Human Subjects Research Protocol

PROTOCOL SUMMARY

Project Title:	**Protocol Version Date (required for each protocol modification):**
A randomized controlled trial of smoking cessation treatment for young adult dual users of combustible and electronic cigarettes	8-11-22

Principal Investigator: Elias Klemperer, PhD

TYPE OF REVIEW

Which type of IRB review are you requesting? Full [x] Expedited [ ] Complete category.

Your research may be expeditable if the research activities (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories: (CHECK THE CATEGORY(IES) THAT APPLY.

[x] (1) **Clinical studies of drugs and medical devices only when condition (a) or (b) is met.**
(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (NOTE: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review).
(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

[ ] (2) **Collection of blood samples** by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week: or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

[x] (3) Prospective **collection of biological specimens** for research purposes by noninvasive means.

[x] (4) **Collection of data through noninvasive procedures** (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.

[ ] (5) Research involving **materials** (data, documents, records, or specimens) that have been collected, or will be **collected solely for nonresearch purposes** (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 .CFR 46.101 (b)(4). This listing refers only to research that is not exempt.)

[ ] (6) **Collection of data from voice, video, digital, or image recordings** made for research purposes.

[x] (7) **Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.** (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3)).

PURPOSE AND OBJECTIVES

Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

2. SPECIFIC AIMS

Combustible cigarette (CC) smoking is the most preventable cause of death in the United States[1] but the yearly rate of smoking cessation remains low (7.4%).[2] The recent increase in electronic cigarette (EC) use[3] has been most pronounced among young adults[4-6] and those who also smoke CCs (i.e., dual users).[7-9] Dual use among young people has raised concerns that ECs may increase nicotine dependence[10,11] and thereby prevent CC cessation.[6,12-16] Conversely there is evidence that ECs can be used to promote CC cessation.[17-21] There is a particular need for effective smoking cessation treatments for young adult dual users given the high prevalence of EC use[4,6] and the strong evidence that cessation early in life can completely avoid tobacco-related mortality.[22-26] Though more likely to try to quit,[27] young adults are less likely to use treatment[28-31] and less likely to succeed at quitting CCs than older adults.[27,32] Though text-message based interventions appear effective for young adults[33,34] and some treatments for older adults appear effective for young adults,[35] there is a paucity of research on pharmacological treatments for young adults.[36] For example, though nicotine replacement therapy

(NRT) is a common, non-prescription, first-line cessation treatment,[37,38] there have been no randomized trials on NRT for smoking cessation in young adults.[36,39] Furthermore, despite the rapidly increasing prevalence of dual use,[7-9] there are no empirically based smoking cessation treatments for dual CC and EC users. Thus, we propose a 2x2 factorial randomized controlled trial (RCT) of nicotine replacement therapy (NRT) for smoking cessation[37] among young adults with dual CC and EC use.

Given the high rate of dual use of CCs and ECs in young adults, effective smoking cessation treatment should be adapted to address dual users' additional source of nicotine: ECs. However, it is unclear whether continued EC use aids or impedes CC cessation among dual users.[9,21,40,41] Thus, it remains unclear whether dual users who want to quit smoking should attempt to quit CCs and ECs simultaneously or quit CCs only and, at least temporarily continue ECs until ready to quit those as well. This RCT will test treatment for cessation when participants are assigned to continue versus discontinue EC use to identify the most effective approach to achieve CC cessation among young adult dual users.

The overarching aim of this proposed RCT is to test NRT with text message support for two smoking cessation approaches among young adult dual users of CCs and ECs. We will use a 2x2 factorial design (Table 1) to randomize 390 participants to receive A) NRT plus text messages to quit CCs only, B) NRT plus text messages to quit CCs and ECs simultaneously, C) text messages alone to quit CCs only, or D) text messages alone to quit CCs and ECs simultaneously. Our primary outcome will be CO-verified 7-day point-prevalence abstinence at the end of treatment (i.e., 3 months after randomization). We will recruit participants using national advertising strategies that have been effective in consenting >10 young adult smokers per week in one of our ongoing COBRE-funded trials. All treatment will be provided remotely in order to increase treatment access and comply with COVID-19 restrictions. The proposed RCT addresses the following specific aims:

Aim 1: To test whether NRT is an effective smoking cessation treatment for young adult dual users of ECs and CCs.
Hypothesis 1: Participants who receive NRT plus text messages of either type will be more likely to achieve 7-day point prevalence abstinence from CCs at the 3-month follow up (i.e. the end of treatment) than those who receive text message support only.

Aim 2: To identify the influence of continued EC use versus stopping ECs on achieving CC abstinence among young adult dual users of ECs and CCs.
Hypothesis 2: Participants who receive text messages to quit CCs and continue ECs will achieve greater 7-day point prevalence abstinence from CCs at the 3-month follow up than those who receive treatment to quit both CCs and ECs simultaneously.

Aim 3: To identify whether continued EC use results in more acute adverse events than stopping ECs among young adult dual users who are quitting CCs.
Hypothesis 3: There will be no significant differences in serious adverse events between participants assigned to quit versus continue ECs during the 3-month treatment period.

Consistent with the Vermont Center on Behavior and Health's mission, the proposed RCT tests a treatment tailored to a vulnerable population at higher risk for inability to stop smoking and thus a higher risk of chronic disease and premature mortality due to CC smoking. Further this RCT builds on ongoing[27,36,42] COBRE-funded research on smoking cessation treatment for young adults as well as our prior[43-49] and ongoing research on tobacco treatment. Importantly, findings from this RCT will be used to provide preliminary data for an R01 research proposal to further develop and test the effectiveness of a smoking cessation intervention for young adult dual users of CCs and ECs.

3. RESEARCH STRATEGY

3.A. SIGNIFICANCE

3.A.1 Need for smoking cessation treatment for young adults

Young adulthood (i.e., ages 18-29) is a pivotal developmental period when there is high risk of becoming a long-term cigarette smoker[26,50,51] and thus a crucial need for effective smoking cessation treatment.[52] Above all, cessation in young adulthood can prevent long-term morbidity and mortality from cigarettes.[22-26] Though young adults are more likely to attempt to quit[27,53,54] they are less likely to succeed[27] than older adults. Further, young adults are less likely to use evidence-based treatments when trying to quit[28-31] which may reflect the paucity of acceptable and effective smoking cessation treatments for this age demographic.[36,39] Thus, there is a need for research to tailor effective smoking cessation treatments for young adults.

As outlined by NCI's Tobacco Control Research Priorities, innovative treatments that adapt to young adults' changing demographics and dual use are needed.[52] In line with this report, our recent systematic review identified the need for research on pharmacological smoking cessation treatment for young adults.[36] Nicotine replacement therapy (NRT) is effective for smoking cessation[37] and internationally recognized as a first-line treatment for adults who want to quit smoking cigarettes.[38,55-58] Use of NRT increases the success of smoking cessation by approximately 50% to 60% in adults.[37] Though self-selected use of NRT is associated with increased smoking cessation among young adults,[59] we know of no RCTs of NRT using a sample of young adults.[36,39] Research on NRT specific to young adult smokers is particularly important given that they are more likely to use additional tobacco products[60] and less likely to use tobacco daily than older adults,[61] which could influence the effectiveness of NRT (e.g.[62]). Further, the relative ease of obtaining NRT in the United States (i.e., NRT is sold over-the-counter) may make it more appealing than other prescription medications given that young adults are less likely than older adults to engage in formal treatment.[28-31] Thus, there is a need for research on NRT for smoking cessation among young adults. This need will be directly addressed by Aim 1 of the proposed RCT.

Though NRT is sometimes delivered by healthcare providers in conjunction with counseling,[63] text-message based

support may be more acceptable to young adults.[36] Today's young adults are digital natives[64] and thus accustomed to integrated technology for communication and daily activities. For example, 99% of US young adults own a cellphone and 96% own a smartphone.[65] Dependence on a cellphone for internet access is most common among young adults in the US, nearly 100% use text messaging,[66] and almost half (48%) report they are "almost constantly" online.[67] Given the ubiquity of cellphone use in young adults, mobile phone-based interventions are a promising means of engaging and treating young adult smokers.[36] Meta-analyses indicate text message-based smoking cessation interventions are effective[68,69] and increase the effectiveness of other cessation treatments.[69,70] Further, mobile phone-based interventions appear to increase engagement in treatment and adherence to nicotine replacement therapy.[71,72] Among young adults, mobile phones appear to be an acceptable platform for smoking cessation interventions.[34,73] Two prior trials of text message-based smoking cessation interventions found a doubling in the odds of 7-day point prevalence abstinence.[33,34,36] Our group has been engaged in COBRE funded research to develop a remote, text-message based smoking cessation intervention for young adults and our RCT is ongoing. The proposed RCT will use text message support for all conditions and build on our prior research by comparing text-messages to quit CCs only versus text-messages to quit CCs and ECs simultaneously among young adult dual users. This comparison is addressed within Aim 2 of the proposed RCT.

3.A.2 Need for smoking cessation treatment for dual users

Nearly 70% of EC users also smoke CCs[7] and this dual use is now the most common polytobacco use combination in the US.[60] However there are no empirically validated CC cessation treatments for dual users. This is particularly concerning given that most dual users want to quit smoking[74] and most (85%) start using ECs to help cut down or quit CCs.[75,76] However, once initiated, dual CC and EC use appears most likely to result in sustained CC smoking among young adults.[77] Thus there is a particular need for CC smoking cessation treatment for young adult dual CC and EC users. One recent exploratory study found that dual users' self-selected use of varenicline predicted cessation of both CCs and ECs.[78] We know of no published empirically validated smoking cessation treatments for dual CC and EC users.

Dual users differ from exclusive CC smokers and thus research is needed to adapt CC smoking cessation treatments for dual users. For example, one international study found that, in comparison to exclusive CC smokers, dual users appear more likely to be young adults, to be female, to have tried to quit or have plans to quit CCs, and to have a more positive overall opinion of smoking.[79] Further, dual users are less restricted in their nicotine use; they often have the option to continue inhaling nicotine in areas where CCs are prohibited or socially unacceptable.[76,80] Importantly, though evidence is mixed on how dual use affects cessation[40] there is some evidence that nicotine use and overall dependence is greater among dual users than exclusive CC smokers.[11,14,15,79,81] Thus, dual users may respond to treatment differently than exclusive CC smokers given the apparent differences between the two groups.

One important decision for dual users is whether CC cessation should include temporary EC continuation or simultaneous CC and EC cessation. Complete CC cessation is necessary for harm reduction to occur.[82] However the evidence is mixed on whether EC use prevents or promotes CC cessation.[40] Using ECs to try to quit CCs is common,[75] and can serve as an aid to CC cessation,[17,18,21,79,83,84] especially when used daily.[85] On the other hand, most dual users use ECs intermittently[79] which does not appear to aid CC cessation. In contrast, there is some evidence that dual CC smoking with intermittent EC use is associated with increased smoking and nicotine dependence,[11,14,15,81] and decreased CC cessation in comparison to those who smoke CCs only.[15,41] For example, in a US nationally representative sample, self-selected ongoing EC use was associated with CC relapse among former smokers.[32,86] Thus, there is a need for randomized controlled trials of the effectiveness of CC cessation treatment when quitting CCs and continuing ECs versus quitting CCs and ECs simultaneously. This need will be directly addressed by Aim 2 of the proposed RCT.

Similarly, it remains unclear whether temporarily continuing ECs results in more acute adverse events than quitting ECs among young adult dual users who are quitting CCs. In the prior RCT of ECs versus NRT for smoking cessation among adult exclusive CC smokers, there were no differences between conditions in terms of serious adverse events, and none were judged as related to study participation.[17] Throat or mouth irritation was reported more frequently and nausea less frequently in the EC compared to the NRT condition. Perhaps most important, respiratory symptoms declined more for the EC than the NRT condition.[17] Nonetheless, we will assess adverse events weekly throughout the treatment period (weeks 1 through 12). We will form a data safety monitoring review board (DSMB) to monitor study procedures and review serious adverse events in order to determine whether it is necessary to stop the study early. Aim 3 of the proposed RCT will assess whether continued EC use results in more serious adverse events than discontinuing EC use among young adult dual users who are quitting CCs.

Another important treatment consideration is whether young adult dual users should switch from ECs to NRT or continue ECs without NRT when quitting CCs. A recent RCT of NRT versus ECs for smoking cessation among exclusive CC smoking adults found ECs were more effective than NRT at achieving long term abstinence from CCs.[17] However, we know of no experimental research that has tested NRT versus ECs among young adults or dual users. By definition, dual users use ECs and have either failed to quit CCs or chosen to continue CC smoking. Thus, ECs may be less effective for smoking cessation among people with ongoing dual use than for the exclusive CC smokers who were introduced to ECs in the prior RCT.[17] On the other hand, dual using young adults are unlikely to engage in treatment[28-31] but, as dual users, are already engaged in EC use. Thus, the apparent acceptability of ECs may make ECs more effective than NRT for smoking cessation among young adult dual users. In addition to our primary aims, our proposed 2x2 factorial RCT will provide an experimental test of whether switching to NRT versus continuing ECs is more effective for smoking cessation among young adult dual users. For example, in one condition, participants will receive text message support to discontinue ECs and begin

NRT as they quit CCs. In another condition, participants will receive text message support to continue ECs without NRT as they quit CCs. A comparison between these conditions will directly inform smoking cessation treatment for young adult dual users.

References. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.

1. Jacobs Eric J, Newton Christina C, Carter Brian D, et al. What proportion of cancer deaths in the contemporary United States is attributable to cigarette smoking? *Ann. Epidemiol.* 2015;25(3):179-182. e171.
2. Babb S., Malarcher A., Schauer G., Asman K., Jamal A. Quitting Smoking Among Adults - United States, 2000-2015. *MMWR Morb. Mortal. Wkly. Rep.* 2017;65(52):1457-1464.
3. Levy D. T., Yuan Z., Li Y., Mays D., Sanchez-Romero L. M. An Examination of the Variation in Estimates of E-Cigarette Prevalence among U.S. Adults. *Int. J. Environ. Res. Public Health.* 2019;16(17).
4. Dai H., Leventhal A. M. Prevalence of e-Cigarette Use Among Adults in the United States, 2014-2018. *JAMA.* 2019;322(18):1824-1827.
5. Johnson A. L., Collins L. K., Villanti A. C., Pearson J. L., Niaura R. S. Patterns of Nicotine and Tobacco Product Use in Youth and Young Adults in the United States, 2011-2015. *Nicotine Tob Res.* 2018;20(suppl_1):S48-s54.
6. Services U.S. Department of Health and Human. E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. In: U.S. Department of Health and Human Services CfDCaP, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, ed. Atlanta, GA2016.
7. Coleman B. N., Rostron B., Johnson S. E., et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Tob. Control.* 2017;26(e2):e117-e126.
8. Baig S. A., Giovenco D. P. Behavioral heterogeneity among cigarette and e-cigarette dual-users and associations with future tobacco use: Findings from the Population Assessment of Tobacco and Health Study. *Addict. Behav.* 2020;104:106263.
9. Glasser A. M., Collins L., Pearson J. L., et al. Overview of Electronic Nicotine Delivery Systems: A Systematic Review. *Am. J. Prev. Med.* 2017;52(2):e33-e66.
10. Azagba S., Shan L., Latham K. Adolescent Dual Use Classification and Its Association With Nicotine Dependence and Quit Intentions. *J. Adolesc. Health.* 2019;65(2):195-201.
11. Martínez Ú, Martínez-Loredo V., Simmons V. N., et al. How Does Smoking and Nicotine Dependence Change After Onset of Vaping? A Retrospective Analysis of Dual Users. *Nicotine Tob Res.* 2020;22(5):764-770.
12. Gmel G., Baggio S., Mohler-Kuo M., Daeppen J. B., Studer J. E-cigarette use in young Swiss men: is vaping an effective way of reducing or quitting smoking? *Swiss Med. Wkly.* 2016;146:w14271.
13. Prevention Centers for Disease Control and. Quick Facts on the Risks of E-cigarettes for Kids, Teens, and Young Adults. 2020; https://www.cdc.gov/tobacco/basic_information/e-cigarettes/Quick-Facts-on-the-Risks-of-E-cigarettes-for-Kids-Teens-and-Young-Adults.html. Accessed May, 7, 2020.
14. Glantz S. A., Bareham D. W. E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. *Annu. Rev. Public Health.* 2018;39:215-235.
15. Al-Delaimy W. K., Myers M. G., Leas E. C., Strong D. R., Hofstetter C. R. E-cigarette use in the past and quitting behavior in the future: a population-based study. *Am. J. Public Health.* 2015;105(6):1213-1219.
16. Doran N., Brikmanis K., Petersen A., et al. Does e-cigarette use predict cigarette escalation? A longitudinal study of young adult non-daily smokers. *Prev. Med.* 2017;100:279-284.
17. Hajek P., Phillips-Waller A., Przulj D., et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N. Engl. J. Med.* 2019;380(7):629-637.
18. Piper M. E., Baker T. B., Benowitz N. L., Jorenby D. E. Changes in Use Patterns Over 1 Year Among Smokers and Dual Users of Combustible and Electronic Cigarettes. *Nicotine Tob Res.* 2020;22(5):672-680.
19. Zhu Shu-Hong, Zhuang Yue-Lin, Wong Shiushing, Cummins Sharon E, Tedeschi Gary J. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ.* 2017;358:j3262.
20. Farsalinos K. E., Niaura R. E-cigarettes and Smoking Cessation in the United States According to Frequency of E-cigarette Use and Quitting Duration: Analysis of the 2016 and 2017 National Health Interview Surveys. *Nicotine Tob Res.* 2020;22(5):655-662.
21. Hartmann-Boyce J., Begh R., Aveyard P. Electronic cigarettes for smoking cessation. *BMJ.* 2018;360:j5543.
22. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *Br. Med. J.* 2004;328:1519-1527.
23. Doll R., Peto R., Boreham J., Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br. J. Cancer.* 2005;92(3):426-429.
24. Jha P., Ramasundarahettige C., Landsman V., et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N. Engl. J. Med.* 2013;368(4):341-350.
25. Pirie K., Peto R., Reeves G. K., Green J., Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet.* 2013;381(9861):133-141.
26. Sussman S., Arnett J. J. Emerging Adulthood: Developmental Period Facilitative of the Addictions. *Eval. Health Prof.* 2014;37(2):147-155.
27. West J. C., Villanti A. C., Graham A. L., Mays D., Mermelstein R. J., Higgins S. T. Tobacco Use and Cessation Behaviors in Young Adults: 2016 National Health Interview Survey. *Am. J. Public Health.* 2019;109(2):296-299.

28. Lantz P. M. Smoking on the rise among young adults: implications for research and policy. *Tob Control.* 2003;12 Suppl 1:i60-70.
29. Centers for Disease Control and Prevention (CDC). Use of cessation methods among smokers aged 16-24 years--United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2006;55(50):1351-1354.
30. Curry S. J., Sporer A. K., Pugach O., Campbell R. T., Emery S. Use of tobacco cessation treatments among young adult smokers: 2005 National Health Interview Survey. *Am J Public Health.* 2007;97(8):1464-1469.
31. Hughes J. R., Cohen B., Callas P. W. Treatment seeking for smoking cessation among young adults. *J Subst Abuse Treat.* 2009;37(2):211-213.
32. Dai H., Leventhal A. M. Association of electronic cigarette vaping and subsequent smoking relapse among former smokers. *Drug Alcohol Depend.* 2019;199:10-17.
33. Ybarra M. L., Holtrop J. S., Prescott T. L., Rahbar M. H., Strong D. Pilot RCT results of stop my smoking USA: a text messaging-based smoking cessation program for young adults. *Nicotine Tob Res.* 2013;15(8):1388-1399.
34. Buller D. B., Borland R., Bettinghaus E. P., Shane J. H., Zimmerman D. E. Randomized trial of a smartphone mobile application compared to text messaging to support smoking cessation. *Telemed J. E Health.* 2014;20(3):206-214.
35. Suls Jerry M, Luger Tana M, Curry Susan J, Mermelstein Robin J, Sporer Amy K, An Larry C. Efficacy of smoking-cessation interventions for young adults: a meta-analysis. *Am. J. Prev. Med.* 2012;42(6):655-662.
36. Villanti A. C. , West J. C., Klemperer E. M., et al. Smoking cessation interventions for U.S. young adults: New evidence from a systematic review. *Am. J. Prev. Med.* In press.
37. Hartmann-Boyce J., Chepkin S. C., Ye W., Bullen C., Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst. Rev.* 2018(5).
38. Fiore M, Jaen C, Baker T, et al. *Treating Tobacco Use and Dependence: Clinical Practice Guideline.* Washington, DC: US Public Health and Human Services; 2008.
39. Fanshawe T. R., Halliwell W., Lindson N., Aveyard P., Livingstone-Banks J., Hartmann-Boyce J. Tobacco cessation interventions for young people. *Cochrane Database Syst. Rev.* 2017;11:Cd003289.
40. El Dib Regina, Suzumura Erica A, Akl Elie A, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. *BMJ open.* 2017;7(2):e012680.
41. Kalkhoran S., Glantz S. A. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med.* 2016;4(2):116-128.
42. Klemperer E. M., West J. C., Peasley-Miklus C., et al. Prevalence and reasons for reducing or quitting vaping in young adults: Findings from the PACE Vermont Study. Society for Research on Nicotine and Tobacco; 2020; New Orleans, LA.
43. Klemperer E. M., Hughes J. R. Does the Magnitude of Reduction in Cigarettes Per Day Predict Smoking Cessation? A Qualitative Review. *Nicotine Tob Res.* 2015:88-92.
44. Klemperer Elias M, Hughes John R, Callas Peter W, Benner Joy A, Morley Nicholas E. Effectiveness of switching to very low nicotine content cigarettes plus nicotine patch versus reducing daily cigarette consumption plus nicotine patch to decrease dependence: An exploratory randomized trial. *Addiction.* 2019.
45. Klemperer E. M., Hughes J. R., Callas P. W., Solomon L. J. A Mediation Analysis of Motivational, Reduction, and Usual Care Interventions for Smokers Who Are Not Ready to Quit. *Nicotine Tob Res.* 2017.
46. Klemperer E. M., Hughes J. R., Callas P. W., Solomon L. J. Working alliance and empathy as mediators of brief telephone counseling for cigarette smokers who are not ready to quit. *Psychol. Addict. Behav.* 2017;31(1):130-135.
47. Klemperer E. M., Hughes J. R., Naud S. Reduction in Cigarettes per Day Prospectively Predicts Making a Quit Attempt: A Fine-Grained Secondary Analysis of a Natural History Study. *Nicotine Tob Res.* 2019;21(5):648-654.
48. Klemperer E. M., Hughes J. R., Solomon L. J., Callas P. W., Fingar J. R. Motivational, reduction, and usual care interventions for smokers who are not ready to quit: A randomized controlled trial. *Addiction.* 2016:n/a-n/a.
49. Klemperer Elias M, Hughes John R, Callas Peter W. Increasing Quit Attempts by Transitioning to Very Low Nicotine Content Cigarettes Versus Reducing Number of Cigarettes Per Day: A Secondary Analysis of an Exploratory Randomized Trial. *Nicotine & Tobacco Research.* 2019;21(Supplement_1):S81-S87.
50. Arnett J. J. Emerging adulthood. A theory of development from the late teens through the twenties. *Am Psychol.* 2000;55(5):469-480.
51. Arnett J. J. Conceptions of the Transition to Adulthood: Perspectives From Adolescence Through Midlife. *Journal of Adult Development.* 2001;8(2):133-143.
52. Mermelstein R, Fiore MC, Bernstein SL, et al. Tobacco control research priorities for the next decade: working group recommendations for 2016-2025. *Rockville, MD: National Cancer Institute.* 2016.
53. Curry L, Sporer A, Pugach O, Campbell R, Emery S. Use of tobacco cessation treatments among young adult smokers: 2005 National Health Interview Survey. *Am. J. Public Health.* 2007;97:1464-1469.
54. Messer K, Trinidad D, Al-Delaimy WK, Pierce J. Smoking cessation rates in the United States: A comparison of young adult and older smokers. *Am. J. Public Health.* 2008;98:317-322.
55. LeFoll B., Melihan-Cheinin P., Rostoker G., Lagrue G., AFSSAPS Working Group of. Smoking cessation guidelines: Evidence-based recommendations of the French Health Products Safety Agency. *Eur. Psychiatry.* 2005;20(5-6):431-441.
56. Excellence National Institute for Health and Clinical. Public Health Guidelines [PH10] Stop Smoking Services. 2008.

57. McRobbie Hayden, Bullen Chris, Glover Marewa, Whittaker Robyn, Wallace-Bell Mark, Fraser Trish. New Zealand smoking cessation guidelines. *NZ Med J.* 2008;121(1276):57-70.
58. Zwar N, Richmond R, Borland R, et al. Supporting smoking cessation: a guide for health professionals. *Melbourne: The Royal Australian College of General Practitioners.* 2011.
59. Buller D. B., Halperin A., Severson H. H., et al. Effect of nicotine replacement therapy on quitting by young adults in a trial comparing cessation services. *J. Public Health Manag. Pract.* 2014;20(2):E7-e15.
60. Sung H. Y., Wang Y., Yao T., Lightwood J., Max W. Polytobacco Use and Nicotine Dependence Symptoms Among US Adults, 2012-2014. *Nicotine Tob Res.* 2018;20(suppl_1):S88-s98.
61. Reyes-Guzman C. M., Pfeiffer R. M., Lubin J., et al. Determinants of Light and Intermittent Smoking in the United States: Results from Three Pooled National Health Surveys. *Cancer Epidemiol. Biomarkers Prev.* 2017;26(2):228-239.
62. Shiffman S., Scholl S. M., Mao J., et al. Using Nicotine Gum to Assist Nondaily Smokers in Quitting: A Randomized Clinical Trial. *Nicotine Tob Res.* 2020;22(3):390-397.
63. Fiore MC. A clinical practice Guideline for treating tobacco use and dependence: 2008 update. *Am. J. Prev. Med.* 2008;35(2):158-176.
64. Prensky Marc. *Don't Bother Me, Mom-I'm Learning!* St. Paul, MN: Paragon House; 2006.
65. Center Pew Research. Who owns cellphones and smartphones. 2019; https://www.pewresearch.org/internet/fact-sheet/mobile/#who-owns-cellphones-and-smartphones. Accessed May 13, 2020.
66. Smith Aaron. U.S. Smartphone Use in 2015. 2015; http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/. Accessed May 11, 2015.
67. Perrin A., Kumar M. About three-in-ten U.S. adults say they are 'almost constantly' online. 2019; https://www.pewresearch.org/fact-tank/2019/07/25/americans-going-online-almost-constantly/. Accessed May 13, 2020.
68. Ybarra M. L., Jiang Y., Free C., Abroms L. C., Whittaker R. Participant-level meta-analysis of mobile phone-based interventions for smoking cessation across different countries. *Prev. Med.* 2016;89:90-97.
69. Whittaker R., McRobbie H., Bullen C., Rodgers A., Gu Y., Dobson R. Mobile phone text messaging and app-based interventions for smoking cessation. *Cochrane Database Syst. Rev.* 2019(10).
70. Do Huyen Phuc, Tran Bach Xuan, Le Pham Quyen, et al. Which eHealth interventions are most effective for smoking cessation? A systematic review. *Patient preference and adherence.* 2018;12:2065.
71. Graham A. L., Papandonatos G. D., Cha S., Erar B., Amato M. S. Improving Adherence to Smoking Cessation Treatment: Smoking Outcomes in a Web-based Randomized Trial. *Ann. Behav. Med.* 2018;52(4):331-341.
72. Graham A. L., Papandonatos G. D., Cha S., et al. Improving Adherence to Smoking Cessation Treatment: Intervention Effects in a Web-Based Randomized Trial. *Nicotine Tob Res.* 2017;19(3):324-332.
73. Gulliver A., Farrer L., Chan J. K., et al. Technology-based interventions for tobacco and other drug use in university and college students: a systematic review and meta-analysis. *Addict. Sci. Clin. Pract.* 2015;10:5.
74. Watkins S. L., Thrul J., Max W., Ling P. M. Cold Turkey and Hot Vapes? A National Study of Young Adult Cigarette Cessation Strategies. *Nicotine Tob Res.* 2020;22(5):638-646.
75. Yong H. H., Borland R., Cummings K. M., et al. Reasons for regular vaping and for its discontinuation among smokers and recent ex-smokers: findings from the 2016 ITC Four Country Smoking and Vaping Survey. *Addiction.* 2019;114 Suppl 1:35-48.
76. Patel D., Davis K. C., Cox S., et al. Reasons for current E-cigarette use among U.S. adults. *Prev. Med.* 2016;93:14-20.
77. Niaura R., Rich I., Johnson A. L., et al. Young Adult Tobacco and E-cigarette Use Transitions: Examining Stability Using Multistate Modeling. *Nicotine Tob Res.* 2020;22(5):647-654.
78. Hajek Peter, Peerbux Sarrah, Phillips-Waller Anna, Smith Charlotte, Pittaccio Kate, Przulj Dunja. Are 'dual users' who smoke and use e-cigarettes interested in using varenicline to stop smoking altogether, and can they benefit from it? A cohort study of UK vapers. *BMJ Open.* 2019;9(3):e026642.
79. Borland R., Murray K., Gravely S., et al. A new classification system for describing concurrent use of nicotine vaping products alongside cigarettes (so-called 'dual use'): findings from the ITC-4 Country Smoking and Vaping wave 1 Survey. *Addiction.* 2019;114 Suppl 1(Suppl 1):24-34.
80. Simonavicius E., McNeill A., Arnott D., Brose L. S. What factors are associated with current smokers using or stopping e-cigarette use? *Drug Alcohol Depend.* 2017;173:139-143.
81. Ruther T., Wissen F., Linhardt A., Aichert D. S., Pogarell O., de Vries H. Electronic Cigarettes-Attitudes and Use in Germany. *Nicotine Tob Res.* 2016;18(5):660-669.
82. Warner Kenneth E. How to Think—Not Feel—about Tobacco Harm Reduction. *Nicotine & Tobacco Research.* 2018;21(10):1299-1309.
83. Brose L. S., Hitchman S. C., Brown J., West R., McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction.* 2015;110(7):1160-1168.
84. Biener L., Hargraves J. L. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res.* 2015;17(2):127-133.
85. Giovenco D. P., Delnevo C. D. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addict. Behav.* 2018;76:129-134.

86. McMillen R., Klein J. D., Wilson K., Winickoff J. P., Tanski S. E-Cigarette Use and Future Cigarette Initiation Among Never Smokers and Relapse Among Former Smokers in the PATH Study. *Public Health Rep.* 2019;134(5):528-536.
89. Caponnetto P., Maglia M., Polosa R. Efficacy of smoking cessation with varenicline plus counselling for e-cigarettes users (VAREVAPE): A protocol for a randomized controlled trial. *Contemp Clin Trials Commun.* 2019;15:100412.
90. Meltzer L. R., Simmons V. N., Sutton S. K., et al. A randomized controlled trial of a smoking cessation self-help intervention for dual users of tobacco cigarettes and E-cigarettes: Intervention development and research design. *Contemp. Clin. Trials.* 2017;60:56-62.
91. Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *J. Consult. Clin. Psychol.* 2004;72:1144-1156.
92. Joseph A.M., Willenbring M.L., Nugent S.M., Nelson D.B. A randomized trial of concurrent versus delayed smoking intervention for patients in alcohol dependence treatment. *Journal of Studies of Alcohol.* 2004;65(6):681.
93. Cooney Ned L., Litt Mark D., Sevarino Kevin A., et al. Concurrent alcohol and tobacco treatment: Effect on daily process measures of alcohol relapse risk. *J. Consult. Clin. Psychol.* 2015;83(2):346-358.
94. Graham A. L., Amato M. S. Twelve Million Smokers Look Online for Smoking Cessation Help Annually: Health Information National Trends Survey Data, 2005-2017. *Nicotine Tob Res.* 2019;21(2):249-252.
95. Klemperer E. M., Hughes J. R., Naud S. Study characteristics influence the efficacy of substance abuse treatments: A meta-analysis of medications for smoking cessation. *Nicotine Tob Res.* 2018.
96. Lindson N., Klemperer E., Hong B., Ordonez-Mena J. M., Aveyard P. Smoking reduction interventions for smoking cessation. *Cochrane Database Syst. Rev.* 2019;9:Cd013183.
97. Klemperer E. M., Mermelstein R., Baker T. B., et al. Predictors of smoking cessation attempts and success following motivation-phase interventions among people initially unwilling to quit smoking. *Nicotine Tob Res.* 2020.
98. Nighbor T. D., Klemperer E. M., Hughes J. R., Reed E. N., Simone S., West J. C. Both reducing cigarettes per day and transitioning to very low nicotine content cigarettes decrease demand for usual-brand cigarettes. *Exp. Clin. Psychopharmacol.* In press.
99. Villanti A. C., Vallencourt C., West J. C., et al. Recruiting and retaining youth and young adults in online longitudinal research: Lessons from a randomized trial of participant compensation in the PACE Vermont Study. *J. Med. Internet Res.* In press.
100. Hughes J. R., Klemperer E. M., Peasley-Miklus C. Possible New Symptoms of Tobacco Withdrawal II: Anhedonia-A Systematic Review. *Nicotine Tob Res.* 2018.
101. Klemperer E. M., Hughes J. R., Peasley-Miklus C. E., et al. Possible New Symptoms of Tobacco Withdrawal III: Reduced Positive Affect-A Review and Meta-analysis. *Nicotine Tob Res.* 2020.
102. Klemperer Elias M, Fagerstrom Karl O, Hughes John R. Abrupt versus gradual smoking cessation with pre-cessation nicotine replacement therapy for cigarette smokers motivated to quit. *Annals of Translational Medicine.* 2016;4(19).
103. Klemperer E. M., Hughes J. R., Naud S. Distal Measurements Can Produce False Negative Results: A Prospective Secondary Analysis of a Natural History Study. *Nicotine Tob Res.* 2019;21(12):1727-1730.
104. Hughes J.R., Hatsukami D.K. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatr.* 1986;43:289-294.
105. Hughes J.R, Keely J., Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction.* 2004;99:29-38.
106. Hughes J.R., Keely J., Niaura R., Ossip-Klein D., Richmond R., Swan G. Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine & Tobacco Research.* 2003;5:13-25.
107. Hughes J.R., Gust S.W., Keenan R.M., Fenwick J.W., Healy M.L. Nicotine vs placebo gum in general practice. *JAMA.* 1989;261:1300-1305.
108. Hughes JR. An updated algorithm for choosing among smoking cessation treatments. *J. Subst. Abuse Treat.* 2013;45:215-221.
109. Rath Jessica M, Villanti Andrea C, Abrams David B, Vallone Donna M. Patterns of tobacco use and dual use in US young adults: the missing link between youth prevention and adult cessation. *J. Environ. Public Health.* 2012;2012.
110. Villanti Andrea C, Richardson Amanda, Vallone Donna M, Rath Jessica M. Flavored tobacco product use among US young adults. *Am. J. Prev. Med.* 2013;44(4):388-391.
111. Villanti AC, McKay HS, Abrams DB, Holtgrave DR, Bowie JV. Smoking-cessation interventions for U.S. young adults. *Am. J. Prev. Med.* 2010;39:564-574.
112. Mermelstein R.J., Colby S.M., Patten C., et al. Methodological issues in measuring treatment outcome in adolescent smoking cessation studies. *Nicotine & Tobacco Research.* 2002;4:395-403.
113. Curry S. J., Emery S., Sporer A. K., et al. A national survey of tobacco cessation programs for youths. *Am. J. Public Health.* 2007;97(1):171-177.
114. Hedeker D., Demirtas H., Mermelstein R. J. A mixed ordinal location scale model for analysis of Ecological Momentary Assessment (EMA) data. *Stat Interface.* 2009;2(4):391-401.
115. Hedeker D., Mermelstein R. J., Berbaum M. L., Campbell R. T. Modeling mood variation associated with smoking: an application of a heterogeneous mixed-effects model for analysis of ecological momentary assessment (EMA) data. *Addiction.* 2009;104(2):297-307.
116. Carpenter Kelly M., Watson Jennifer M., Raffety Brian, Chabal Charles. Teaching brief interventions for smoking cessations via an interactive computer-based tutorial. *J. Health Psychol.* 2003;8(1):149-160.

117. Carpenter M. NRT sampling: A nationwide randomized clinical trial for cessation induction among unmotivated smokers. 2/16/11 AD presented at SRNT, 2011, Toronto, Canada, 2011.
118. Carpenter MJ, Alberg AJ, Gray KM, Saladin ME, Hughes JR. Cessation induction for unmotivated smokers: A randomized clinical trial of NRT sampling.
119. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ. Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: A randomized clinical trial. *Arch. Intern. Med.* 2011;171:1901-1907.
120. Carpenter MJ, Jardin BF, Burris JL, et al. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: A review of the literature. *Drugs.* 2013;73:407-426.
121. Carpenter Matthew J, Wahlquist Amy E, Dahne Jennifer, et al. Nicotine replacement therapy sampling for smoking cessation within primary care: Results from a pragmatic cluster randomized clinical trial. *Addiction.* 2020.
122. Shiffman S., Brockwell S.E., Pillitteri J.L., Gitchell J.G. Use of smoking-cessation treatments in the United States. *Am. J. Prev. Med.* 2008;34:102-111.
123. !!! INVALID CITATION !!! 102-138.
124. Villanti A. C., Johnson A. L., Rath J. M., et al. Identifying "social smoking" U.S. young adults using an empirically-driven approach. *Addict. Behav.* 2017;70:83-89.
125. Boudreaux E. D., Sullivan A., Abar B., Bernstein S. L., Ginde A. A., Camargo C. A., Jr. Motivation rulers for smoking cessation: a prospective observational examination of construct and predictive validity. *Addict. Sci. Clin. Pract.* 2012;7(1):8.
126. Piper M. E., McCarthy D. E., Baker T. B. Assessing tobacco dependence: a guide to measure evaluation and selection. *Nicotine Tob Res.* 2006;8(3):339-351.
127. Piper M. E., Baker T. B., Benowitz N. L., Smith S. S., Jorenby D. E. E-cigarette Dependence Measures in Dual Users: Reliability and Relations With Dependence Criteria and E-cigarette Cessation. *Nicotine Tob Res.* 2020;22(5):756-763.
128. Zvorsky I., Nighbor T. D., Kurti A. N., et al. Sensitivity of hypothetical purchase task indices when studying substance use: A systematic literature review. *Prev. Med.* 2019;128:105789.
129. Cox L. S., Tiffany S. T., Christen A. G. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3(1):7-16.
130. Velicer W. F., Diclemente C. C., Rossi J. S., Prochaska J. O. Relapse situations and self-efficacy: an integrative model. *Addict. Behav.* 1990;15(3):271-283.
131. Hughes J. R. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res.* 2007;9(3):315-327.
132. Fagerstrom K-O. Time to first cigarette; the best single indicator of tobacco dependence? *Monaldi Arch. Chest Dis.* 2003;59:95-98.
133. Hughes J. R., Naud S., Fingar J. R., Callas P. W., Solomon L. J. Do environmental cues prompt attempts to stop smoking? A prospective natural history study. *Drug Alcohol Depend.* 2015;154:146-151.
134. Benowitz Neal L, Bernert John T, Foulds Jonathan, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. *Nicotine & Tobacco Research.* 2019.
135. McNeill Ann, Brose Leonie S, Calder Robert, Bauld Linda, Robson Debbie. Evidence review of e-cigarettes and heated tobacco products 2018. *A report commissioned by Public Health England. London: Public Health England.* 2018;6.
136. National Academies of Sciences Engineering, Medicine. *Public health consequences of e-cigarettes.* National Academies Press; 2018.
137. Farsalinos K., Cibella F., Caponnetto P., et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern. Emerg. Med.* 2016;11(1):85-94.
138. Polosa R., Morjaria J. B., Caponnetto P., et al. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir. Res.* 2016;17(1):166.
139. Shahab L., Goniewicz M. L., Blount B. C., et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. *Ann. Intern. Med.* 2017;166(6):390-400.
140. Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch. Gen. Psychiatry.* 2009;66:1253-1262.
141. Shiffman S., Ferguson S. G. Nicotine patch therapy prior to quitting smoking: a meta-analysis. *Addiction.* 2008;103(4):557-563.
142. Haustein K.O. Study 980-CHC-0013: A double-blind, randomized, placebo-controlled multicenter trial of a nicotine chewing gum in smoking reduction.: Pfizer Ltd; 2002.
143. Squiers L., Brown D., Parvanta S., et al. The SmokefreeTXT (SFTXT) Study: Web and Mobile Data Collection to Evaluate Smoking Cessation for Young Adults. *JMIR Res Protoc.* 2016;5(2):e134.
144. Stoyneva Iva, Coa Kisha, Pugatch Jillian, Sanders Amy, Schwarz Mary, Cole-Lewis Heather. SmokefreeTXT behaviour change technique analysis. *Journal of Smoking Cessation.* 2017;12(4):231-243.
145. Michie S., Hyder N., Walia A., West R. Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. *Addict. Behav.* 2011;36(4):315-319.
146. Augustson E., Cole-Lewis H., Sanders A., et al. Analysing user-reported data for enhancement of SmokefreeTXT: a national text message smoking cessation intervention. *Tob. Control.* 2017;26(6):683-689.

147. Baggett T. P., McGlave C., Kruse G. R., Yaqubi A., Chang Y., Rigotti N. A. SmokefreeTXT for Homeless Smokers: Pilot Randomized Controlled Trial. *JMIR Mhealth Uhealth.* 2019;7(6):e13162.
148. Coa K. I., Wiseman K. P., Higgins B., Augustson E. Associations Between Engagement and Outcomes in the SmokefreeTXT Program: A Growth Mixture Modeling Analysis. *Nicotine Tob Res.* 2019;21(5):663-669.
149. Hoeppner B. B., Hoeppner S. S., Schick M. R., et al. Using the text-messaging program SmokefreeTXT to support smoking cessation for nondaily smokers. *Subst. Use Misuse.* 2019;54(8):1260-1271.
150. McCarthy D. E., Adsit R. T., Zehner M. E., et al. Closed-loop electronic referral to SmokefreeTXT for smoking cessation support: a demonstration project in outpatient care. *Transl. Behav. Med.* 2019.
151. Hughes J. R., Naud S., Budney A. J., Fingar J. R., Callas P. W. Attempts to stop or reduce daily cannabis use: An intensive natural history study. *Psychol. Addict. Behav.* 2016;30(3):389-397.
152. Armitage P. Exclusions, losses to follow-up, and withdrawals in clinical trials. Shapiro, S. H. and Louis, TA (Eds.): Clinical trials. Marcel Dekker, NY and Basel; 1983.
153. Rubin D.B. *Multiple imputation for nonresponse in surveys.* New York: Wiley; 1987.
154. Shiffman S.; Gorsline, J.; Gorodetzky, C. W. Efficacy of over-the-counter nicotine patch. *Nicotine Tob Res.* 2002;4(4):477-483.

Objectives: Clearly state the primary and secondary objective(s) of the study.

The primary objectives of this study are:

Aim 1: To test whether NRT is an effective smoking cessation treatment for young adult dual users of ECs and CCs.
Aim 2: To identify the influence of continued EC use versus stopping ECs on achieving CC abstinence among young adult dual users of ECs and CCs.
Aim 3: To identify whether continued EC use results in more acute adverse events than stopping ECs among young adult dual users who are quitting CCs.

The secondary objectives of this study are to explore 1) the interaction between the treatment arms (NRT versus no NRT by continue EC versus quit EC) with CO-verified 7-day point-prevalence abstinence as the outcome, 2) the effect of EC continuation versus NRT on CC abstinence by comparing Group B (quit CCs and ECs with NRT) versus Group C (quit CCs and continue ECs without NRT) using logistic regression, and 3) a series of sensitivity analyses using 30-day abstinence at the 6-month follow up as the outcome and condition as a predictor of time to relapse after quit day. Additional secondary analyses will explore moderators and intervention effects on relevant smoking outcomes.

METHODS AND PROCEDURES

Study Design: Describe the research design, including a description of any new methodology and its advantage over existing methodologies.

3.C.3. Research Design

Using a 2x2 factorial design (Table 1), young adults who smoke CCs and use ECs will be randomly assigned to one of four conditions: A) NRT plus text messages to quit CCs only, B) NRT plus text messages to quit CCs and ECs simultaneously, C) text messages alone to quit CCs only, or D) text messages alone to quit CCs and ECs simultaneously. We will recruit, consent, and randomize 390 participants with the aim of retaining 312 (80%) by the end of treatment. Participants in each condition will complete a survey at baseline, weekly surveys throughout the 3-month treatment period, brief daily surveys for one week before and one week after the assigned quit date, an end of treatment survey, and a survey at a follow-up 6 months after treatment began (Figure 1). In addition, participants will be encouraged but not required to submit breath CO samples at baseline, all weekly surveys, the end of treatment, and the 6-month follow-up using the CoVita iCO personal smokerlyzer (https://www.covita.net/ico-overview/).

Table 1. 2x2 factorial design

		Text-messages to quit CCs only vs quit CCs & ECs	
		Quit CCs & continue ECs	*Quit CCs & quit ECs*
Nicotine replacement therapy (NRT)	*Yes*	A) NRT & text messages to quit CCs & continue ECs	B) NRT & text messages to quit CCs & quit ECs
	No	C) Text messages alone to quit CCs & continue ECs	D) Text messages alone to quit CCs & quit ECs

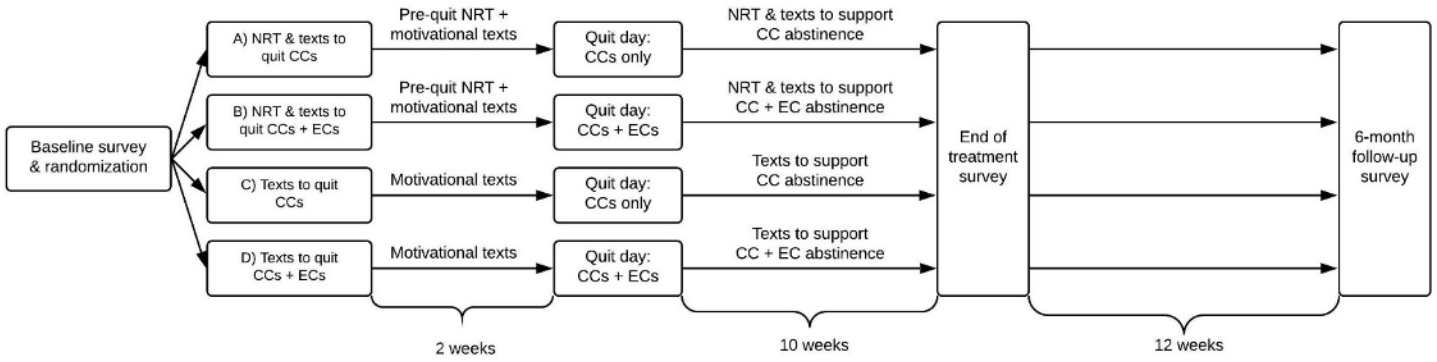

Figure 1. Timeline of study procedures. CC=Combustible cigarettes; EC=Electronic cigarette; NRT=Nicotine replacement therapy.

Procedures: Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc.

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Participants. Participants will be recruited using internet and social media recruitment strategies demonstrated to be effective in recruiting young adult smokers in prior[99] and ongoing COBRE-funded research. In addition, we will recruit from a list of people who screened for previous studies at our center and consented to be contacted for future research opportunities. Our prior recruitment strategies indicate that we can feasibly consent approximately 10 new participants per week.

We will recruit young adult dual users who are daily smokers because predominant smokers are the most common dual users[79] and appear unlikely to quit on their own.[85] For inclusion, participants must be a) 18 to 29 years old, b) have smoked CCs and used ECs ≥ once per month for ≥ 3 months, c) smoked ≥ 5 CCs daily for 25 or more of the past 30 days and meet DSM 5 criteria for tobacco use disorder, d) used ECs containing nicotine ≥ 10 days in the past 30 days, e) would like to completely quit CCs in the next 6 months, f) is willing to set a quit date in the next 2 weeks, g) is willing to use NRT to quit CCs, h) reports no contraindications for NRT, i) is not currently using NRT, varenicline, or bupropion or received smoking cessation counseling , j) has access to an iPhone or a smartphone with the Android operating system that can receive text messages on a daily basis, k) has access to a computer, tablet, or phone with internet to complete surveys at baseline, end of treatment, and the 6-month follow-up, l) is a US citizen or a permanent resident alien with a green card, m) is comfortable reading and writing in English, n) is not currently participating in another study that affects the way they smoke CCs or use ECs, and o) is not currently breastfeeding or planning to breastfeed in the next 3 months. If a participant is female, she will be excluded if she is pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active with a male partner and not using protection or on birth control. Individuals who meet the study criteria described above and provide electronic informed consent using REDCap's e-consent procedure will be randomized to one of the four conditions described above.

Assessments. All assessments will be remote and accessible by smartphone, tablet, or computer. After confirming eligibility and consenting to participate, participants will be randomly assigned to one of the four study groups (Table 1) and study personnel will mail a welcome package including study information, a CoVita iCO personal smokerlyzer device, and NRT (for groups A and B only). Upon receipt of the welcome package, participants will complete a brief baseline survey on the internet (Table 2) and will be encouraged but not required to submit a baseline breath CO sample using the CoVita iCO device and iCOquit mobile application which is compatible with Mac iOS and Android operating systems for smartphones and tablets. We will not ask participants to return their personal CoVita iCO Smokerlyzer. All participants will be free to keep their personal CoVita iCO Smokerlyzer after the conclusion of their participation.

Table 2. Schedule of assessments

	Baseline	Daily 1 wk pre- and 1 wk post-quit	Weekly surveys and End of Tx	6-Month follow-up

Individual-level factors				
Socio-demographic information	x			
Tobacco use history & breath CO	x			
Motivation rulers for CC & EC cessation[125]	x		x[a]	x[a]
CC and EC dependence and demand				
CC Strong dependence questionnaire	x		x[a]	x[a]
EC Strong dependence questionnaire	x		x[a]	x[a]
Cigarette & e-Cigarette Purchase Tasks [128]	x		x[a]	x[a]
Minnesota Nicotine Withdrawal Scale[131]	x		x	x
Intervention engagement & adverse effects				
Preference for quitting CCs only versus CCs + ECs simultaneously	x			
Frequency of EC use (groups A & C) or EC abstinence (groups B & D)		x	x	x
NRT use and perceived helpfulness (groups A & B)		x	x	
Responses to text messages and perceived helpfulness		x	x	
Study-related adverse effects		x	x	x
Outcomes				
Primary: CO-verified 7-day point prevalence CC abstinence			x	x
Secondary:				
CO-verified 30-day CC abstinence			x	x
Self-reported attempts to quit CCs		x	x	x
Cigarettes per day	x	x	x[a]	x[a]
Time to first CC after waking[132] and CC addiction ladder	x	x	x[a]	x[a]

[a]Assessed only among participants who relapsed or failed to quit CCs. CC=Combustible cigarettes; EC=Electronic cigarette; NRT=Nicotine replacement therapy; Tx=Treatment.

All participants will complete brief daily surveys for two weeks: one week pre- and one week post-quit date.. Participants will receive a daily text and/or email containing a link for the daily survey and will be able to complete the survey via internet on a smartphone, tablet or computer. Prior research from our group indicates 2 weeks of daily surveys is feasible with good retention (95%).[133] Participants will report CC smoking, EC use, NRT use (groups A and B only), text message utilization, nicotine dependence, quit attempts, and adverse events on daily surveys (Table 2). At the conclusion of the 12-week treatment period, participants will complete an end of treatment survey to report CC smoking or EC use and withdrawal symptoms. Those still smoking will also report motivation to quit, nicotine dependence, and self-efficacy to quit. In addition, participants will be encouraged but not required to submit another breath CO sample using their CoVita iCO device. The primary outcome for this RCT is CO confirmed 7-day point-prevalence abstinence from CCs at the end of treatment (i.e., at the 3-month follow-up). Per the Society for Research on Nicotine and Tobacco (SRNT) report on biochemical verification,[134] we will use CO of < 6 parts per million (ppm) as the cutoff for confirming CC abstinence. We will not contact participants for the 12 weeks following the treatment period. All participants will then complete a 6-month follow-up survey (i.e., 24 weeks after the baseline assessment) to report any CC smoking or EC use and withdrawal symptoms. Those who relapsed or continued to smoke CCs will also report motivation to quit, nicotine dependence, and self-efficacy to quit. In addition, all participants will be encouraged but not required to submit a final breath CO sample using their CoVita iCO device.

Adverse events will be assessed weekly throughout the 12-week treatment period, at the end of treatment follow-up, and at the 6-month follow-up. Participants who report they have experienced one or more problems related to their study participation will be prompted to rate the severity of their problem. Research personnel will contact all participants who report one or more severe problems related to study participation to further evaluate the nature of the adverse event(s). Research personnel will then consult with the study licensed medical provider to determine whether further evaluation is needed, whether the participant should be withdrawn from the study, or whether the participant should be referred to their local hospital. Any FDA-defined “serious” and possibly-related AEs will be reported within 72 hours to our IRB and our data and safety monitoring and review board (DSMB). In addition, all participants will be provided with a study telephone number and email at the outset of the study and instructed to contact research personnel with questions about symptoms or study procedures. It is possible that some participants in conditions A and C will increase their EC use when quitting CCs. An increase in EC use among those who completely quit CCs will not be considered an adverse event because completely switching from CCs to ECs is likely to result in substantial harm reduction.[82,135-139] In contrast, self-reported increases in EC use of > 100% among participants who continue to smoke CCs will be considered an adverse event. Research personnel will call any participant who continues to smoke CCs and reports an increase in EC use from baseline of >100% for one week (i.e., 7 consecutive days) or more and encourage them to reduce their EC use or quit CCs. Any participant who continues to smoke CCs and use > 100% of baseline ECs for two consecutive weeks will be referred to the national quitline and removed from this study.

Data and safety monitoring review board (DSMB). We will form a DSMB who will be charged with monitoring and evaluating the 1) study progress and 2) safety of the proposed RCT. With regard to study progress, screening, recruitment, and retention data will be reviewed on a regular basis to assure that the study can be completed in a reasonable time frame to be of significant clinical relevance. With regard to safety, interim safety data for the trial will be reviewed on a regular basis in order to assure the continuing safety of participants. Of note, all serious adverse events, study or non-study related, will be reported to the DSMB, as well as our IRB, by the principal investigator (PI) within 72 hours of the PI learning of the event. The DSMB may also review adverse events reported to the sponsor or IRB as applicable. The DSMB will meet approximately every 6-12 months to review interim data reports provided by the PI. Following each study review, the DSMB will recommend either 1) continuation of the trial using the current protocol, 2) continuation of the

trial with modifications, 3) placing the trial on hold until clarifications requested by the Board are resolved, or 4) termination of the trial. The trial will continue to be reviewed by the DSMB until all interventions are discontinued and issues raised by the Board are concluded to the Board's satisfaction.

Treatment. The consent form explains that a primary aim of this RCT is to test whether quitting versus continuing ECs is more effective when quitting CCs, and currently there is mixed evidence supporting both strategies. After randomization, all participants will receive information about the study including instructions to set a quit date and which product(s) to quit. Written instructions for the intervention will be provided and participants will also be asked to view a supplementary video presentation. We will provide participants in groups A and C with instructions to quit CCs but continue using ECs with the rationale that ongoing use of ECs could help them abstain from CCs. Specifically, we will instruct participants in groups A and C to use ECs in place of CCs to help cope with cravings or urges to smoke CCs. In contrast, participants randomized to conditions B and D will receive instructions to quit CCs and quit ECs with the rationale that quitting ECs could help them abstain from CCs. We will instruct participants in groups B and D to abstain from vaping because ECs could trigger relapse to CCs. Participants in groups A and B will also receive instructions for how to use NRT.

Participants randomized to conditions A and B will be mailed 3 one-month supplies of dual 14 mg NRT patches and 4 mg mini-lozenge because this appears to be the most effective non-prescription medication combination for smoking cessation.[140] However, participants will have the option to stop receiving NRT from the study. Participants will be instructed to start using both forms of NRT 2 weeks prior to their quit date because pre-quit NRT appears to increase the effectiveness of NRT.[141] Further, the recommended use for the NRT has recently been changed to incorporate use while smoking because "the FDA has determined that there are no significant concerns with using NRT products at the same time as another nicotine-containing product like a cigarette (https://www.nicodermcq.com/faq.html)." We will instruct participants to use one patch per day and use mini-lozenges when they have cravings to smoke CCs (condition A) or cravings to smoke CCs or use ECs (condition B), without surpassing 24 mini-lozenges in one 24-hour period. Anyone for whom NRT is contraindicated will be excluded from the proposed RCT. In addition, though risk of serious adverse events from NRT is low (eg.[142]), we will assess adverse events related to study procedures on weekly surveys.

All participants will receive daily text message support throughout the 12-week treatment period. We will use texts from SmokefreeTXT, a free interactive text message cessation service provided by Smokefree.gov that has been used with young adult smokers,[143] uses empirically validated Behavior Change Techniques,[144,145] and has been employed to support engagement in prior smoking cessation research.[146-150] Data from our ongoing research indicate young adult smokers generally find daily text messages to be helpful and acceptable. For example, in open-ended feedback participants reported that daily text messages about smoking cessation *"…made me realize that there's a way to cope," "…felt like I had someone there to help," "…reminded me of my goal to stop smoking,"* and *"…[were] very helpful!"* We will use qualitative and survey data from Dr. Villanti's COBRE-funded research to modify messages from SmokefreeTXT to optimize appeal and engagement for young adult dual users in the proposed RCT. In addition, we will modify text messages according to participants' assigned group. For example, text messages for participants in groups A and B will encourage regular use of NRT throughout the study period. Text messages for groups B and D will support CC and EC cessation while messages for groups A and C will support CC cessation and EC continuation. The text message service will be interactive for all participants. In addition to receiving daily texts, participants will have the opportunity to send text messages to our service which will prompt automatic responses. For example, a participant who texts *"help"* will receive a pre-programmed text message response containing suggestions for coping with urges to smoke cigarettes. We will work with ICF incorporated, the provider for National Cancer Institute's SmokefreeTXT platform, to deliver all daily text messages and to deliver links to daily surveys.

Dissemination and future directions. We will disseminate findings from this RCT by 1) presenting at national conferences (e.g., the Society for Research on Nicotine & Tobacco) and 2) publishing in peer-reviewed journals. In addition, we will disseminate smoking cessation treatment strategies for young adult dual users directly to tobacco treatment specialists by providing a summary of pertinent findings to local and national providers at the University of Vermont Medical Center, Vermont Psychological Services, the Vermont Department of Health, and the Association for the Treatment of Tobacco Use and Dependence (ATTUD).

Outcomes from this RCT will be used to inform an NIH R01 grant application to replicate and build on findings in a larger sample. For example, if findings indicate a benefit to quitting both CCs and ECs, future research will be needed to compare simultaneous cessation (i.e., quit CCs and quit ECs on the same day) versus sequential cessation (i.e., quit CCs first, then quit ECs later) among dual users. Further, if findings indicate NRT improves cessation among the primarily CC smoking dual users (people who smoke CCs daily and use ECs non-daily) in this trial, future research will be needed to test NRT among dual users who are primarily EC users (people who use ECs daily and smoke CCs non-daily) or heavy dual users (people who use of both products daily).[79] Finally, future research will be needed to modify treatment for young adult dual users who are not motivated to quit smoking at baseline. Thus, the proposed RCT will provide important findings to inform future research and continue to develop smoking cessation treatment for young adult dual users of CCs and ECs.

Timeline. The first three quarters of the funding period will be used for study startup including hiring and training research personnel, obtaining IRB approval, modifying the SmokefreeTXT text-message library for young adult dual users, developing baseline material to instruct participants in each condition, and purchasing study supplies (e.g., CoVita iCO smokerlyzers and NRT). Recruitment will begin after all startup procedures are complete. We will enroll participants for the proposed RCT during the subsequent year of the funding period. The final follow-up will be completed 6 months after the last participant is enrolled. We will conduct data analysis during the next two quarters of the funding period and the final two quarters will be spent writing and submitting manuscripts to peer-reviewed journals, presenting findings at national scientific conferences, and preparing an NIH R01 grant submission to build on the tobacco treatment findings for young adult dual users from this RCT.

Table 3. Study timeline

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
[a]Study startup:	x	x	x									
Participant enrollment:				x	x	x	x					
Participant follow-up:					x	x	x	x	x			
Data analysis:										x	x	
Dissemination:											x	x
R01 grant preparation:											x	x

[a]Study startup includes hiring and training research personnel, obtaining IRB approval, modifying the SmokefreeTXT text-message library, developing baseline animated, audio, and written material, and purchasing study supplies.

Describe required screening procedures performed before enrollment and while on study.

Recruitment and Retention Plan

Recruitment

Recruitment will be conducted through an online campaign and from an existing list of people who screened for prior research in our center and consented to be contacted for future research opportunities. We will place paid online ads for study participation through Facebook, Instagram, and Google ads. In addition, we will post Craigslist ads and post recruitment material from our social media accounts (Facebook and Instagram). We will email and call people who screened for prior research in our center and consented to be contacted for future research opportunities. All study recruitment material will direct potential participants to our study website which will provide detailed information about the study and a link to a screening survey to determine eligibility. Potential participants who screen eligible for participation will be asked to read and sign an electronic consent form using REDCap's e-consent procedure in order to participate in this study. Consented participants will be directed to an online version of the University of Vermont Participant Payment Form to provide their name and address.

Potential participants will respond to our emails, calls or internet advertisements and will be routed to our study website. Our study website will contain a description of study procedures and link to the screener for eligibility. Participants who respond via telephone will have the information presented on our website read to them by research personnel. Participants who screen eligible will be provided with an electronic consent form to read and will be required to complete a brief "consent quiz" to ensure that they understand the study procedures and consent form before they consent to participate. Participants will have unlimited attempts to answer the questions correctly and the correct answer will be explained to the participant upon selecting it. They will not be able to complete the consent process until all correct answers have been selected. After completing the "consent quiz" eligible potential participants will be asked to provide an electronic signature via REDCap's e-consent procedure in order to participate. Data from consenting participants' screener questionnaire will become part of their research record. All participants will be provided with a phone number and email address for study personnel and encouraged to contact study personnel with any questions about participation or study procedures. Eligible participants will be provided with a copy of the electronic consent form to save for their own records.

Screener data from people who are ineligible will be retained and used to document ineligible screens and to identify duplicate attempts to screen for our study. We will notify people who screen ineligible that we will retain their data unless they contact us to request that we delete their data. We will provide people who are ineligible with our contact information.

Given that all recruitment and study procedures will be conducted remotely, there is a greater likelihood of ineligible, duplicate, and fraudulent responses in this study than studies that involve an in-person component. Thus, we will follow the screening protocol used in prior remote studies from our group and include a number of internal and external controls to confirm that participants are eligible and ensure the validity of all responses. For example, we will include a number of screening items, such as age, birth date, and state of residence, which will be used to compare responses on various measures for consistency. In addition, we will include a CAPTCHA item in the initial online screener to confirm that respondents are human and not bots. If responses regarding location and residence are inconsistent, we will use the study address information that the participant provides on the University of Vermont Participant Payment Form to ensure eligibility. In addition, we will screen study e-mail addresses and phone number to flag potentially fraudulent responses by comparing to information provided on other forms. We will email potentially fraudulent responses with a request for a valid e-mail response, which provides verification of e-mail addresses and confirms interest in participation. We will also schedule short Zoom or phone calls with participants to see their photo ID and answer any questions they might have about their participation. If a participant chooses to have their initial call via telephone, we will ask them to text or email a picture of their photo ID in order to confirm their identity. Participants who do not display their photo ID on a Zoom call or send a picture of their photo ID will be excluded. Participants will be compensated with $15 for completing this call to increase initial retention. During a prior study from our group, this approach was used to successfully exclude approximately 1,000 ineligible respondents (i.e., 35% of all screenings completed) and identify 336 fraudulent responses (18% of the initially eligible responses).

All participants will have the option to refer others to participate in the study and will receive $25 compensation for each person that they refer who completes a baseline survey. Participants will have the opportunity to refer a maximum of 5 participants. During the ID check Zoom call, we will ask all new participants whether they were referred from someone currently enrolled in the trial. If they were, we will ask them to provide the name of the person that referred them. After the ID check Zoom call, the research assistant will look up the referral source in our REDCap database and provide a $25 gift card and payment acknowledgment to the referral source if the individual who was referred completes the baseline survey.

Retention

We will employ a series of strategies to retain participants for the entirety of this 6-month study:

1) Proximal compensation for survey completion. Participants will receive electronic gift cards soon after completing each of the study surveys.

2) Personalized reminders to complete study surveys. All participants will receive reminders to complete any missed weekly, baseline, 3-month or 6-month surveys.

3) Personalized thank you messages in response to completing surveys. We will send emails following the completion of the baseline and 3-month surveys to thank participants and encourage continued participation.

All participants will have the opportunity to earn up to $493 in gift cards for participating in this 6-month study. The table below outlines compensation for each study activity:

Study activity	**Compensation**
Initial call and ID verification	**$15 total**
Baseline survey	$30 total
Viewing short informational video	$10 total
2 weeks of daily questionnaires	$2 per log entry for a total of $28
Week 1 + 2 surveys ($10 each)	$20 total
Week 3 + 4 surveys ($15 each)	$30 total
Week 5 + 6 surveys ($20 each)	$40 total
Week 7 + 8 surveys ($25 each)	$50 total
Week 9 + 10 surveys $30 each)	$60 total
Week 11 survey ($35)	$35 total
3 month and 6 month surveys	$50 each for a total of $100
Bonus for providing breath samples on baseline survey, weekly surveys, and 3-month and 6-month follow-up surveys	$5 per bonus for a total of $70
Total possible compensation	**$493**

For research involving survey, questionnaires, etc.: Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation.

☐ **Not applicable**

All surveys and questionnaires will be administered remotely via the University of Vermont College of Medicine's REDcap account, which is a secure, HIPAA-compliant platform. We will text participants links to their daily questionnaires during weeks 2 and 3 of the study. We will email participants secure links to their baseline, weekly, 3-month, and 6-month surveys. We will mail all participants a personal iCO Smokerlyzer device (https://www.bedfont.com/ico). We will instruct participants to download the Smokerlyzer iCOquit application on their smartphone or tablet.Participants will use their email address to create an account and access the app and complete the CO testing at their baseline, weekly, 3-month, and 6-month surveys. At each survey, participants will be encouraged but not required to submit a breath sample using their device and the Smokerlyzer iCOquit app on their cell phone or tablet. De-identified breath CO results will be stored in coVita's iCOquit app database for the duration of the study. Participants will also manually enter their results into the appropriate REDCap survey. Research personnel will access the breath CO data through emailand will download the data to the University of Vermont College of Medicine secure drive. Results from the Smokerlyzer iCOquit application will be securely coded with the participants' unique ID and securely stored with other participant data.

The daily surveys during weeks 2 and 3 of the treatment period will be completed on the college of medicine's secure REDCap platform. Links to the REDCap daily survey will be sent via text message as part of the text message support administered by ICF Inc. Participants will be required to enter their participant ID into the daily survey to complete each daily survey.

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)

Check all that apply.

X	Survey (mail, telephone, in-person, on-line)	☐	Blood drawing:	Vol.		Over days, weeks?	
☐	Medical exams/history					Type & Amt.	
☐	Deception ***see below**	☐	Surgery	☐	Collection of Urine and/or Feces		
☐	Observation	☐	Drug Administration	☐	HIV Testing		
☐	Photographs	☐	Device Use	☐	Ultrasound (e.g. echocardiogram)		
☐	Audio Recording	☐	Exercise	☐	Imaging (e.g. CT scan, DEXA, mammogram, PET scans, SPECT)		

☐	Video Recording	☐	Diet	☐	Use of Radiation treatment
☐	Interviews in person or by phone	☐	Pathology Specimens (retrospective)	☐	Use of Radioactive substances (e.g. radiolabeled antibodies, drugs or contrasts)
☐	Focus Groups	☐	Genetic Materials (DNA)*	☐	MRI (for treatment studies)
☐	Review of prospective data	x	Questionnaires	☐	MRI (not for treatment studies)
☐	Review of retrospective data	☐	Diaries	☐	Tissue (obtained for clinical purposes)
☐	Recording of Identifiable Data	☐	Pregnancy Tests	☐	Tissue (obtained solely for research)
☐	Electrocardiograms				
☐	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)	(specify):			

***If genetic information is being collected, GINA language must be added to the consent form.**

*Deception typically involves withholding information from the potential subject and would require an alteration to the consent process.

Statistical Considerations: Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.

Statistical methods. Baseline participant characteristics, including socio-demographic information and tobacco use history, will be compared between the four conditions using analyses of variance for continuous and chi-square tests for categorical variables. Differences between conditions at baseline will be considered as potential covariates in subsequent analyses. Consistent with the intent-to-treat approach,[152] our primary analysis will include all randomized participants who complete the baseline survey, independent of early dropout. Participants who are missing abstinence data will be assumed to be smoking. Missing survey data on other outcomes will be imputed using multiple imputation.[153] For our Aim 1 primary outcome, we will compare the proportion of participants who achieved CO-verified (< 6 ppm) 7-day point-prevalence abstinence at the end of treatment between conditions that were provided NRT versus no NRT using logistic regression. For our Aim 2 primary outcome we will compare the proportion of participants who achieved CO-verified 7-day point-prevalence abstinence at the end of treatment between conditions assigned to quit CCs only versus quit CCs and Ecs simultaneously. For our Aim 3 primary outcome we will compare the conditions assigned to quit CCs only versus quit CCs and Ecs simultaneously on 1) the proportion of participants who report a serious study-related adverse event using a chi-square test and 2) the total number of reported study-related adverse events during the treatment period using a t-test or nonparametric test, depending on the distribution. In addition, we will conduct an exploratory analysis using logistic regression to examine the interaction between the treatment arms (NRT versus no NRT by continue EC versus quit EC) with CO-verified 7-day point-prevalence abstinence as the outcome. We will also examine the effect of EC continuation versus NRT on CC abstinence by comparing Group B (quit CCs and Ecs with NRT) versus Group C (quit CCs and continue Ecs without NRT) using logistic regression. We will conduct a series of sensitivity analyses using 30-day abstinence at the 6-month follow up as the outcome and test condition as a predictor of time to relapse after quit day using Cox proportional hazards regression survival analyses. Finally, we will conduct sensitivity analyses when missing data are treated as missing.

Additional secondary analyses will explore moderators and intervention effects on relevant smoking outcomes. For example, we will test days of NRT use as a moderator of NRT's effect on abstinence using logistic regression. Similarly, we will test days of EC use as a moderator of the effect of being assigned to continue versus quit Ecs on CC abstinence using logistic regression. We will assess baseline preference for continuing versus quitting Ecs as a moderator of the effect of being assigned to continue versus quit Ecs on CC abstinence using logistic regression. Among participants who fail to quit CCs, we will examine condition as a predictor of change in amount of CC use, self-reported attempts to quit CCs, nicotine dependence, self-efficacy to quit CCs, and motivation to quit CCs. Analyses will be performed using SAS Statistical Software V9.4 (SAS Institute, Cary, NC). Statistical significance will be determined based on $p<.05$ for all analyses.

Sample size justification. We propose recruiting, consenting, and randomizing a sample of 390 participants. Given the high rate of fraudulent responses in remote studies, we anticipate that we will need to consent 1,030 individuals in order to verify the identification and randomize 390 participants. Based on prior remote tobacco treatment research among young adults,[33] we estimate 80% retention of randomized participants and thus anticipate retaining 312 participants by the end of treatment when we will assess our primary outcome. This proposed sample size is based on having sufficient power for detecting group differences on the primary outcome of 7-day point-prevalence abstinence at the end of treatment (i.e., week 12) for the treatment comparisons in Aims 1 and 2. A sample size of 78 in each of the 4 treatment groups will give over 90% power to detect a difference between NRT and No NRT and 80% to detect a difference between CC+CE and CC only in 7-day point-prevalence abstinence rates, assuming overall rates of 31% in the NRT and 12% in the No NRT group and overall rates of 15% in the CC+CE and 28% in the CC only group with $\alpha=.05$. While we know of no prior trials of NRT for young adults or smoking cessation treatment for dual users, these estimates are based on relevant prior trials of NRT or text messages for smoking cessation.[37,69,140,154]

Risks/Benefits: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Description of Potential Risks. Risks include breach of confidentiality, nicotine withdrawal, and adverse events related to nicotine replacement therapy (NRT).

Breach of confidentiality. Study data include contact information, socio-demographic characteristics, and tobacco use information. The risk of a breach in confidentiality is low and we will take precautions to minimize this risk as described below in the Adequacy of Protection Against Risk section.

Nicotine withdrawal. Participants who succeed in quitting combustible cigarettes (CC) may experience withdrawal symptoms (i.e. anxiety, depression, difficulty concentrating, hunger/weight gain, insomnia, irritability and restlessness). For participants who are randomized to receive NRT or continue electronic cigarettes (EC), these symptoms may be mitigated by NRT or EC use. There is a small risk that if a participant had a psychiatric problem, it might become worse or return after they quit CCs.

Nicotine replacement therapy (NRT). Nicotine replacement therapy may produce several minor adverse events (AE), most of which are skin rash (from NRT patch) and insomnia. Approximately 10% or less of smokers have to stop NRT due to Aes. FDA-defined serious Aes have been very rare and dependence on the NRT is rare. The current labeling on the NRT explains that 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 physician before using the patch. Thus, we will exclude any potential participant who meets criteria for these contraindications and does not have approval from their physician to use NRT. The NRT labeling also recommends keeping the medication out of reach of children and pets. Thus, we will recommend all participants keep their NRT in a secure location out of reach from children and pets. Studies of NRT use while continuing to use tobacco have not found greater Aes than when NRT is used after tobacco cessation. Further, the recommended use for NRT has recently been changed to incorporate use while smoking because "the FDA has determined that there are no significant concerns with using NRT products at the same time as another nicotine-containing product like a cigarette (https://www.nicodermcq.com/faq.html)."

2. Protection against Risk.

All study data will be confidential and accessible only by IRB-approved study personnel. All study data will be downloaded directly into the password-protected study database and stored on the University of Vermont College of Medicine's secure server. Each participant will be assigned a unique identification code (ID) to maintain confidentiality. Participants' names, contact information (telephone number and e-mail address), informed consent documents, and payment form and a document describing each participant's ID number will be kept in a secure file on the University of Vermont College of Medicine's secure server. Participation will entail a text message intervention. Thus, we will ask participants to text a third party vendor (ICF Incorporated's SmokefreeTXT) to initiate the text message support services. In addition, participants will be asked to share their email address with Rybbon, a third party vendor that we will use to distribute digital gift cards as compensation for participating. During the consent process, we will inform all potential participants that, if they decide to participate, we will ask them to enroll in our study text message services, which will require sharing their phone number with ICF Incorporated and we will ask them to share their email address with Rybbon to receive compensation. Participants' contact information will remain confidential and will not be accessible by anyone other than those previously described. All research personnel will receive training in confidentiality.

Participants will be informed about possible Aes in the consent. At study onset, participants will be provided with a phone number and e-mail to report any Aes that are urgent. We will withdraw participants who have an FDA-defined serious AE (SAE) that are likely or probably related to the study procedures as well as participants who become pregnant or begin breast feeding. Traditional methods of collecting Aes can be insensitive, thus we will inquire about Aes weekly during the 3-month study period and instruct participants to contact research personnel if they experience a severe AE. We will also assess whether participants have become pregnant or started breastfeeding on weekly questionnaires during the treatment period. Any participant who indicates they became pregnant or began breastfeeding during the treatment period will be withdrawn from the study and provided with a referral to tobacco treatment. In addition, we will encourage participants to contact research personnel if they have questions about withdrawal symptoms or believe any withdrawal symptoms require treatment. A study licensed medical provider will be available by phone to discuss any questions about withdrawal symptoms or Aes.

Potential participants are free not to participate in this study and participants are free to withdraw at any time. Potential participants who screen ineligible or do not consent to participate will be provided with resources to help them quit smoking outside of this study.

3. Potential Benefits to Participants and Others

The primary potential benefit to participants is that they may quit smoking cigarettes. People who smoke cigarettes have approximately a 50% chance of dying from smoking-related illness. Participation in this study could increase the chances of smoking cessation and prevent long-term morbidity and mortality from cigarettes. This research also stands to provide scientific benefit by improving understanding of the influence of NRT and continued EC use during a smoking cessation intervention. Further, the smoking cessation intervention for young adult dual users tested in this research has the potential to benefit public health by decreasing the substantial personal and societal costs associated with tobacco use in the United States. Thus, we believe the risks to participation in the proposed research are reasonable in relation to the anticipated benefits.

Therapeutic Alternatives: List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.

☐ **Not Applicable**

Currently, there are no empirically validated treatments for smoking cessation among dual users. However, we will offer all potential participants a referral to the national quitline (1-800-QUIT-NOW) so that they can access tobacco cessation services in their state. In addition, we will offer all participants who continue to smoke cigarettes or use e-cigarettes a referral to the national quitline at the conclusion of the study.

Data Safety and Monitoring: The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.

Nicotine replacement therapy (NRT) has been extensively tested, is sold over the counter, and is generally considered low risk. Nonetheless, the proposed study is a novel test of NRT given that all participants will be dual users of combustible cigarettes (CC) and electronic cigarettes (EC). Thus, a primary aim of the proposed RCT is to assess whether continued EC use after NRT aided CC cessation is associated with experiencing adverse events (AE). We will assess Aes weekly throughout the first 3 months of the study period. The principal investigator (PI) and research personnel will closely monitor Aes and promptly report serious adverse events (SAE) to the University of Vermont Institutional Review Board (IRB). In addition, we will utilize a data safety monitoring review board (DSMB) to monitor data security and participant safety throughout the study.

Patient eligibility and status

All intake data collection will be conducted online using a secure platform (e.g., REDCap). The PI and trained IRB-approved research personnel will review intake data as needed to determine eligibility. Research personnel and the PI will review the status of all active participants during weekly study meetings. We will follow the screening protocol used in prior remote studies from our group and include a number of internal and external controls to confirm that participants are eligible and ensure the validity of all responses.

Rigorous data management/Quality assurance

All data will be collected via secure, HIPAA-compliant software (e.g., REDCap). With the exception carbon monoxide (CO), all data will be collected using self-report questionnaires. We will mail participants a personal iCO Smokerlyzer to measure breath CO at baseline, weekly, 3-month and 6-month follow ups. Participants will be instructed to download the Smokerlyzer iCOquit App to use their iCO device and to report CO data on REDCap surveys. All participant data will be directly loaded from the secure online surveys (e.g., REDCap) to a University of Vermont College of Medicine secure server. Participants' identities will be disguised using ID numbers keyed to a master list. Identifying information such as telephone number and email address will be stored in a separate, secure, and password protected data file. All data will be accessible to only the PI and IRB-approved research personnel. The IRB approved biostatistician and PI will consult regularly to discuss ongoing data management and any problems that arise.

Data and safety monitoring review board (DSMB)

We will form a DSMB who will be charged with monitoring and evaluating the 1) study progress and 2) safety of the proposed RCT. With regard to study progress, screening, recruitment, and retention data will be reviewed on a regular basis to assure that the study can be completed in a reasonable time frame to be of significant clinical relevance. With regard to safety, interim safety data for the trial will be reviewed on a regular basis in order to assure the continuing safety of participants. Of note, all serious adverse events, study or non-study related, will be reported to the DSMB, as well as our IRB, by the PI within 72 hours of the PI learning of the event. The DSMB may also review adverse events reported to the sponsor or IRB as applicable. The DSMB will meet approximately every 6-12 months to review interim data reports provided by the PI. Following each study review, the DSMB will recommend either 1) continuation of the trial using the current protocol, 2) continuation of the trial with modifications, 3) placing the trial on hold until clarifications requested by the Board are resolved, or 4) termination of the trial. The trial will continue to be reviewed by the DSMB until all interventions are discontinued and issues raised by the Board are concluded to the Board's satisfaction.

Auditing procedures

The PI and study personnel will meet weekly to review any problems related to the quality of data collection and any Aes or SAEs that occurred during the past week. In addition, we will conduct an interim analysis of Aes halfway through data collection as well as interim analyses of as required by the DSMB. We will present findings from all interim analyses to the DSMB.

Reporting mechanisms of Aes and SAEs

The proposed research will use the US Food and Drug Administration's definitions of Aes and SAEs. We will screen for Aes on all weekly surveys, the 3-month follow up, and the 6-month follow up. Throughout the treatment period. Research personnel will contact any participant who reports a severe AE to assess the quality of the AE and whether the AE is related to the study procedures. Any SAE will be brought to the attention of the PI as soon as possible and not longer than 24 hours after reported by the participant. Any SAE, whether or not related to study intervention, will be reported to the study DSMB and the University of Vermont IRB using the University of Vermont Adverse Event Reporting Document within 5 days of the event. Both the IRB and the DSMB will make determinations as to whether additional reporting requirements are needed. All SAEs will be followed through ongoing consultation with the physian caring for the patient until they resolve, result in death, or stabilize and are not expected to improve.

Data sharing plan

During the study period data will be accessible only to University of Vermont IRB-approved research personnel. After all participants complete the study, all data are collected, and the primary results have been published, de-identified data will be made available to other qualified investigators upon request. Each request will be reviewed and evaluated individually by the PI to ensure that it meets reasonable demands of scientific integrity.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. "stopping rules).

Criteria for continuation, modification or termination of the entire study will be determined by an external data safety monitoring review board (DSMB).

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. **Forward copies of the data and safety monitoring reports to the 1) IRB, 2) CRC (if applicable), and/or 3) UVMCC (if applicable).**

- [ ] Monthly
- [ ] Quarterly
- [x] Bi-annually
- [ ] Annually
- [ ] Other (e.g. by dosing level, no. of subjects enrolled):

Will the sponsor be conducting data monitoring visits for this study?

- [ ] Yes
- [x] No
- [ ] NA

If yes, how often?

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.

The guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed.

Withdrawal Procedures: Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).

We will withdraw participants if we think it is harmful for them to participate (e.g., if they experience an SAE related to study procedures) or if we believe the information they are providing us is not valid. Participants will be free to withdraw at any time and will be provided with email and telephone contact information for study personnel to communicate if they would like to be withdrawn from the study.

Sources of Materials: Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.

Computerized surveys from baseline, weekly, 3-month and 6-month surveys as well as results from participants' personal iCO Smokerlyzers will be obtained specifically for research purposes. In addition, data from daily surveys during weeks two and three of the treatment period will be obtained specifically for research purposes.

DRUG INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [ ] **Not applicable**

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source.

Nicotine replacement therapy (NRT)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

The NRT will be prepared by the manufacturer in the form of NRT patch and NRT lozenge.

Storage and stability – for both intact and mixed products.

We will store NRT in a secure and locked cabinet at room temperature.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

We will instruct participants to use both NRT patch and NRT lozenge according to instructions on the product insert. NRT patches will be applied to bare skin once per day and NRT lozenges will be ingested orally as needed to manage cravings for cigarettes.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Nicotine replacement therapy (NRT) is an FDA approved over-the-counter smoking cessation medication. NRT may produce several minor Aes, most of which are skin rash (patch) and insomnia. Approximately 10% or less of smokers have to stop NRT due to Aes. FDA-defined serious Aes have been very rare and dependence on the NRT is very rare. The current labeling on the NRT explains that 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 physician before using the patch. Thus, we will exclude potential participants with any of these contraindications unless they receive approval to participate from their physician. Studies of NRT use while smoking cigarettes have not found greater Aes than when the patch is used for cessation. We will also recommend keeping NRT out of reach of children and pets.

Is it FDA approved: (include FDA IND Number)

1. in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.
   Yes
2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.
   Yes
3. for the intended action?
   Yes

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: Provide rationale for subject selection in terms of the scientific objectives and proposed study design.

Participants will be young adults who are interested in quitting cigarettes and currently smoke combustible cigarettes and use electronic cigarettes regularly because the purpose of our study is to test smoking cessation treatment among young adult dual users. Further, we will recruit young adult dual users who are predominant smokers (i.e., daily CC and non-daily EC users) because predominant smokers are the most common dual users and appear unlikely to quit on their own.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, Non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

x **Not applicable**

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.

We will recruit young adult dual users who are daily smokers because predominant smokers are the most common dual users[79] and appear unlikely to quit on their own.[85] For inclusion, participants must be a) 18 to 29 years old, b) have smoked CCs and used Ecs ≥ once per month for ≥ 3 months, c) smoked ≥ 5 CCs daily for 25 or more of the past 30 days and meet DSM 5 criteria for tobacco use disorder, d) used Ecs containing nicotine ≥ 10 days in the past 30 days, e) would like to completely quit CCs in the next 6 months, f) is willing to set a quit date in the next 2 weeks, g) is willing to use NRT to quit CCs, h) reports no contraindications for NRT, i) is not currently using NRT, varenicline, or bupropion or received smoking cessation counseling , j) has access to an iPhone or a smartphone with the Android operating system that can receive text messages on a daily basis, k) has access to a computer, tablet, or phone with internet to complete surveys at baseline, end of treatment, and the 6-month follow-up, l) is a US citizen or a permanent resident alien with a green card, m) is comfortable reading and writing in English, n) is not currently participating in another study that affects the way they smoke CCs or use Ecs, and o) is not currently breastfeeding or planning to breastfeed in the next 3 months. If a participant is female, she will be excluded if she is pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active with a male partner and not using protection or on birth control. Individuals who meet the study criteria described above and provide electronic informed consent will be randomized to one of the four conditions described above.

Inclusion of Minorities and Women: Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.

Inclusion of Women

Neither sex nor gender will be a selection or inclusion factor for study participation. Though women compose approximately 50%

of the US general population, the majority of adults who complete internet survey research are women. Based on internet recruitment for our group's current remote smoking cessation treatment study for young adult smokers, we anticipate approximately 80% of recruited participants will be women. We will do all that we can to ensure that women are represented in this research, including using a national online recruitment campaign using multiple platforms to ensure that information regarding this study reaches as diverse of a population as possible.

Inclusion of Minorities

There will be no exclusion criteria concerning race or ethnicity. National estimates of race/ethnicity among young adults who use both combustible cigarettes (CC) and electronic cigarettes (EC) are approximately 84% White, 4% Black, 18% Hispanic, and 12% Other. Based on internet recruitment for our group's current remote smoking cessation treatment study, we anticipate our recruited participants will be approximately 77% White, 9% Black, 1% American Indian or Alaska Native, 2% Asian, 1% Native Hawaiian or Pacific Islander, 2% Other, and 8% more than one race. With regard to ethnicity we anticipate approximately 12% of recruited participants will be Hispanic. We will do all that we can to ensure that minorities are represented in the research, including the recruitment efforts to reach a diverse group of potential participants described above.

Inclusion of Children: Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

This study focuses specifically on smoking cessation in young adults (ages 18 to 20) because prior research indicates this age group is particularly vulnerable to nicotine dependence and the harmful effects of tobacco. Thus, we will only recruit participants aged 18 to 29 years old and will exclude children under the age of 18.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

If a participant is female, she will be excluded if she is pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active with a male partner and not using protection or on birth control.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X **Not applicable**

Will the SONA psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool* Yes [ ] No [x]

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

N/A

Compensation for participation: Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.

[ ] **Not applicable**

All participants will have the opportunity to earn up to $493 in online gift cards for participating in this 6-month study. Links to digital gift cards will primarily be sent via Rybbon, a vendor that we work with to deliver gift cards. Depending on availability, we may also send participants Amazon.com digital gift cards directly from our study email account (quit.smoking.study@uvm.edu). The table below outlines compensation for each study activity:

Study activity	**Compensation**
Initial call & ID verification	**$15 total**
Baseline survey	$35 total
Viewing short informational video	$10 total
2 weeks of daily daily questionnaires	$2 per log entry for a total of $28
Week 1 + 2 surveys ($10 each)	$20 total
Week 3 + 4 surveys ($15 each)	$30 total

Week 5 + 6 surveys ($20 each)	$40 total
Week 7 + 8 surveys ($25 each)	$50 total
Week 9 + 10 surveys ($30 each)	$60 total
Week 11 survey ($35)	$35 total
3 month and 6 month surveys	$50 each for a total of $100
Bonus for providing breath samples on baseline, weekly surveys, and 3-month and 6-month follow-up surveys	$5 per bonus for a total of $70
Total possible compensation	**$493**

Collaborating Institutions

Will this research be conducted in collaboration with other sites at other locations? Yes [ ] No [x]

If so, complete the following for all collaborating institutions:

Institution Name	Describe Involvement	Is there an IRB? If yes, attach approval or explanation	Are other permissions required? If yes, attach approval or explanation

INFORMED CONSENT

a. Type of Consent

i. Are you obtaining Written Consent? [x] Yes [ ] No

If yes, will there be more than one consent document? [x] Yes [ ] No

If yes, how many consent documents and for what populations.

Potential participants will review an electronic consent form via REDCap. Potential participants will be provided with a study phone number and e-mail and encouraged to contact study personnel if they have any questions about the study or consent form. After reviewing, the potential participant will be asked to provide and electronic consent by using REDCap's e-consent program. After the electronic consent, participants will complete the electronic consent survey, which evaluates their understanding of the information from the consent form. This survey will provide immediate, correct responses for any items answered incorrectly. We will also include consent process documentation.

ii. Are you requesting a Waiver of Informed Consent? [ ] Yes [x] No

This request means that you will not be obtaining verbal nor written consent. **If yes**, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

iii. Are you requesting an Alteration of Informed Consent Procedures? [ ] Yes [x] No

This is a request to alter an individual's informed consent or elements of informed consent. Deception in research would be one example when consent would be altered. See Policies and Procedures Manual for more information about when a subject's consent may be altered. **If yes**, complete the smart form Request for a Waiver of Informed Consent/ Authorization/ Documentation in UVMClick.

iv. Are you requesting a Waiver of Documentation of Informed Consent? [ ] Yes [x] No

This request means you are obtaining verbal or implied consent without obtaining the subject's signature on a consent form. See manual for the criteria required to obtain this type of waiver.

If yes, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

v. Do you intend to obtain consent from a legally authorized representative? [ ] Yes [x] No

If yes, describe the process. ☐ ☐

vi. Are you requesting a short form consent process for non-English speaking subjects? ☐ Yes ☒ No
If yes, please describe. Guidance available in the Policies and Procedures Manual.

b. Consent Process

i. Once a prospective subject is identified, who initiates the informed consent discussion and answers questions presented by the subject or the subject's family?

The informed consent process will be initiated electronically. People who are interested in participating will be directed to a website with information regarding the study. Potential participants will be provided with a study phone number and e-mail and encouraged to contact IRB-approved research personnel if they have any questions about the study or consent form.

ii. Where (in what setting) is the informed consent process initiated? How much time is the subject given to decide?

Consent will be obtained remotely using e-consent procedures through REDCap. Participants will have as long as they need to review the consent form and ask questions.

iii. Is the principal investigator present for the initial and subsequent informed consent discussions with the subject?

The PI will not be present at the time of consent although his contact information is available on the consent form for questions and the research assistant will have him speak with the potential participant prior to consent as needed.

iv. What other method of documentation is used to record the informed consent process, in addition to the executed consent form? See an example of documentation of the informed consent **process** under consent templates on our forms page. *(This separate documentation is required to document the consent process with the research subject)*

We are using a consent survey to document understanding of key procedures from the consent form. We will also include consent process documentation.

Information Withheld From Subjects: Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.

☒ **Not applicable**

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.