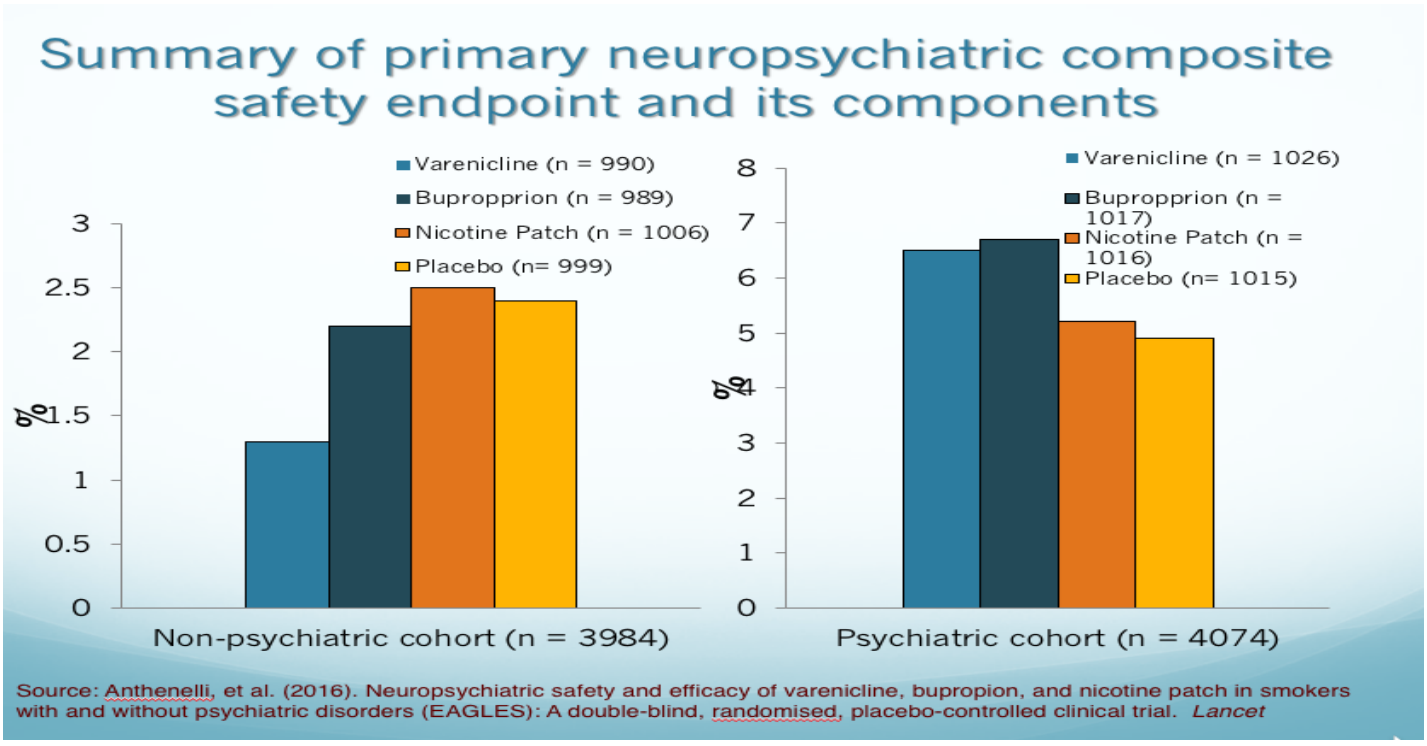
1.3.1 Risk of using varenicline: Up through 2015, FDA required a black-box warning for varenicline, largely due to media/anecdotal reports of self-injury, including suicide. A number of reviews and meta-analyses of varenicline have shown safety. [52,61-64,114] For example, in a pooled analyses of 10 varenicline RCTs, across 5,000 smokers, only insomnia was related to active medication:[115]

Table HS1: Review of Psychiatric Adverse Events: Pooled analyses of 10 Varenicline RCTs

	Varenicline	Placebo	RR	95% CI
Incidence of psychiatric d/o	10.7%	9.7%	1.02	0.9 - 1.2
	(excluding insomnia)			
Mood Disturbance (depressed)	2.8%	1.9%	1.4	.96 - 2.08
Anxiety Disturbance	4.5%	5.0%	.86	0.67 - 1.12
Suicidal and Self Injurious	0%	.1%	--	--
Sleep Disturbance (insomnia)	25.1%	14.5%	1.7	1.5 - 1.92

In 2016, the EAGLES trial was published,[59] and this gave further reassurance of varenicline safety. This trial, the largest and likely most rigorous of all varenicline trials, recruited approximately 8,000 participants, 50% of whom had an established/current psychiatric history (major depression, etc). A neuropsychiatric index (combination index of all neuro/behavioral/psychological adverse events) was calculated and showed clear safety of varenicline, in both psychiatric and non-psychiatric samples (figures below). The EAGLES trial served as the major impetus for FDA to remove the black box warnings. We are told that Pfizer is moving forward with OTC indication for varenicline.

Figure HS1: Summary of neuropsychiatric endpoints: EAGLES trial



The EAGLES trial also provided a full listing of all adverse events experienced by at least 1% of the study sample. As anticipated, and per Figure above and Tables HS2 and HS3 below, those in the psychiatric cohort reported higher incidence of neuropsychiatric adverse events. The profile of adverse events exhibited (eg, abnormal dreams more common for varenicline and nicotine patch compared with placebo) was consistent with previous reports. Suicidal ideation (second table below) was reported in 0.3% of smokers in the varenicline group (non-psychiatric cohort). Overall, the treatments were well tolerated.

Table HS2: EAGLES Adverse Event Listing (reported by ≥1% of study population)

	Non-psychiatric cohort† (n=3984)				Psychiatric cohort† (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Psychiatric disorders	315 (32%)	332 (34%)	301 (30%)	259 (26%)	405 (39%)	435 (43%)	420 (41%)	354 (35%)
Abnormal dreams	83 (8%)	47 (5%)	111 (11%)	39 (4%)	118 (12%)	84 (8%)	140 (14%)	53 (5%)
Agitation	32 (3%)	29 (3%)	28 (3%)	25 (3%)	47 (5%)	56 (6%)	39 (4%)	41 (4%)
Anger	3 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	11 (1%)	4 (<1%)	4 (<1%)	5 (<1%)
Anxiety‡	46 (5%)	64 (6%)	45 (4%)	57 (6%)	86 (8%)	105 (10%)	93 (9%)	63 (6%)
Depressed mood	31 (3%)	13 (1%)	27 (3%)	29 (3%)	47 (5%)	47 (5%)	52 (5%)	52 (5%)
Depression	17 (2%)	13 (1%)	8 (1%)	15 (2%)	49 (5%)	45 (4%)	47 (5%)	46 (5%)
Depressive symptom	5 (1%)	3 (<1%)	2 (<1%)	2 (<1%)	11 (1%)	8 (1%)	12 (1%)	13 (1%)
Initial insomnia	7 (1%)	6 (1%)	10 (1%)	4 (<1%)	15 (1%)	8 (1%)	10 (1%)	2 (<1%)
Insomnia	95 (10%)	126 (13%)	91 (9%)	73 (7%)	94 (9%)	119 (12%)	104 (10%)	66 (7%)
Irritability	34 (3%)	29 (3%)	47 (5%)	37 (4%)	48 (5%)	42 (4%)	61 (6%)	67 (7%)
Major depression	3 (<1%)	0	1 (<1%)	3 (<1%)	7 (1%)	10 (1%)	4 (<1%)	2 (<1%)
Middle insomnia	7 (1%)	15 (2%)	13 (1%)	6 (1%)	11 (1%)	16 (2%)	13 (1%)	8 (1%)
Nervousness	14 (1%)	18 (2%)	11 (1%)	9 (1%)	21 (2%)	19 (2%)	17 (2%)	27 (3%)
Nightmare	9 (1%)	7 (1%)	26 (3%)	3 (<1%)	13 (1%)	9 (1%)	30 (3%)	14 (1%)
Panic attack	2 (<1%)	7 (1%)	2 (<1%)	3 (<1%)	9 (1%)	19 (2%)	13 (1%)	11 (1%)
Restlessness	14 (1%)	14 (1%)	15 (1%)	14 (1%)	17 (2%)	20 (2%)	14 (1%)	9 (1%)
Sleep disorder	31 (3%)	37 (4%)	17 (2%)	19 (2%)	34 (3%)	36 (4%)	28 (3%)	23 (2%)
Tension	2 (<1%)	10 (1%)	2 (<1%)	2 (<1%)	9 (1%)	5 (<1%)	10 (1%)	6 (1%)

Table HS3: Suicidal Ideation & Behavior: EAGLES trial

	Non-psychiatric cohort*(n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
During treatment and ≤30 days after last dose								
Assessed	988	983	996	995	1017	1012	1006	1006
Suicidal behaviour and/or ideation	7 (1%)	4 (<1%)	3 (<1%)	7 (1%)	27 (3%)	15 (1%)	20 (2%)	25 (2%)
Suicidal behaviour†‡	0	0	1 (<1%)	1 (<1%)§	0	1 (<1%)	0	2 (<1%)
Suicidal ideation	7 (1%)	4 (<1%)	3 (<1%)	6 (1%)	27 (3%)	15 (1%)	20 (2%)	25 (2%)
During follow-up (>30 days after last treatment dose and through end of study)								
Assessed	807	816	800	805	833	836	824	791
Suicidal behaviour and/or ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)
Suicidal behaviour†¶	0	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Suicidal ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)

In the current pilot trial, we provide a 4-week mailed sample of varenicline (.5mg BID; as compared to 1mg BID as per convention) to smokers who do and do not want to quit, with minimal direct involvement from clinician. Each of these study elements has precedent (see Table HS4 below). The only design issue that is truly unprecedented here is the self-determined/self-paced use of varenicline, i.e., sampling. Though this does require added instructions for titration/use, we do not believe this does anything to increase risk. Sampling could lead to haphazard use, using some days but not others. This is an outcome we will track, but for purposes here, we view inconsistent use as similar to <100% compliance that would be anticipated for any conventional RCT of varenicline for smoking cessation. Less than full compliance is the norm for any medication trial; sampling messaging merely more accepting of it.

Table HS4: Current Pilot Trial vs. Prior RCTs of Varenicline: Comparison of Methods

	No Direct Clinical Interview	Mailed Varenicline?	Includes unmotivated smokers?	.5mg BID dosing?	≤1 month medication duration?	Self-Determined/Self-Paced Used?
Biazzo et al 2010[73]	X	X			X	
Ebbert et al 2015[65]			X			
Fouz-Rosón et al 2017[99]				X		
Niaura et al 2008[101]						X
Oncken et al 2006[100]				X		
Renard et al 2012[67]						[flexible quit dates]
Rojewski et al (in press)[74]	X				X	
Selby et al 2015[75]	X	X				
Sansores et al 2016[116]			X			
Swan et al 2010 (COMPASS trial)[76]	X	X				
Current pilot RCT	**X**	**X**	**X**	**X**	**X**	**X**

1.3.2 Diversion to other smokers, non-smokers: We will be mailing varenicline (a prescription medication) to participant's home address, and there is potential that someone else other than the study participant could use it.

1.3.3 Loss of confidentiality: A final risk is loss of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

All research personnel have up to date CITI Certification for Protection of Human Subjects, and will keep this training current throughout the course of the study. Study participants will be recruited through statewide media outlets, including social media. Potential participants will be screened online (redcap survey) to determine study eligibility. Eligible participants will provide contact information, and either receive (their preference) 1) a mailed packet with consent form (2 copies), baseline survey, along with postage paid return envelope, or 2) doxy.me teleconsent. We have used each of these consenting options in our prior and ongoing trials. On all

correspondence with potential participants, we provide our toll-free number if any questions or problems arise. A returned, signed consent form will comprise the consented sample; in the past, about 45-50% of individuals who are mailed a consent return it; we do not badger those who decline. However, not all consenting individuals are able to be reached (~10% from previous studies) and those that are (~90%) will comprise the intent-to-treat enrolled sample. Thus, to reach our intended sample of 100 enrollees, we plan for consent of up to 120 consented. We will abide by all HIPAA regulations as set forth by our institution. The PI will supervise all aspects of the recruiting process.

2.2 Protection Against Risk

2.2.1 Use of Varenicline Participants will be screened for eligibility for varenicline. Our eligibility criteria are largely more constrictive than many of the RCTs for varenicline, most notably the EAGLES trial. We screen out for current suicidal ideation or any past attempt, as well any major psychoses (schizophrenia, bipolar). We will also exclude smokers who have a history of seizures from participating. Smokers who report pregnancy or breast-feeding will also be excluded, and females (age ≤55yrs) will be mailed a pregnancy test to confirm. Language is included in the consent form that women should not be pregnant, breastfeeding, or planning to become pregnant.

Our dosing is .5mg BID, lower than most prior RCTs (though we do allow for smokers to decide, if they want, to titrate to 2mg). Two studies have shown roughly similar efficacy rates of 1mg (vs. 2mg), with fewer side effects and one other allowed smokers to self-titrate as they wish. Thus, we: a) provide .5mg tablets only, 56 total, b) with instructions to titrate as noted within instructions below, c) give instructions to take no more than two in the morning and two in the evening, d) give the participant the ultimate choice to self-pace usage. This choice and pattern of titration becomes an interesting study outcome that aligns with our focus on feasibility/viability. It is also wholly consistent with our naturalistic intent. Thus, we view the sampling experience as lasting 2-4 weeks depending on participant choice. For anyone who might ignore the titration schedule and either start or restart with 2mg, nausea is the most likely consequence, nothing worse.

During our phone call and within our mailings, we will include instructions to:

- Start with 1 pill per day (morning) for three days
- Then take 2 pills per day (once in morning and once in evening) for a week
- Then, if you want, you can go up to 2 pills in the morning and 2 in the evening
- Take no more than 4 pills per day
- If you ever stop taking the medication, but wish to re-start, begin again with 1 pill per day for three days

During follow-up assessment surveys, we will assess adverse events as per established procedures. Two study clinicians (Drs. Gray and Hoover), both of whom have long standing history of varenicline administration, will be available for consult for all adverse events. Any adverse events will be reported to the IRB. The most likely adverse events include insomnia, headache, and/or nausea. Changes in mood are also possible, all of which are tracked. All participants will be provided with cessation information (referrals to Quitline) as part of this study.

2.2.2 Diversion to other individuals Varenicline has no inherent reinforcement value, and there is no known abuse liability.[117] Mailing of varenicline is already routine within MUSC smoking cessation program (led by Dr. Hoover). We will instruct all participants not to share with others and to keep out of reach of children. Varenicline will be dispensed in child-resistant bottle packaging.

2.2.3 Confidentiality After a participant is deemed eligible for the study and indicates that he/she is interested in learning more about the study, we will collect contact information (name, phone number, address, e-mail address) **solely for the purposes of reaching out to the participant to provide additional information about the study and/or mailing the consent form/scheduling a doxy.me session.** All screening data are secure via RedCap, and all consents are kept in a locked file, stored centrally at our study office. Copies of informed consent will be kept by research personnel under lock and key. Research material obtained from the participants include responses to phone surveys, collected directly within secure databases (likely REDCap: supervised by research staff), wherein the participant can see only his/her responses. Each participant will be assigned a

number. 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 in locked files at the Cancer Control Program, with limited access to the study personnel. All database files will include password protection to further ensure confidentiality. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA.

Only study team members who are involved in recruitment and data collection will have access to PHI. We will use the participant's name and phone number for prescreening documents, which will be stored in a password protected file on a secure network drive at MUSC. Subject names and numbers will be deleted from the file at the close of the study (after analyses are complete).

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

As for benefit to study enrollees, all participants will receive a referral to the SC Quitline, an evidence-based, free, and anonymous service. Half of the participants will receive a 1 month supply of varenicline, inarguably the best available cessation medication. We do expect higher rates of treatment engagement, and cessation-related behavior (quit attempts, abstinence) among those who receive varenicline.

4. Importance of Knowledge to be Gained

We have previously shown the pragmatic value of medication sampling as a method to get more smokers to make better quit attempts sooner. Whether the same rationale applies for varenicline is unclear. It would be a leap to suggest that varenicline sampling would compare to NRT sampling, and this is the very reason why this proposal offers innovation. Indeed, if varenicline sampling is found not effective to promote quitting, then this would suggest: a) sampling should be restricted to OTC products, b) sampling should be restricted to products that do not have rigid instructions for administration, and/or c) physician guidance is needed for varenicline use. In contrast, if varenicline sampling does show promise, then this would further demonstrate that minimal provider involvement is adequate, which further diminishes barriers to access. Either way, we believe this is an important research question and will answer some important questions for our field. We are unaware of any randomized controlled trial that tests varenicline sampling. Much like our prior work on NRT sampling, we believe that varenicline sampling will be a catalyst for cessation, motivating more smokers to make better, evidence-based quit attempts sooner.

5. Data and Safety Monitoring Plan

5.1 Summary of the Protocol

This application proposes a pilot RCT to determine the feasibility of varenicline sampling, as well as assess early determinants of intervention mechanism and effect sizes as compared to non-sampling control condition. Adult smokers (N=100 enrollees, up to 120 consented) from across South Carolina will be recruited via print and social media outlets. With the exception of varenicline medication, our methods strictly adhere to our prior RCTs of NRT sampling, also done remotely. Thus, a central focus here is whether varenicline sampling, as delivered remotely, is feasible to do. Participants will be screened for eligibility criteria, more conservatively than prior RCTs, including seminal EAGLES trial. Upon consent, they will be randomized to receive a one-time, 4-week sample of varenicline (.5mg tablets, 56 tablets maximum) or not. The selected dosage balances competing perspectives to: a) provide maximum therapeutic benefit, while b) not imposing undo confusion of escalating with varying dosages, and c) giving the participant ultimate choice of use. All participants are asked to complete daily diaries during the sampling period, and follow-up assessments will continue for 12 weeks beyond study enrollment. As a pilot study, our main focus is on 1) feasibility: operationally defined as: a) efficiency of recruitment (goal: 5/month, b) use of medication (incidence, quantity, patterns of use), and c) adverse events, 2) Mechanisms include measures of motivation, confidence, knowledge of and attitudes toward medication, autonomy to quit, expectancies, and cessation fatigue, and 3) early estimation of treatment effect size (cessation related-outcomes: quit attempts, medication conversion), all of which will inform a larger trial.

5.2 Trial Management

All aspects of the study will be run through the MUSC Department of Psychiatry and Behavioral Sciences, where the PI holds faculty appointment. The target population is described in Section 1.1 of Human Subjects Protections, and the adjoining Planned Enrollment Table. The study timetable is as follows:

	Year 1 (months)	**Year 2** (months)
Refine all procedures / IRB	1-2	
Procure supplies	2-3	
Hire and Train Personnel	3-4	
Study Enrollment		
Cumulative N to start**	(40)	(100)
First Participant Starts	5	
First Participant Completes	8	
Last Participant Starts		19
Last Participant Completes		23
Data Analysis		23-24
Manuscript Preparation		24

All numbers reflect months within total study duration (**with the exception of cumulative N)

5.3 Data Management and Analyses

Data will be collected by the appropriate individual (research assistant, MPI, Co-I) within scheduled phone (Week 0) and by the participant during online follow-up contact. Responses are entered directly into RedCap databases, using only participants' study ID (no identifying information). All databases are password protected and limited to study approved (CITI and IRB certified personnel). Direct entry into Redcap ensures high standards for quality assurance (see below). The codes linking the name of the participant to the study ID will be kept confidential in a secured database accessible only to PI and statistician. RedCap is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). In no instance do we have paper copies of participant responses, as these invite data entry errors. The data analysis plan is outlined in Section C3f.

5.4. Quality Assurance

The REDCap system has validation options to 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.

5.5. Regulatory Issues

Prior to the start of the study, the protocol will be registered on the clinical trials registry (clinicaltrials.gov). We have consulted with various colleagues and none of them believe an IND is required for this study, largely due to conceptually similar studies of varenicline: see Section 1.3.1 within Human Subjects Protections. Our use conforms to most cessation trials, though our cessation message is less firm and in fact is messaged around sampling of medication.

All serious adverse events will be reported to the MUSC Institutional Review Board (IRB) within 24 hrs. Follow-up of all serious adverse events will be reported as well. All adverse events are reviewed weekly by the PI and yearly by both the DSMB and the IRB. Any significant actions taken by the local IRB, including significant protocol changes, will be relayed to funding agency (Hollings Cancer Center in this instance). We anticipate the serious

adverse event rate to be extremely low. If monitoring indicates otherwise, we will convene a special meeting of the Data and Safety Monitoring Board (DSMB).

5.6. Trial Safety

Adverse events will be tracked and rated as mild, moderate or severe by the patient and rated as related (or not) to varenicline by the research assistant using guidelines. We will determine if any adverse events result in dropouts or are serious according to FDA guidelines. A DSMB will assist in determining if the rate or severity of adverse events exceeds expectations.

Monitoring for Suicidality: Suicidality will be assessed as part of the final eligibility screening during the baseline assessment and at all follow-up assessments. Those who endorse suicidality during the baseline assessment will be excluded from the study, yet will still be managed via procedures outlined below. Suicidality during the baseline assessment will be defined as a response of "yes" to any of the 5 items on the NIMH toolkit for suicidal ideation (1. In the past few weeks have you wished you were dead? 2. In the past few weeks, have you felt that you or your family would be better off if you were dead? 3. In the past week have you been having thoughts about killing yourself? 4. Have you ever tried to kill yourself? 5. Are you having thoughts of killing yourself right now?).

Participants who endorse suicidality during the Week 0 (baseline) will complete a risk assessment with Dr. Carpenter via phone. During this phone call, Dr. Carpenter will follow the same procedures as outlined below for risk-assessment throughout the follow-up period.

Our follow-up assessments include PHQ9, which assesses for depression and includes an item on suicidal ideation. We have established procedures to automate a "red flag" process within our RedCap database anytime (in real time) a participant reports EITHER of the following: a) has a dramatic increase in total PHQ scoring with an overall score of at least 10 ($\geq$5 point increase from baseline and resulting score $\geq$10), OR b) any value $\geq$1 for item 9/suicidal ideation). These redflag indictors are checked daily, and met with appropriate response from our clinical team (Drs. Carpenter, Dahne, Hoover, Gray). Suicidality assessments across follow-up time points will be examined once per day via REDCap by Dr. Carpenter and/or an IRB approved member of Dr. Carpenter's research team. We have utilized this approach in three IRB approved trials within our research group (Pro00074015, Pro00063813, Pro00053203), and have established a REDCap report that allows us to quickly identify such instances. In the event that a participant reports suicidality at any point during the study, including during screening, Dr. Carpenter, a licensed clinical psychologist, will complete a risk assessment with the participant via phone. Dr. Carpenter will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, Dr. Carpenter will call emergency services and will remain on the phone with the participant until emergency services arrives. In the event that Dr. Carpenter makes contact with the participant (e.g., via phone), the participant expresses an imminent likelihood of harming him/herself, and the connection is lost, Dr. Carpenter will contact emergency services and will provide emergency services with the participant's contact information, including address. In the event that the participant is not in imminent danger, Dr. Carpenter will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. Dr. Carpenter will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later. In the event that a participant endorses suicidal ideation but is not responsive to Dr. Carpenter's phone call within 48 hours, Dr. Carpenter will e-mail the participant a list of local mental health resources and will suggest that the participant seek additional treatment. Dr. Carpenter will also ask that the participant respond to Dr. Carpenter either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to Dr. Carpenter's email within an additional 48 hours (4 days from completion of the assessment) **and** endorse "Yes" to "Are you having thoughts of killing yourself right now" on the NIMH suicidality toolkit at study screening, Dr. Carpenter will call emergency services and provide emergency services with the participant's name and address.

Across the three IRB protocols noted above, there has been one instance where a participant reported suicidal ideation during the course of study. This instance was successfully managed by our study team, without need to contact emergency services.

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 hours 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 we provide varenicline for a few weeks only, 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, and Dr. Hoover, a PharmD, will be available for on-site medical supervision.

5.7 Trial Efficacy
Given two-year scope of pilot trial, we do not plan for interim analyses of efficacy. However, the DSMB may request an interim efficacy report to review while trial is ongoing. Final efficacy analysis will occur after all participants have completed all visits. As a behavioral intervention, our sampling approach is not blinded.

5.8 Data and Safety Monitoring Plan Administration
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.

5.9 Data and Safety Monitoring Board
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 varenicline group. This panel will include 3 clinicians with expertise in smoking cessation trials, and a statistician. 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 DSMB will meet three times: once prior to study start, once upon 50% recruitment, and once at trial end. Each meeting will focus on (or review plans to track) adverse events related to the study, as well as review any data management related errors. 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.

ClinicalTrials.gov Requirements
Our trial will be registered within CT.gov.

Inclusion of Women
Women will be included in this protocol, expected to be approximately 50% of study sample. We have newly established methods, through our online screener, to ensure this, or at least require at 40% of each gender.

Inclusion of Minorities
We intend to enroll an Intent-to-Treat sample of 100 participants, comprised of at least 30% African American smokers. We have newly established methods, through our online screener, to ensure this. However, a number of consented participants will not necessarily enroll in the trial (defined as completing initial/Week 0 phone call) and thus we plan for 120 consented participants (again, ≥30% African American). No more than 100 will enroll.

Inclusion of Children

Children under 18 will be excluded, as per current approved use of varenicline.

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