The University of Oklahoma Health Sciences Center

Study Protocol
Institutional Review Board

Title of Project: A comparison of the effectiveness of combination varenicline and oral nicotine replacement therapy versus varenicline alone for smoking cessation: A pilot study

Principal Investigators: Darla E. Kendzor, Ph.D.; Department of Family and Preventive Medicine, Stephenson Cancer Center, OUHSC

Emily T. Hébert, DrPH; University of Texas Health Sciences Center at Houston, School of Public Health Austin

Co-Investigators: Jasjit S. Ahluwalia, MD, MPH, MS; Department of Behavioral and Social Sciences and Center for Alcohol and Addiction Studies, Brown University School of Public Health

Michael S. Businelle, Ph.D.; Department of Family and Preventive Medicine, Stephenson Cancer Center, OUHSC

Summer G. Frank-Pearce, Ph.D., Department of Biostatistics and Epidemiology, OUHSC

Lourdes Planas, Ph.D.; Department of Pharmacy: Clinical and Administrative Sciences; OU College of Pharmacy, OUHSC

Abstract: Varenicline is considered to be a first-line tobacco cessation treatment.[1] Previous studies have evaluated the impact of the combination of varenicline and nicotine patches (versus varenicline alone) on smoking cessation, though findings have been equivocal.[2-5] ***No studies to date have evaluated the combination of varenicline and oral nicotine replacement therapy*** (NRT; i.e., nicotine lozenges or gum). Nicotine lozenges and gum can provide acute relief during cravings and high risk situations, which offers individuals the flexibility to deliver nicotine when they need it most (in contrast with the continuous and passive delivery of nicotine offered via the patch). Prospective clinical trials are needed in real-world settings to determine whether the combination of varenicline and oral nicotine replacement therapy (i.e., lozenges, gum) is superior to varenicline alone for smoking cessation. The proposed ***pilot*** randomized trial would enroll 100 participants over 1 year (≈8 participants per month) utilizing a 2x2 factorial design. Twelve weeks of a pharmacological intervention [varenicline + oral NRT (VAR+N) vs. varenicline alone (VAR)] will be crossed with automated medication reminders (reminder messages vs. no reminder messages). All participants will receive an adapted version of the standard counseling offered through the Tobacco Treatment Research Program (TTRP). The primary outcomes will be biochemically-verified smoking cessation at 12 and 26 weeks following a scheduled quit attempt (1 week after enrollment). Smartphone-based ecological momentary assessment (EMA) will be employed to measure withdrawal symptoms, medication adherence, side effects, and adverse events using the Insight™ platform developed by the Stephenson Cancer Center (SCC) mHealth Shared Resource.[6] This pilot study will provide information regarding the feasibility, acceptability, and preliminary efficacy of combination varenicline and oral NRT for smoking cessation, which will support an NIH funding application

for a larger, adequately powered study.

Specific Aims:

Aim 1: To determine whether the combination of varenicline and oral NRT (gum or lozenges based on participant preference) increases the likelihood of biochemically-verified smoking cessation relative to varenicline alone at 12 and 26 weeks following a scheduled quit attempt. *It is hypothesized that there will be a trend towards higher cessation rates in the VAR+N compared with the VAR group, with a p-value of ≤ 0.2 supporting further investigation in a larger trial.*

Aim 2: To determine the effect of medication reminders on pharmacotherapy adherence and cessation. Participants will be randomly assigned to receive either reminder messages or no reminder messages to take their varenicline as prescribed each day. In addition, those assigned to VAR+N with medication reminders will receive smartphone reminder prompts to use oral NRT at regular intervals. *It is hypothesized that those who are randomized to medication reminders will be more adherent to the medication regimen and more likely to quit smoking than those who do not receive reminders.*

Aim 3: To characterize and compare the course of withdrawal symptoms and side effects within the VAR+N and VAR groups measured in real time via EMA, and to determine their influence on the likelihood of cessation. *It is hypothesized that those in the VAR+N group, who are using two pharmacotherapies to address nicotine dependence, may experience less severe withdrawal symptoms than those in the VAR group. However, those in the VAR+N group may also report more medication side effects because two pharmacotherapies are employed. It is expected that withdrawal symptom severity and the presence and severity of medication side effects may mediate the relations between treatment type and cessation outcomes.*

A. Background and Significance

Smoking is the leading preventable cause of death and disease in the United States[7] resulting in over 480,000 premature deaths each year.[8] Although the prevalence of smoking has declined over the past 5 decades, approximately 15.1% of adults continue to smoke in the U.S.[9] Nearly 70% of smokers report that they want to quit smoking, and 55% of all smokers try to quit each year,[10] but only 20% of smokers report that they are planning to quit within the next 30 days.[11] Effective pharmacotherapies to aid cessation are available, and the combination of behavioral support with pharmacotherapy provides optimal cessation outcomes.[12] Most recently, research has focused on evaluating combination pharmacotherapies in an effort to refine current evidence-based treatment approaches. Varenicline alone is currently considered a first-line tobacco cessation treatment.[1] A few studies have evaluated the combination of varenicline and nicotine patches (versus varenicline alone), though the findings have been equivocal.[2-5] No studies to date have evaluated the combination of varenicline and oral NRT (i.e., nicotine lozenges or gum). Nicotine lozenges and gum can provide acute relief during cravings and high risk situations, which offers individuals the flexibility to deliver nicotine when they need it most, in contrast with the continuous and passive delivery of nicotine offered via the patch. Little is known about the utility of using smartphone apps to provide automated medication reminders.[14,15] Notably, in clinical trials of combination bupropion and nicotine gum, participants' use of the gum was infrequent,[16,17] making it difficult to determine whether there might be an added benefit of oral NRT beyond the impact of bupropion alone. Plausibly, scheduled medication reminders might increase adherence to both varenicline and oral NRT. Prospective clinical trials are needed in real-world settings to determine whether the combination of varenicline and oral NRT is superior to varenicline alone, and to evaluate the impact of medication reminders on varenicline and oral NRT adherence.

B. Preliminary Studies/Study Team

Tobacco Treatment Research Program (TTRP).The TTRP[18] led by **Dr. Darla Kendzor**[19] and located at the University of Oklahoma Health Science Center (OUHSC), offers free tobacco cessation treatment to adults from campus or the community who would like to quit using tobacco. The proposed study would take place within the context of the TTRP. Individuals are linked with the TTRP via the electronic medical record and 1-click referrals from clinical departments at the OUHSC or SCC; or from the community by phone [(405) 271-QUIT (7848)], email (ttrp@ouhsc.edu), or fax referrals. Treatment includes counseling with a Tobacco Treatment Specialist either in-person or over the telephone and pharmacological treatment. Participants pick up their prescribed medication from the Family Medicine Center (FMC) pharmacy on campus, and the cost of the medication is charged to the TTRP. The TTRP is an Institutional Review Board (IRB)-approved observational research study (OUHSC protocol #6951) where participants complete relevant questionnaires via tablet computers as they receive tobacco dependence treatment. Participants are followed for 27 weeks and compensated for providing smoking status information at key visits (including biochemical verification). Appointments are the TTRP are scheduled by a Tobacco Treatment Navigator, who also manages appointments with counselors for individual treatment. An appointment letter with directions to the TTRP and a map is mailed or emailed to participants after they are scheduled for their first appointment. Participants are reminded of all future appointments via telephone, mail, email, and/or text. Participants with transportation difficulties living in the Oklahoma City metro area may be scheduled for pick-up and drop-off for key visits with SendaRide (https://sendaride.com) through their secure dashboard. *The TTRP also serves as a recruitment resource for ongoing research studies, and offers a strong resource and structure through which to facilitate the delivery of both empirically-supported and experimental treatments.*

Since inception in Oct. 2016, the TTRP has enrolled ≈ 500 participants into standard treatment or clinical trials. Enrollment numbers will continue to increase as new OUHSC clinical departments are linked via the electronic medical record, as evidenced by the ≈ 300 participants enrolled in the TTRP over the past 12 months. In addition, advertising will be employed to increase enrollment specifically in the proposed research study. TTRP participants are primarily White (55.4%), Black (27.7%), and American Indian (5.6%), and the majority are female (62.1%). Participants report smoking an average of 17.0 (*SD*=9.7) cigarettes per day prior to quitting, for an average of 29.7 (*SD*=13.1) years. Participants are socioeconomically disadvantaged with 21.1% reporting less than a high school education, 44.1% reporting an annual household income of < $20,000, and 54.4% reporting that they are uninsured or receiving Medicaid benefits.

Study Investigators. Overall, the study team has an impressive track record of tobacco-related research, and the investigators have varied and complementary expertise, with significant strengths in tobacco cessation intervention and mobile health research. **Dr. Kendzor**[21] is an Associate Professor in the Department of Family and Preventive Medicine in the University of Oklahoma College of Medicine. Her research focuses largely on tobacco cessation intervention among socioeconomically disadvantaged adults, and she is currently conducting two NIH-funded studies within the TTRP that focus on using small financial incentives as an adjunct to standard treatment to improve smoking cessation rates (both studies utilize smartphone-based EMA).[22,23] **Dr. Hébert**[24] is an Assistant Professor at the School of Public Health Austin and, and her research interests include the use of technology for health promotion, tobacco prevention and cessation, EMA, and the role of social media in tobacco marketing and health communication. **Dr. Businelle**[25] is an Associate Professor in the Department of Family and Preventive Medicine in the University of Oklahoma College of

Medicine He is also the scientific director of the mHealth Shared Resource[26] at the NCI-designated Stephenson Cancer Center, which has developed the Insight™ Platform, to be used in the proposed study, which empowers researchers to build, test, and launch technology-based assessment and intervention tools. **Dr. Jasjit S. Ahluwalia**[27] is a Professor of Social and Behavioral Sciences and Professor of Medicine at Brown University and an internationally recognized scientist. His research has primarily focused on nicotine addiction and smoking cessation in African-American smokers, has led or co-led nine large single site cessation clinical trials, worked on three treatment trials with varenicline, and has previously led a NIH-funded R01 2x2 factorial RCT.[13,28-31] **Dr. Summer Frank-Pearce**[32] is an Assistant Professor of Research in Biostatistics at the University of Oklahoma Health Sciences Center. She has developed numerous collaborations with investigators at the OTRC, including Drs. Kendzor, Businelle. **Dr. Lourdes Planas**[33] is an Associate Professor in the Dept. of Pharmacy: Clinical and Administrative Sciences at the University of Oklahoma College of Pharmacy. Her research focuses on medication optimization intervention in community and primary care settings.

C. Research Design and Methods

Study Design. The study will utilize a **2x2 factorial design** in which participants are randomized to pharmacological treatment (VAR+N or VAR) and medication reminders (reminders or no reminders) at baseline (see Table 1). All participants will receive 12 weeks of varenicline after the standard 1-week titration period, with half of participants additionally receiving oral NRT (gum or lozenges, based on participant preference). Those assigned to VAR+N with medication reminders will receive smartphone prompts at scheduled intervals (during waking hours) with a reminder to use oral NRT regularly and as directed. The primary study outcomes will be carbon monoxide (CO)-confirmed 7-day point prevalence abstinence at 12 and 26 weeks post-quit date.

Table 1. 2 x 2 Factorial Design

	Pharmacological Intervention (VAR+N or VAR)	
Medication Reminders (Reminders vs. No Reminders)	VAR+N + Reminders	VAR + Reminders
	VAR+N + No Reminders	VAR + No Reminders

Study Procedures.

Recruitment and Screening (Telephone). Adults who are referred to the OTRC Tobacco Treatment Research Program (TTRP), those who respond to study advertisements, and those who have previously enrolled in treatment at the TTRP but remain non-abstinent six months after enrollment will be eligible to be screened for this study (this will allow us to help participants who have failed to quit smoking after receiving treatment). Research staff will contact individuals who may be eligible for this study. Those who are interested in participating will complete a phone- or web-based REDCap screener. Those who meet the initial study inclusion criteria will be scheduled to complete a baseline visit where final screening for study inclusion criteria will be conducted.

Informed Consent/Screening. Informed consent will be obtained from all participants either in-person at the TTRP or remotely using REDCaps electronic signature feature. Individuals will be included in the study if they: 1) are ≥ 18 years of age, 2) demonstrate > 6th grade English literacy level, 3) agree to install the study smartphone application onto their personal phone (or agree to carry a study-provided phone with the app), 4) agree to complete phone-based or in-person surveys through 26 weeks post-quit date, 5) currently smoke ≥ 5 cigarettes per day, 6) are willing to initiate a quit attempt 7 days after the baseline visit (enrollment), 7) are willing to use nicotine gum/lozenges, 8) are eligible to receive Chantix after a consult with the study physician. Individuals will be excluded from the study if they 1) have a history of seizures, 2) have had an allergic reaction to varenicline, 3) report current suicidality (screen with the MINI Suicidal Scale[64]), or 4) are pregnant, planning to become pregnant, or currently breastfeeding. Please note that the smartphone application for this pilot study is only available in English.

Remote Enrollment. Remote baseline appointments will take place in 2-parts and participants will required to download a video conferencing smartphone app and/or provide photo identification. Participants will be excluded from the study if they cannot download a video conferencing smartphone app and/or provide photo identification. Part 1 will follow same procedure as an in-person visit (informed consent/screening, randomization, questionnaires, and counseling). At the end of part 1, the participant will be mailed Varenicline and if applicable any additional materials (smartphone, Bedfont iCO smokerlyzer, oral NRT). Part 2 will take place once the participant receives the Varenicline and additional materials. During part 2, the participant will be provided with Varenicline instructions and assisted with Insight™ smartphone application set up. The participant will receive the baseline compensation once they complete part 2.

Study Timeline. Enrolled Participants will be followed for a total of 27 weeks. For an overview of study participation, please see figure 1.

Randomization. At the conclusion of the first visit, participants will be randomized to one of the four cells within the 2x2 factorial design (see Table 1): pharmacological treatment (VAR+N vs. VAR) and medication reminders (VAR+N+reminders vs. VAR+reminders only) at the baseline visit. Adaptive randomization will be used to assign participants to groups based upon race, sex, cigarettes smoked per day, and education.

Questionnaires, Equipment, and Other Measures.
Participants will be asked to complete questionnaires at baseline (1-Week Pre-quit), Quit Day (1-Week Post-Enrollment), 1-Week Post-Quit Day, 2-Weeks Post-Quit Day, 3-Weeks Post-Quit Day, 4-Weeks Post-Quit Day, 8-Weeks Post-Quit Day, 12-Weeks Post-Quit Day, and 26-Weeks Post-Quit Day. At in-person visits, participants will complete self-report questionnaires on a

tablet computer; and have their expired CO, weight, and height measured in a private room to ensure confidentiality. At remote visits, participants will complete self-report questionnaires on their own device via REDCap or complete them over the phone. Participants completing remote appointments will also be provided with a Bedfont iCO smokerlyzer to measure expired CO. The questionnaire appendix will come from the TTRP IRB 6951.

Smartphones. Participants will be guided through the process of downloading the Insight™ smartphone application onto their personal smartphone and will be asked to complete daily EMAs during the 13 week period when they are taking their study medication(s). Those who do not possess a phone that meets the minimum requirements to download the Insight™ app, will be provided with a study phone. The smartphone app home screen will include: 1) a "Call Staff" function/button that automatically calls study staff when participants have problems with the app, and 2) a "Payment" function/button that enables participants to track their current level of compliance with phone-based surveys and level of compensation. At the baseline visit, all participants will receive training about how to use the smartphone app to complete EMAs (i.e., they will watch a "How to Use This App" video) and how to use the "Call Staff" and "Payment" button/options. Participants will be instructed to quit smoking at bedtime or 10:00 pm (whichever occurs first), the night before their scheduled quit day. The app will remind participants about their approaching quit date during each day of the pre-cessation period.

Varenicline. All participants will be evaluated by the study physician, and prescribed varenicline (if eligible). Individuals with a history of seizures, allergic reaction to varenicline, endorse current suicidality, and/or those who are pregnant, planning to become pregnant, or breastfeeding will be excluded from the proposed study. As a precaution, individuals who report current cardiovascular disease will require clearance from the study physician or their personal physician to use varenicline. Notably, recent research has indicated that neither varenicline nor NRT increases the risk of serious cardiovascular events.[37,38] In December 2016, the FDA lifted the boxed warning for varenicline after findings were published from a large clinical trial[39] showing that the risk of neuropsychiatric adverse events associated with varenicline did not differ from the nicotine patch or placebo, and that varenicline was more effective for smoking cessation than the nicotine patch, bupropion, and placebo (the nicotine patch and bupropion were more effective than placebo). As a precaution, female participants will be advised to avoid pregnancy while taking varenicline and to discontinue the medication should they become pregnant. However, the findings of observational research suggests that taking varenicline does not appear to be harmful during pregnancy.[40] During the first (pre-quit) week of the study, participants will continue smoking and begin taking varenicline. Doses are titrated during the first week of medication (days 1-3: 0.5 mg once daily; days 4-7: 0.5 mg twice daily).

Oral NRT. Participants randomized to a VAR+N group will be provided with a supply of 2mg/4mg nicotine lozenges or 2mg/4mg gum (depending on participant preference) and instructed to use a piece as directed after they quit smoking, especially when they have the urge to smoke. Participants will be instructed to chew a piece of gum as follows:

Baseline: every 1-2 hours (12-24 per day)
4-Weeks Post-Quit: every 1-2 hours (12-24 per day), and to begin reducing to at least every 2-4 hours (6-12 per day)
8-Weeks Post-Quit: every 2-4 hours (6-12 per day), and to begin reducing to at least every 4-8 hours (3-6 per day)

Additional supply of gum or lozenges will be provided during in-person visits or through the mail. Participants assigned to VAR+N with medication reminders will receive smartphone prompts (through the Insight™ app) (during waking hours) reminding them to use a piece of gum or a

lozenge every 3 hours through 4 weeks post-quit, every 4 hours during post-quit weeks 5-8, and every 6 hours during post-quit weeks 12.

Reminders. Participants assigned to the reminder groups will receive reminders to take varenicline and/or oral NRT as follows:

Varenicline Reminders. Participants will receive varenicline reminders that correspond with the medication schedule. The reminders will provide a message and then ask the participant if they have taken medication. Reminder 2 will only appear if the participant has reported "no" to reminder 1. Reminder 3 will only appear if the participant has reported "no" to reminder 2. On the 3rd reminder the participant will be asked why they did not take their medication.

Pre-Quit Day 1: Only PM reminder (1 white pill (0.5 mg) daily)

Pre-Quit Days 2-3: Only AM reminder (1 white pill (0.5 mg) daily)

Pre-Quit Days 4-7: AM and PM reminders (1 white pill (0.5 mg) in the morning and 1 in the evening)

Day 8 to end of treatment: AM and PM Reminders (1 blue pill (1 mg) in the morning and 1 in the evening)

Table 2. Varenicline reminders

Pre-Quit Day 1 Message	**Don't forget to take your Chantix pill tonight!**		
Pre-Quit Days 2-3 Message	**Don't forget to take your Chantix pill this morning!**		
Pre-Quit Day 4-7	**Don't forget to take your Chantix pill twice daily (morning and night)!**		
Day 8 to end of treatment	**Don't forget to take your Chantix pill twice daily (morning and night)!**		
AM		PM	
Reminder 1 (30 minutes after Daily Diary)	You were scheduled to take your morning Chantix pill at [INSERT TIME] AM. Have you taken your Chantix pill this morning? (Yes/No)	Reminder 1 (2 hours and 30 minutes after before sleep time)	You were scheduled to take your evening Chantix pill at [INSERT TIME] PM. Have you taken your Chantix pill this morning? (Yes/No)
Reminder 2 (1 hour after Reminder 1)	You were scheduled to take your morning Chantix pill at [INSERT TIME] AM. Have you taken your Chantix pill this morning? (Yes/No)	Reminder 2 (1 hour after Reminder 1)	You were scheduled to take your evening Chantix pill at [INSERT TIME] PM. Have you taken your Chantix pill this morning? (Yes/No)
Reminder 3 (1 hour after Reminder 2)	You were scheduled to take your morning Chantix pill at [INSERT TIME] AM. Have you taken your Chantix pill this morning? (Yes/No)	Reminder 3 (1 hour after Reminder 2)	You were scheduled to take your evening Chantix pill at [INSERT TIME] PM. Have you taken your Chantix pill this morning? (Yes/No)

	If no: What are the main reasons that you did not take your Chantix pill this morning? (Check all that apply) 1. I forgot to take it. 2. I was away from home. 3. I experienced side effects. 4. I didn't feel like I needed it. 5. I didn't think it is working. 6. I have decided not to quit smoking. 7. Other		If no: What are the main reasons that you did not take your Chantix pill this evening? (Check all that apply) 1. I forgot to take it. 2. I was away from home. 3. I experienced side effects. 4. I didn't feel like I needed it. 5. I didn't think it is working. 6. I have decided not to quit smoking. 7. Other

NRT Reminder. Participant will receive a message and then be asked if they have used NRT in the past 2, 4, or 8 hours.

Quit Day – 4 Weeks Post-Quit: Reminder every 3 hours

5 Weeks Post-Quit – 8 Weeks Post-Quit: Reminder every 4 hours

9 Weeks Post-Quit – 12 Weeks Post-Quit: Reminder every 6 hours

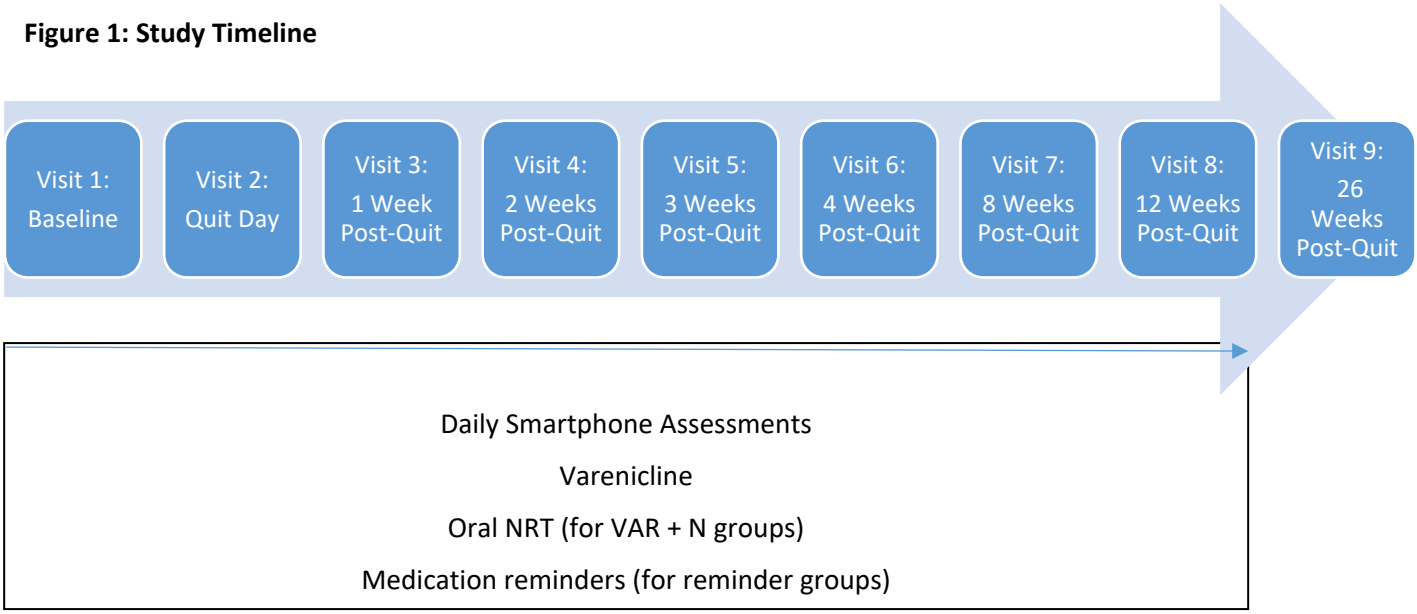
Table 3. NRT reminders

1.	**Don't forget to use nicotine gum/lozenges regularly throughout the day! It is recommenced that you use a piece of gum/lozenge every 1-2 hour.** After you have been smoke free for 6 weeks, taper down to using a piece of gum/lozenge every 2-4 hours and then after being smoke free for 8 weeks, taper down to a piece every 4-8 hours.	
2.	Have you used a piece of gum/lozenge within the past 2 hours?	No Yes
3.	(If 2 = No) Have you used a piece of gum/lozenge within the past 4 hours?	No Yes
4.	(If 3 = No) Have you used a piece of gum/lozenge within the past 8 hours?	No Yes

Table 4. Study compensation schedule (all groups)

Visit	Weeks Post-Quit	QuestionnairesQuestionnaires	Smartphone Assessments	Total Per Week
1	-1	$20		$20
2	0	$20	up to $10	$30
-	1	-	up to $10	$10
-	2	-	up to $10	$10
-	3	-	up to $10	$10
3	4	$20	up to $10	$30
	5	-	up to $10	$10
	6	-	up to $10	$10
	7	-	up to $10	$10
4	8	$20	up to $10	$30
	9	-	up to $10	$10
	10	-	up to $10	$10
	11	-	up to $10	$10
5	12	$20	up to $10	$30
6	26	$20	-	$20
			Total Possible	**up to $250**

Figure 1: Study Timeline



Developing a Quit Plan. At baseline, eligible participants will meet with a tobacco cessation counselor who will provide an overview of the tobacco cessation program, and help participants to set and prepare for their quit date. Participants will be asked to quit smoking the evening prior to their next weekly appointment (Visit 2).

Counseling. Participants will complete counseling session in-person or remotely with a Tobacco Treatment Specialist at the baseline visit and each visit through 4 Weeks Post-Quit . The counselor will check in with participants about the difficulties and successes they have experienced, and plan for any challenging situations that are anticipated. Advice and support will be provided as needed. Topics will include 1) the impact of tobacco on health/benefits of quitting, 2) stress management strategies, 3) making positive lifestyle changes, 4) developing

coping skills, and 5) relapse prevention. The counselor will check in with participants each week about the difficulties and successes they have experienced, and plan for any challenging situations that are anticipated.

Compensation. Participants will receive a $20 payment for completion of the Baseline visit, Quit Day, 4 Weeks Post-Quit, 8 Weeks Post-Quit, 12 Weeks Post-Quit, and 26 Weeks Post-Quit. (see Table 4 for study compensation schedule). In addition, participants will receive up to $10 weekly for completing the daily smartphone assessments. Specifically, they will receive $10 for completing at least 6 out of 7 EMAs, and $5 for completing at least 4 out of 7 EMAs each week. Participants who complete 3 or fewer EMAs will not receive additional compensation. Participants may earn up to $250 for participation in the study.

Discontinuing Reminders, Varenicline, or NRT. Using the following guidelines a participant may continue in the study if: 1) they no longer wants to receive reminders via the app, we will disable app reminders, 2) they no longer wants to take varenicline, we will have them delete the app, but will still ask that they come in to the clinic for in-person visits for follow-up, 3) they no longer wants to take NRT, they will be asked to answer that they didn't chew gum on the EMAs.

Remote Treatment Follow-up Visits. Due to the evolving circumstances regarding COVID-19, participants may complete any follow-up visits remotely. The requirements and compensation for remote visits will be identical to in-person visits. Participants will remotely complete web-based questionnaires and provide a smartphone-based CO measurement using a Bedfont iCO smokerlyzer. Participants may also keep the study smartphone until the 26 Weeks Post-Quit visit if necessary.

Study Measures.

Screening Measures (online or over the phone). Screening data will be collected using the secure web-based REDCap platform, which provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules. The initial online screening will include assessment of demographics, smoking history, readiness to quit, and other eligibility criteria.

Traditional Questionnaire Measures. Questionnaire data, including measures of tobacco/health history, sociodemographic characteristics, nicotine dependence,[41] withdrawal symptom severity,[42] depression,[43] perceived stress,[44] mental health,[45] beliefs about medications,[46] medication adherence,[47] and self-efficacy[48] will be collected via REDcap on tablet computers. The amount of time needed for participants to complete the computer-administered questionnaires varies by study visit. It is estimated that the longest visit (baseline) will require one hour to complete. We have found that even individuals with no experience using computers have had few problems completing study assessments. The questionnaire appendix will come from the TTRP IRB 6951.

Biological/Anthropometric Measures. Expired CO levels will be measured at each visit either in-person using the portable Vitalograph ecolyzer or remotely using the Bedfont iCO smokerlyzer which will interface the Insight™ smartphone application. Please note that the Insight™ smartphone application has integrated automated and secure (i.e., encrypted) facial recognition software to ensure that only the participant provides a CO breath sample. Self-reported abstinence from smoking will be verified with a CO level of ≤ 6 ppm at all subsequent post-quit visits. Body Mass Index (BMI) will be calculated (kg/m²) based on height and weight measurements collected at the baseline visit.

Ecological Momentary Assessment (EMA). EMA can accurately measure phenomena in real-time, natural settings.[50,51] EMA items will identify fluctuations in key variables that predict study outcomes with less bias than traditional in-person assessments.

Scheduled EMAs. The EMA methodology used in this study will be similar to what was used in our previous studies, and by other researchers.[52-60] All participants will download the study app onto their personal or study-provided phone and will be asked to complete scheduled EMAs once a day for 13 weeks. The scheduled EMAs will be prompted by the smartphone app, 30 minutes after the participant's scheduled wake time. The phone will ring and vibrate to cue these EMAs for 30 seconds. If the participant has not responded after 5 prompts, the assessment will be rescheduled and will be prompted again (e.g., 15 minutes later). This process will continue until the participant acknowledges the prompt, or the assessment is recorded as missed (i.e., 4 prompts spaced 15 minutes apart). These EMAs will ask questions about current and past 24-hour thoughts, feelings, experiences, behaviors (e.g., smoking lapses), physical symptoms, and medication adherence.

Programming. The mHealth Shared Resource at the OUHSC and Stephenson Cancer Center (SCC) offers resources that empower researchers to build, test, and launch technology-based assessment and intervention tools. The mHealth resource employs a program manager and 3 senior programmers who develop and maintain web and mobile applications and relational databases. Applications are developed using state-of-the-art cross-platform design tools. The Insight™ platform has already been developed and is being used by the OTRC investigators in other studies. The platform will allow the project investigators to quickly set up scheduled EMAs and messaging that are unique to the proposed study.

Smartphone application training. As in all of our studies, participants will watch a brief step-by-step video tutorial (created by the researchers) at the baseline visit that demonstrates use of all app features and participants will receive hands-on training. This training approach has minimized participant difficulties in our past research.

Data loss prevention. In order to overcome potential loss of data, phones will be programmed to connect to our secure server to upload encrypted data every 1.5 hours. This will ensure that no collected EMA data are lost. This tactic will also allow the researchers to remotely monitor each participant's EMA completion rate and intervene (e.g., call the participant) when this rate is low. Importantly, EMA data are password protected and encrypted on the phone and only encrypted data are transmitted to our secure server. Thus, study data are ONLY accessible by the research team. In addition, all study data can be remotely wiped from phones once the study is completed.

EMA alert settings. At the baseline visit, a phone set-up wizard is used to set participant sleep and wake times for each day of the week. This practice reduces the likelihood that the phone will ring when participants are sleeping. In addition, participants may delay EMAs by up to 20 minutes (i.e., by clicking the snooze assessment option when an EMA is pushed).

D. Statistical Methods

All questionnaires will be scored using methodology described in the published literature. Sociodemographic information will be summarized using frequencies with associated percentages (categorical/binary outcomes) or means with standard deviations (continuous outcomes). The 2x2 factorial design will be evaluated using logistic regression models, where

smoking status (12 or 26 weeks post-quit date) is included as the dependent variable. The dichotomous variables, medication type (NVAR vs. VAR) and message reminder type (medication reminders vs. no reminders), will be included as independent variables, as well as the interaction term. Sociodemographic covariates and nicotine dependence will be included in the model as covariates. Generalized Linear Mixed Models (GLMM) will be used to examine the influence of EMA variables that are measured repeatedly and are therefore correlated within subjects. The PROCESS macro for SPSS/SAS (described in Hayes, 2013[61] and available online[62]) will be used to conduct mediation analyses with the goal of identifying variables (e.g., withdrawal symptom severity) that mediate the relation between treatment condition and smoking cessation outcomes. This method uses an ordinary least squares path analytic framework to estimate direct and indirect effects in single and multiple mediation models, and bootstrapping methods are incorporated to generate confidence intervals. The data collected in the proposed study will provide preliminary information for future external funding applications.

E. Gender/Minority/Pediatric Inclusion for Research

The study has no inclusion/exclusion criteria based on gender or race/ethnicity. Individuals ≥18 years of age will be eligible for participation in this study. Children < 18 years of age will be excluded from the study.

F. Human Participants

1. **Subject Population.** Individuals will be included in the study if they: 1) are ≥ 18 years of age, 2) demonstrate > 6th grade English literacy level, 3) agree to install the study smartphone application onto their personal phone (or agree to carry a study-provided phone with the app), 4) agree to complete phone-based or in-person surveys through 26 weeks post-quit date, 5) currently smoke ≥ 5 cigarettes per day,5) are willing to initiate a quit attempt 7 days after the baseline visit (enrollment), 7) are willing to use nicotine gum/lozenges, 8) are eligible to receive Chantix based on the study physicians discretion. Please note that participants who enroll remotely will be required to download a video conferencing smartphone application and/or provide a photo identification. Individuals will be excluded from the study if they 1) have a history of seizures, 2) have had an allergic reaction to varenicline, 3) report current suicidality (screen with the MINI Suicidal Scale[64]), or 3) are pregnant, planning to become pregnant, or currently breastfeeding. Please note that the smartphone application for this pilot study is only available in English.

2. **Sources of Research Material.** Demographic, psychosocial, environmental, and behavioral data will be collected via: 1) REDCap (online or over the phone), 2) traditional REDcap self-report questionnaires completed in-person on a laptop/tablet computer and completed via secure online web portal, 3) EMAs completed via secure smartphone application, 4) smoking status based on expired CO and self-report, and 6) anthropometric information including height and weight.

3. **Recruitment and Informed Consent.** Individuals who complete the initial online/phone screener and meet the initial study inclusion criteria will be invited to complete the in-person screening visit. Upon arrival to the TTRP, participants will be provided with detailed information about the study and given the opportunity to have their questions answered within a private room to ensure confidentiality. Written informed consent will be obtained from those who are interested in participating.

4. **Risks.** Participation in this study poses risk to participants. However, one potential, although unlikely, risk is loss of confidentiality. The severity of harm in the case of loss of confidentially may range from mild to severe depending upon the individual and the specific circumstances. However, the risks of participation in the study are similar to that of participation in standard clinic care, as loss of confidentially may be experienced in either case. The

investigators are unaware of any risks associated with the use of the Vitalograph BreathCO monitor for the measurement of expired CO levels.

Medication Risks. All tobacco cessation medications offered or prescribed as part of this research protocol are FDA-approved for tobacco cessation. Nicotine replacement therapy is available over-the-counter, while varenicline requires a prescription. Possible risks of *nicotine gum* include: increased heart rate and blood pressure; mouth, teeth, and jaw problems; irregular heartbeat or palpitations; symptoms of nicotine overdose including nausea, vomiting, dizziness, weakness, and rapid heartbeat; or allergic reaction such as difficulty breathing or rash. Possible risks of *nicotine lozenges* include: increased heart rate and blood pressure; mouth, teeth, and jaw problems; indigestion or sore throat; irregular heartbeat or palpitations; symptoms of nicotine overdose including nausea, vomiting, dizziness, weakness, and rapid heartbeat; or allergic reaction such as difficulty breathing or rash. Nicotine replacement medications may have enough medication to make children and pets sick. The most common adverse reactions to *varenicline* include nausea, abnormal dreams, constipation, flatulence, and vomiting. Serious risks include new or worsening seizures, cardiovascular events (particularly among those with known cardiovascular disease), angioedema and hypersensitivity reactions, and serious skin reactions. Increased effects of alcohol and accidental injuries (e.g., traffic accidents) have been reported while taking varenicline. Serious neuropsychiatric symptoms have been reported including changes in mood (depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, panic, suicidal ideation, suicide attempts, and completed suicide. The study physician working in the clinic will prescribe these medications, monitor treatment response and medication side effects, and make adjustments as needed. Varenicline prescribing information is available at: https://www.pfizermedicalinformation.com/en-us/chantix

5. **Protections against Risk.**

General Procedures. Each participant will be assigned an identification number that will be utilized in place of names in all electronic and print data files. The file containing the links between participant names and identifiers will be kept in a file that will be stored in a locked filing cabinet when not in use and will be destroyed 12 months after the completion of the study. All print information including informed consent, screening questionnaires, and smoking status questionnaires will be stored in locked filing cabinets at the OTRC. Electronic data (with names omitted) will be maintained on the investigators' computers, and all computers and electronic files will be password protected. Participants will complete questionnaire data on a laptop/tablet computer through RedCAP. Participants will complete smartphone assessments through an encrypted mobile application, and all data will be automatically saved and sent to study servers. Baseline anthropometric measures and CO will be collected at the TTRP. All project staff will receive training focused on each of the following topics: 1) project rationale and objectives, 2) the informed consent process, 3) general data collection procedures (e.g., computer data collection, privacy), 4) measurement of anthropometric data, and 5) use of the CO measurement devices.

EMA Confidentiality Procedures. The following features are designed to address smartphone/EMA data security issues: 1) the data stored on the smart phone device are in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users); 2) a $\geq$ 8 character password (only known to researchers) is required to authenticate the current user before data can be manually accessed or manually downloaded from the smart phone to the server; 3) the web browser application linking the investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption), which will guarantee the data transfer from web browser to the backend database is well protected; and, 4) the backend databases are

hosted by Microsoft Azure and the University of Oklahoma Health Science Center. These steps will ensure the security of EMA data.

Medication Risk Management. Adverse events will be monitored in-person by research personnel at in-person visits or over the phone during counseling or follow-up calls. Qualified study staff will also follow-up with participants in person and via phone to monitor the use of NRTs and other tobacco cessation medications. The OTRC protocol for handling mental health emergencies will be followed as needed. All serious adverse events that meet reporting criteria will be promptly reported to the OUHSC IRB.

6. Potential Benefits. Potential benefits to participants include the possibility that the intervention will have a beneficial impact on smoking cessation outcomes. In addition, the knowledge gained from this study may be utilized to improve our understanding of the barriers to quitting and predictors of relapse. All study participants who are still smoking at the conclusion of the 26 week study period will be referred to the Oklahoma Tobacco Helpline to receive additional free smoking cessation resources.

7. Risks in relation to Benefits. The possible risks of participation in this study are minimal and reasonable in relation to benefits. The potential health benefits gained from tobacco cessation interventions far outweigh the risks of continued tobacco use.

G. Data and Safety Monitoring Plan

The study poses risk to participants; therefore, continuous monitoring and reporting of events will be undertaken by OTRC investigators (Drs. Kendzor, Hébert, Businelle). Unanticipated problems will be promptly reported to the IRB. Possible (though unlikely) adverse events might include compromised data security and medication side effects. Procedures to minimize the risk of loss of confidentiality are described in section F under the heading *Protections against Risk*.

Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and Safety Monitoring*," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator-initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the

external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

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