ClinicalTrials.gov ID: NCT04250727

Title: Switching to Potential Reduced Exposure Products in Adult Smokers

Date: 2/28/2023

Document: Protocol with SAP

HRP-503B – BIOMEDICAL
RESEARCH PROTOCOL
(Welz et al.)

Protocol Title: **Switching to an oral nicotine product among adult cigarette smokers: Exploring the roles of product characteristics and user history**

Principal Investigator: Lisa Fucito, Ph.D.

Version Date: 2/24/23

(Humphrey et al.) Clinicaltrials.gov Registration #: Pending

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to betested.

We propose to assess the feasibility, acceptability, and potential reduction in harm experienced from switching to a non-combustible form of tobacco use among adult cigarette smokers. This research will have two parts:

In Part One, we will conduct a survey of current smokers with medical co-morbidities who present at hospital outpatient clinics to ascertain their interest in switching to an e-cigarette device compared to other non-combustible tobacco products (e.g., smokeless tobacco/snus) and/or medicinal nicotine (i.e., nicotine

replacement therapy). We will examine whether interest in using these products may vary by: (1) demographic characteristics, (2008 PHS Guideline Update Panel) tobacco use variables, smoking-related, and medical-related characteristics, and/or (3) smokers' perceptions of these products/medications.

In Part Two, we will conduct a preliminary study of Zyn nicotine pouches, the most popular oral nicotine pouch, in 30 adult cigarette smokers who decline smoking cessation services but are willing to try Zyn. Subjects will receive Zyn pouches to use for 4 weeks. Participants will be randomly assigned to receive Zyn pouches with 1 of 2 nicotine concentrations (3mg, 6mg) and asked to select two sample flavors (i.e., unflavored, cool mint, spearmint, wintergreen, peppermint, cinnamon, coffee, citrus) to try at the first visit. At the end of the first week, participants will select a single flavor from among these flavors to use going forward but may change at a later appointment if desired. We will encourage participants to switch to Zyn use in place of smoking. We will examine the effects of nicotine concentration on Zyn use, participant characteristics associated with switching, and biomarkers of harm-reduction. We will also monitor use of flavors. We will recruit adult cigarette smokers who are not interested in quitting smoking at the time of their outpatient visits at hospital clinics and from the community using social media. We will provide participants with Zyn pouches to use for 4weeks.
Participants will be randomly assigned to receive Zyn pouches with 1 of 2 nicotine concentrations (3mg, 6mg) and will be asked to select two sample flavors (i.e., unflavored, cool mint, spearmint, wintergreen, peppermint, cinnamon, coffee, citrus) to try at the first visit. At the end of the first week, participants will select a single flavor from among these flavors to use going forward but may change at a later appointment if desired.

We will encourage participants to switch to Zyn use in place of smoking. We will examine the effects of nicotine concentration on Zyn use, participant characteristics associated with switching, and biomarkers of harm-reduction. We will also monitor use of flavors. At each appointment, we will ask participants to complete measures of satisfaction and subjective effects such as liking/taste, craving/withdrawal relief, willingness to continue use, and smoking behavior, including compensatory use of other tobacco products to estimate the impact of switching to the Zyn pouches on current smokers and will obtain biomarkers of harm such as exposure to tobacco-related toxicants to assess the potential impact of switching to Zyn pouches on harm reduction. We will also monitor the flavors of the pouches used. At the end of 4 weeks, we will assess participant's willingness to continue Zyn pouch use as well as their interest and motivation for quitting smoking to assess product acceptability and impact on smoking behavior and provide resources for quitting. All participants will complete a follow-up at 8 weeks for an evaluation of smoking status.

Overall, the results will provide novel information on the tobacco product preferences and interest in using these products among cigarette smokers who are not interested in quitting smoking as well as how a specific product (i.e., Zyn pouches) may influence smoking satisfaction and behavior and affect exposure to harm. The FDA could use these results to better understand the appeal and use of various nicotine containing products and specifically to predict the effects of switching to oral nicotine pouches among current cigarette smokers. Additionally, the results will inform future study designs by evaluating the feasibility of an oral nicotine pouch switching paradigm. The proposed work aligns with the FDA Center for Tobacco Products (CTP) priority of understanding how changes in tobacco products affect their risk-benefit ratio. Data from this study could inform tobacco regulatory efforts regarding establishing limits on nicotine concentration levels and flavor options to facilitate adult smokers switching to alternative tobacco products but reduce the appeal of these products among youth.

The study will test the following specific aims among adult cigarette smokers:

Aim 1: Evaluate the effect of nicotine concentration on smoking behavior. We will compare HIGH and LOW groups on rates of complete switching from smoking to pouches and secondary outcomes of cigarettes smoked per day over 4 weeks and % non-smoking Hypothesis: We expect that switching behavior and reductions in smoking will be greater in the high vs. low nicotine concentration conditions.

Aim 2: Examine characteristics associated with Zyn use. We will investigate whether switching behavior/smoking reductions vary by participant and Zyn characteristics. Hypotheses: We expect that switching behavior/smoking reductions will be greater among participants who reported only cigarette smoking at baseline compared to dual tobacco/nicotine product users (Vickerman et al., 2013). We will also explore whether flavor choice is associated with switching behavior/smoking reductions.

Aim 3: Evaluate the effect of Zyn use on exposure to tobacco harm. Participants will provide repeated samples for biomarker assessments. Hypotheses: We expect that Zyn use will reduce biomarkers of tobacco toxicant exposure (e.g., total NNAL) (Goniewicz et al., 2018) and that these effects will be greatest among participants who switch completely. We will also explore effects of Zyn use on patient-rated health outcomes (e.g., dyspnea, fatigue).

The funding for this study is pilot funding from the Yale Tobacco Center for Regulator Science which is funded by NIDA and the FDA. NIDA and the FDA have been provided with the revised protocol. We have contacted the FDA regarding the need to submit an ITP application to use Zyn pouches.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.
   2 years. We anticipate recruiting and enrolling ~100 subjects to complete the survey and 30 subjects over 12 months to complete the pilot study. We will complete data entry and analysis by the end of year 3.

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Cigarette smoking remains the leading preventable cause of morbidity and mortality worldwide. Though evidence-based interventions are available to help individuals quit smoking, many smokers are either unable to achieve smoking abstinence with these treatments or not interested in quitting smoking (U.S. Department of Health and Human Services, 2020). Thus, novel strategies are needed to reduce the significant health burden of cigarette smoking.

A new generation of nicotine products have emerged as potential-harm reduction alternatives for individuals who smoke cigarettes. These candidate alternate tobacco products include electronic nicotine delivery systems (ENDS), heat-not-burn nicotine products, and oral nicotine pouches. Research findings, limited to ENDS primarily, suggest that harm reduction only occurs for individuals who completely switch to alternate tobacco products from smoking. Nevertheless, there is only moderate evidence that alternate tobacco products can promote complete switching (Eaton, Kwan, & Stratton, 2018). Moreover, there are concerns that inhaled alternate tobacco products are highly addictive and the e-cigarette products may increase risk of developing COVID-19 and EVALI. From industry surveys, we know that tobacco harm reduction is the most common reason consumers report for using these products and cigarette smokers consider them to be a more attractive alternative than e-cigarettes (Plurphanswat, Hughes, Fagerstrom, & Rodu, 2020). While there is limited evidence on the appeal or toxicity of products like the oral nicotine pouches, these products, relative to ENDS, may be lower risk since they are administered orally. To our knowledge, however, no switching studies have been conducted with these new oral nicotine pouches.

The proposed work aligns with the FDA Center for Tobacco Products (CTP) priority of understanding how changes in tobacco products affect their risk-benefit ratio. Data from this study could inform tobacco regulatory efforts regarding establishing limits on nicotine concentration levels and flavor options to facilitate adult smokers switching to alternative tobacco products the potential benefit from switching to these products on biomarkers of harm.

Several factors may affect switching from combustible smoking to alternate tobacco products among smokers including product type and characteristics (e.g., nicotine concentration, flavors). Prior studies of alternate tobacco products for switching and/or cessation in general samples of smokers evaluated older

generation devices which delivered lower nicotine levels compared to combustible cigarettes. New nicotine salt-based alternate tobacco products, such as JUUL, have emerged that may better mimic the nicotine levels achieved from combustible cigarettes (Hajek et al., 2019; Walker, Parag, Verbiest, Laking, Laugesen, & Bullen, 2020). These attributes, along with ease of use, may account for their high popularity among adult cigarette smokers. Likewise, new oral nicotine pouches (e.g., Zyn, On!, Velo) also contain nicotine salts that may yield higher nicotine concentration levels than pharmaceutical oral nicotine products (e.g., nicotine gum, lozenge), potentially increasing their appeal among smokers while reducing exposure to the harmful constituents in tobacco smoke and potential risks associated with vaping products (Erikson, 2020). In addition, there are a variety of flavors that may appeal to adult smokers, but little is known about their preferences.

With the current e-cigarette flavor ban, nicotine pouches may be filling a void for adult smokers seeking to transition from combustible cigarettes to what they perceive to be a less harmful tobacco product (Eriksen, 2020). However, a potential downside of these products is that these same characteristics may also make them appealing to novice/adolescent users. For example, lower nicotine concentration levels may make it easier for youth to initiate use with fewer adverse effects. Therefore, as part of the regulatory equation, it is important to evaluate whether adult smokers can successfully switch to nicotine pouches from combustible cigarettes and the characteristics of the product that facilitate switching.

While one might anticipate that adult smokers prefer to switch to inhaled products, the most common products that they switch to are pharmaceutical nicotine products such as the nicotine patch, lozenge, or gum (Foulds et al., 2009; Jarvis & Sutherland, 2001). Moreover, many adult smokers have concerns about using e-cigarettes, especially following the EVALI epidemic and now COVID-19. A recent survey of patients in the U.S. during the EVALI outbreak found that most patients did not perceive ENDS to be safe; roughly 55% believed that ENDS were less safe than cigarettes (Patel et al., 2020). Likewise, a recent U.K. report of adult smokers suggests that U.S. EVALI cases impacted smokers' perceptions of ENDS' safety (McNeill et al., 2020). The proportion who reported that ENDS use was safer than smoking declined from 45% in 2014 to 34% in 2019.

In contrast, an industry survey of 1,266 ZYN pouch users found that the most popular reason for using ZYN was that ZYN was perceived as "less harmful to my health than other tobacco products" followed by "ease of use" (Plurphanswat, Hughes, Fagerstrom, & Rodu, 2020). Interestingly, 43% of ZYN users were former tobacco users and 60% of them reported that they used ZYN to quit other tobacco use. Current smokers (over 60%) said they used ZYN to help reduce and/or quit tobacco. The same survey also recruited a consumer panel of 5,179 Zyn-naïve users. Among the subsample of exclusive cigarette smokers in this panel, the likelihood of buying NRT was the highest followed by Zyn and then e-cigarettes suggesting that Zyn is a more attractive alternative than e-cigarettes for current smokers (Plurphanswat, Hughes, Fagerstrom, & Rodu, 2020).

To address this gap, we propose to conduct a preliminary study of Zyn nicotine pouches, the most popular oral nicotine pouch, in 30 adult cigarette smokers who decline smoking cessation services but are willing to try Zyn. Subjects will receive Zyn pouches to use for 4 weeks. Participants will be randomly assigned to receive Zyn pouches with 1 of 2 nicotine concentrations (3mg, 6mg) and will be asked to select two flavors (i.e., unflavored, mint, cinnamon, coffee, citrus) to try at the first visit. At the end of the first week, participants will select a single flavor from among these flavors to use going forward but may change at a later appointment if desired. We will encourage participants to switch to Zyn use in place of smoking. We will examine the effects of nicotine concentration on Zyn use, participant characteristics associated with switching, and biomarkers of harm-reduction. We will also monitor use of flavors. Like the JUUL product, these pouches are derived from nicotine salts and accordingly, may provide deliver a dose of nicotine that better approximates the levels individuals achieve from smoking. The pouches, however, have additional advantages over the JUUL. Due to oral administration, there are fewer concerns about potential pulmonary effects and the rate of absorption and action for nicotine is slower which may reduce its addiction liability.

Because nicotine pouches are not inhaled products, they do not carry the same COVID-19 risks that e-cigarettes may have and would be more acceptable for use in smokers with other co-morbid health conditions. We will use Zyn pouches, the most popular brand in the U.S. according to Nielsen ratings. Zyn pouches come in different nicotine concentrations and flavors so we will still be able to evaluate the effect of nicotine dose on the likelihood of switching as well as participants' flavor preferences and the potential association between flavors and switching.

The current study will add to the literature by assessing the motivation to quit among current smokers (n=100) and obtaining survey information about their perceptions and willingness to use various tobacco products (Part One). This study will also evaluate the effect of switching from a cigarette to an oral nicotine pouch product on exposure to tobacco-related harm (Part Two). The pilot switching study will also assess use patterns and subjective effects to evaluate the feasibility and acceptability of switching from cigarettes to a Zyn pouch product among daily adult smokers. Sales of oral pouches have increased substantially in the last year. The 1-year percent change in sales for the 52 weeks ending in 7/12/20 was 77.1% (Eriksen, 2020) suggesting that these are attractive products. Moreover, nicotine oral pouches have the potential to assist adult smokers who want to transition off cigarettes or other tobacco products. Nicotine pouches come in a range of nicotine concentrations and flavors. Unlike smokeless tobacco, these products do not require spitting. All these features may be appealing to adult smokers. For example, the On! nicotine pouch has 5 nicotine concentrations (1, 2, 3, 4, 8 mg) and 7 flavors (original, berry, coffee, citrus, mint, wintergreen). The maximum approved nicotine dose for pharmaceutical nicotine gum and lozenge is 4mg and underdosing is commonly cited as a reason for the limited efficacy of these cessation aids (Plurphanswat, Hughes, Fagerstrom, & Rodu, 2020). Nicotine pouches, like e-cigarettes, are consumer products so manufacturers cannot make claims regarding cessation and/or health (Plurphanswat, Hughes, Fagerstrom, & Rodu, 2020) and the nicotine concentration levels of these products are not restricted currently by the FDA.

Overall, the results will provide novel information on the tobacco use preferences and interests among cigarette smokers as well as how a specific oral nicotine pouch product (i.e., Zyn pouch) may influence smoking satisfaction and behavior and affect exposure to harm among current smokers who are not interested in quitting smoking. The FDA could use these results to inform product standards and to predict the effects of switching to an oral nicotine pouch product among current cigarette smokers. Additionally, the results will inform future study designs by evaluating the feasibility of an oral nicotine pouch switching paradigm. Lastly, this data could inform tobacco regulatory efforts regarding establishing limits on nicotine concentration levels and flavor options to facilitate adult smokers switching to alternative tobacco products but reduce the appeal of these products among youth.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Overview:
The goals of this study are to provide novel information on the tobacco use preferences and interests among cigarette smokers as well as how a specific oral nicotine pouch product (i.e., Zyn) may influence smoking satisfaction and behavior and affect exposure to harm. In Part One, we will conduct a survey of 100 current smokers to ascertain their interest in switching to several possible non-combustible tobacco products (e.g., various e-cigarettes, snus) and/or pharmaceutical nicotine (i.e., nicotine replacement therapy). There is no link between participants completing part one and part two of the study. In Part Two, we will conduct a pilot study of up to 30 non-treatment-seeking adult smokers to investigate within-person changes in smoking behavior when current cigarette smokers are switched to using a new oral nicotine product, i.e., Zyn.

Through random assignment, participants will receive Zyn pouches with 1 of 2 nicotine concentrations (3mg,

6mg) and will be asked to select two flavors (i.e., unflavored, cool mint, spearmint, wintergreen, peppermint, cinnamon, coffee, citrus) to try at the first visit. At the end of the first week, participants will select a single flavor from among these flavors to use going forward but may change at a later appointment if desired. Participants will receive 8 cans per week of Zyn pouches to use throughout the course of the study. A label will be affixed on each Zyn can that states “use of this product is investigational for the purposes of Yale Study #2000023826”.

We will recruit adults who currently smoke cigarettes but are not interested in quitting smoking. We will provide participants with Zyn pouches to use instead of cigarettes for 4 weeks and will track smoking behavior, Zyn use, and changes in biomarkers. At the end of 4 weeks, we will assess patient interest in quitting smoking, level of nicotine dependence, as well as intentions to continue Zyn use. Participants will be encouraged to quit smoking and, if interested, will be provided standard smoking cessation counseling through the Tobacco Treatment Service. We will conduct a follow-up assessment one month after the end of the study to evaluate smoking status, including Zyn use.

Settings: Participants will be recruited from Yale-New Haven Hospital and through the community using social media. We will recruit current smokers in different clinical settings across Yale-New Haven Hospital, including Tobacco Treatment Service.

Procedures:

Part One: Survey
At the time of screening potential participants for their interest in participating in one of our tobacco treatment interventions, all current smokers will be invited to complete this brief, anonymous, one- time survey to collect their demographic information and interest in switching to several possible non-combustible tobacco products (e.g., various e-cigarette devices, snus) and/or pharmaceutical nicotine (i.e., nicotine replacement therapy). The surveys will be conducted in Qualtrics, Redcap, or paper-and-pencil format. Patients may complete this survey either in a private area of the waiting room or in an exam room.

Part Two: Zyn switching pilot study
Screening: We will conduct a pilot study of up to 30 non-treatment-seeking adult smokers to investigate within-person changes in smoking behavior when current cigarette smokers are switched to using a new oral nicotine product, i.e., Zyn. We will recruit adults who currently smoke cigarettes who indicate that they are not planning on using an evidence-based quit method in the next month, and who express a willingness to try an oral nicotine pouch as a means to replace their use of cigarettes. Interested participants will be invited to attend a baseline/screening visit to determine eligibility and sign written informed consent.
To reduce participant burden, we plan to meet with participants at a convenient location to randomize them to their study assignment. We will do a health questionnaire at baseline and at each visit to monitor for any changes during exposure to oral nicotine pouches.

All research staff and research participants will be screened for COVID-19 symptoms prior to entry into CMHC. These include: fever of 99.9°F or higher, cough, shortness of breath/difficulty breathing, fatigue, repeated shaking with chills, muscle pain or body aches, chills, headache, sore throat, new loss of taste or smell, congestion or runny nose, nausea or vomiting, or diarrhea. Research staff and research participants must additionally affirm that they have not been in close proximity to anyone who is experiencing symptoms, or who have tested positive for COVID-19, within 14 days of a scheduled in-person visit. Research staff and research participants will indicate whether they have traveled anywhere outside of Connecticut within 14 days prior to a scheduled in-person visit. Current Connecticut state guidance on quarantine requirements for those traveling into Connecticut from other states in the USA, or internationally, will be observed.

Randomization: Eligible participants will be invited to participate in the 8-week study. We will meet with participants at a convenient location to provide them with the Zyn pouches, containing either 3mg or 6mg nicotine concentration based on random assignment.

Randomization will be stratified by gender (male/female) and nicotine dependence level using a time to first cigarette metric based on a 30-minute cutoff (i.e., within 30 minutes or after 30 minutes of waking).

4-week Switching Period and Follow-up: At the end of the first week, they will be asked to select a single flavor from among these flavors to use going forward. We will provide participants with their preferred flavor pouches at this point. Participants will be given 8 cans of Zyn pouches per week to use throughout the switching period of this study. Participants will be told that they should not be using more than one can (15 pouches) per day during the switching period. Participants will be given the opportunity to change flavors again if they so choose. Participants will be encouraged to use the Zyn pouches instead of their usual cigarettes.
Participants will return at week 4 to complete a CO test if they report complete switching only. Participants will be asked to return any unused Zyn pouches to track consumption through the 4-week trial. We will assess smoking behavior and biomarkers of tobacco exposure for 4 weeks, with a follow-up at 8 weeks to evaluate smoking status.

We will collect CO readings at baseline, week 4, and week 8 (only if a participant reports complete switching) to assess smoking status. A CO reading ≤4ppm will confirm exclusive use of the Zyn product (vs. cigarettes). Participants will also provide urine samples at baseline and week 4 to examine biomarkers of tobacco exposure, including nicotine/cotinine levels, and patient-rated health outcomes. Participants will rate their satisfaction with the Zyn pouches and report how it compares to their usual cigarette brand. Participants will also be asked to indicate how likely they would be to continue using the product compared to their usual cigarette brand. We will evaluate feasibility by reviewing how many participants switch completely to Zyn pouches during the 4-week switching period.

Screening Assessments: We will recruit adults (21-77 years old) who currently smoke cigarettes daily but are not planning on using evidence-based cessation treatments in the next month. To screen for eligibility, participants will complete several assessments: 1) demographic information, 2) smoking history and a timeline-follow-back interview to assess tobacco use including smoking quantity and frequency such as number of cigarettes per day and number of years smoked, 3) expired breath carbon monoxide (CO) measured in parts per million to confirm baseline smoking status , 4) a urine sample for pregnancy testing, 5) ‘assessment of health problems’ health questionnaire and 6) a cardiovascular risk screening to rule out high-risk participants with unstable cardiac history

In addition, all research staff and research participants will be screened for COVID-19 symptoms prior to entry into CMHC. These include: fever of 99.9°F or higher, cough, shortness of breath/difficulty breathing, fatigue, repeated shaking with chills, muscle pain or body aches, chills, headache, sore throat, new loss of taste or smell, congestion or runny nose, nausea or vomiting, or diarrhea. Research staff and research participants must additionally affirm that they have not been in close proximity to anyone who is experiencing symptoms, or who have tested positive for COVID-19, within 14 days of a scheduled in-person visit. Research staff and research participants will indicate whether they have traveled anywhere outside of Connecticut within 14 days prior to a scheduled in-person visit. Current Connecticut state guidance on quarantine requirements for those traveling into Connecticut from other states in the USA, or internationally, will be observed.

Visit Assessments (Baseline, Week 4, Follow-up Week 8): Eligible individuals will complete self-report assessments at baseline and subsequent research visits.

Measures of smoking consumption (Baseline, Week 4, Follow-up Week 8): Timeline Follow-Back Interview

(TLFB) (Sobell & Sobell, 1995, 2003): A standardized, validated, and reliable interview will be used to obtain quantity and frequency estimates of tobacco use for the 30-days prior to baseline and at each research visit. We will also have participants report tobacco use patterns (e.g., places where tobacco use occurs in their daily life) to examine changes in tobacco use patterns during the 4-week switching period and during the one-month follow-up period. TLFB will be used to assess daily cigarette use and Zyn pouch use during the trial.

Measures of dependence, withdrawal, and craving (Baseline, Week 4, Week 8):

Craving: Measured by the Questionnaire of Smoking Urges-Brief(Cox, Tiffany, & Christen, 2001) (QSU-Brief).

Nicotine Dependence: Measured by the Fagerström Test for Nicotine Dependence(Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), the 4-item NIH PROMIS® measure for daily smokers (Shadel et al., 2014), and a 4-item PROMIS measure adapted for use with alternate tobacco products (Morean et al., 2018) to assess their reactions to Zyn use at week 4 and week 8, the 8-item Adapted Dependence Measure for Oral Nicotine Pouch (Mushtaq et al., 2020), and the 37-item Wisconsin Inventory of Smoking Dependence Motives (Brief WISDM) (Smith et al., 2010).

Nicotine Withdrawal: Measured by the Minnesota Nicotine Withdrawal Scale (MNWS), an 8-item scale assesses current symptoms of nicotine withdrawal including cravings and irritability (John R Hughes & Hatsukami, 1986).

Measures of subjective effects of cigarettes and Zyn product (Baseline, Week 4): Participants will report on subjective evaluation about cigarettes and the Zyn product to evaluate how Zyn pouches compare to their usual cigarette brand. At the end of the study, participants will also be asked to indicate how likely they would be to continue using the Zyn pouch compared to their usual cigarette brand. Subjective evaluation includes items derived from the Modified Cigarette Evaluation Scale (mCEQ, (Cappelleri et al., 2007) adapted for alternate tobacco products, which measures the degree to which participants experience reinforcing effects from Zyn pouches. The scale yields five clusters or domains: Smoking Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Craving Reduction.

Measures for flavor preference (Baseline, Week 4, Week 8): Participants will report on measures that have been used by the TCORS center at Yale to measure their use of and reactions to flavored tobacco products including: a 48-item measure to assess general flavor preference using a Likert scale ranging from 0 (strongly dislike) to 10 (strongly like), a 12-item measure that assess flavor preference for tobacco products and the reason for using these flavored products and an adapted 20-item measure evaluating their preference to pouch flavors using a Likert scale ranging from 0 (not at all) to 10 (extremely).

Measures of patient-rated health outcomes (Baseline, Week 4): Participants will complete standardized PROMIS measures of health outcomes often affected by cigarette smoking including:
Physical Function and Mobility (Rose et al., 2014), Fatigue (Cella et al., 2016), and Dyspnea (Irwin et al., 2015). They will also complete a single item from the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to assess for cough.

Biological Measures (Baseline, Week 4, 8): Expired breath carbon monoxide (CO) will be measured at baseline Week 4, and week 8) to evaluate smoking status (CO≤4ppm confirms self-reported abstinence from cigarettes). Urine samples will be collected at baseline and week 4 to track nicotine/cotinine levels and exposure to toxicants from tobacco use including tobacco-specific nitrosamines (TSNAs) such as NNAL (Chang et al., 2016). Samples will be assayed by Dr. Irina Stepanov from the University of Minnesota. Dr. Stepanov will not have access to participant PHI, only Study ID number and date of collection. Samples will be disposed of after assays are completed.

Standard procedures for biological sample collection:
Collection of breath samples: Expired breath samples will be collected to measure carbon monoxide, a marker of tobacco exposure. Participants are asked to breath out through a tube.

The procedures for collecting a CO breath test while maintaining social distancing guidelines during COVID-19 are listed below. The participant will be asked to wear a face covering at all times except when performing the breath test. A minimum of 6 feet of physical distancing will always be maintained.

1. The research assistant (RA) will wear the appropriate PPE (gloves, face mask and safety glasses/goggles).
2. The RA will explain the CO breath test to the participant.
3. While wearing proper PPE, the RA will place a new straw into the CO device. The straw will be unwrapped, except for the upper portion (approximately 2-3 inches).
4. The RA will verify the participant is ready. Once confirmed, the RA will turn on the device and place it on a surface (i.e. table, bench, ground) that still maintains physical distancing of at least 6 feet. The RA will also place a bottle of hand sanitizer next to the device. The RA will then move away from the device to allow the participant to move forward.
5. The participant will be instructed to use the hand sanitizer and allow it to dry briefly before handling the device. Once the participant's hands have been sanitized, the RA will instruct the participant to collect the device.
6. Once the participant has the device, he/she will remove the remaining paper from the straw. The RA will then instruct the participant how to begin the CO test.
7. Before the participant begins the test, he/she will have the opportunity to ask any questions. After the RA has successfully answered any questions, the participant will begin the test.
8. While performing the test, the participant will remove their face covering and will angle his/her body away from the RA before blowing into the device. The test will be conducted in an open space to minimize any possible exposure to COVID-19.
9. After the test is conducted, the participant will remove the straw from the device and place the monitor back on the surface. The participant will be asked to dispose of the straw themselves. The participant will then be instructed to use hand sanitizer. Once hands have been sanitized and the device is back on the surface, the participant will move backwards to maintain physical distancing while the RA collects the device.
10. The RA will place the used device in an air-tight bag while donning proper PPE. This device will not be removed from the bag for a minimum of 3 days.
11. The RA will wipe down the hand sanitizer bottle and anything else the patient has handled (e.g. pens) with a disinfecting wipe.
12. After a minimum of three days has passed, the RA will disinfect the device with special disinfecting wipes made by the CO device manufacturer.

Collection of urine samples: Urine samples will be collected by trained research staff. Participants will be instructed to void urine into a sterile 120-mL urine container. The sample will be aliquoted into 5-mL cryogenic polyphropylene tubes and labeled with a repository label. Urine aliquots will be stored at -20˚C. Samples will be shipped to Dr. Irina Stepanov following standardized procedures recommended by her to ensure the integrity of the samples.

Weekly Phone Safety Monitoring (in-between study visits): We will contact participants by phone each week to assess their experience using the Zyn pouches including any adverse events.

For additional monitoring during the course of the study: Participants will be asked to report any changes in their health, and trained research staff will administer a health symptom checklist at intake and each subsequent visit to monitor any changes in health status from baseline including headache, dizziness, fainting, gastrointestinal problems (i.e., nausea, vomiting, diarrhea, appetite changes, weight loss, abdominal pain), cardiovascular problems (i.e., rapid heartbeat, chest pain), respiratory problems (i.e., shortness of breath, coughing), signs of infection (i.e., sore throat, fever, sweating, fatigue), or other problems such as sleep disturbance (i.e., vivid dreams, difficulty sleeping), vision problems, and itching/rash. Symptoms will be rated on severity based on functional impairment as either mild (e.g., minimal disruption to

daily living), moderate (e.g., some limitation or disruption to instrumental activities of daily living), or severe (e.g., severe limitation or disruption of instrumental or self-care activities of daily living). Participants will be monitored for any changes in these symptoms. The study physician will be alerted to any severe problems that develop and will make a determination about whether further medical evaluation is needed.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

Participants: We will recruit current adult (21-77 years old) daily smokers from Yale-New Haven Hospital and from the community using social media and posting flyers. We will recruit current smokers across a variety of clinical settings in Yale-New Haven Hospital, including Tobacco Treatment Service. Patients currently enrolled in the Tobacco Treatment Service who are not responding to treatment and do not want to quit imminently can be referred to this study. In this case, both the patient and the clinician must find it appropriate to cease traditional tobacco services for participation in our alternative nicotine product use study. At the completion of the study, these participants will be referred back to the Tobacco Treatment Service if they wish to seek more assistance with smoking cessation. All participants will receive a list of potential cessation resources, or a referral to TTS if they wish, upon the completion of the study. Part One: Survey: Patients seen by the Tobacco Treatment Team who indicate that they are currently smoking cigarettes will be eligible to complete the brief, anonymous survey. We aim to recruit 100 patients to complete the survey. There is no link between participants completing part one and part two of the study. Part Two: Pilot study: We will recruit 30 non-treatment seeking cigarette smokers to participate in a pilot study to evaluate the acceptability and feasibility of switching to a Zyn nicotine pouch product from cigarettes as well as the preliminary effects of Zyn use on smoking behavior and exposure to tobacco-related harm.

Justification for enrolling patients from the Tobacco Treatment Service: The Tobacco Treatment Service accepts tobacco users from across the stages of behavior change. When patients are referred to the Tobacco Treatment Service by a provider or seeking services out of their own initiation, many patients do not have a set plan, or even a desire to quit using their desired source of tobacco. In order to help us better asses which patients may benefit from the study; Dr. Fucito and the Tobacco Treatment Service team recently developed a triage system for new patients seeking the Service. Referred patients can be categorized into one of three groups as determined by a series of questions that they are asked during the initial phone call with the Service Coordinator: A) patients who need to show up for tobacco treatment because they were medically mandated by their treatment team (e.g., surgical candidate); B) patients who want to show up for tobacco treatment because they may have health and/or other personal reasons for quitting and are willing to make a commitment to standard tobacco cessation treatment; and C) patients who do not have a medical mandate for treatment and/or are not willing to make a commitment for standard tobacco cessation treatment. Patients in category C will be given the option to be connected to this study or external resources. The service not only works with patients who are trying to actively quit using tobacco products , but also those who want to reduce their harm or want to cut down on the amount that they are currently using. Many patients in this latter group attend multiple sessions without making changes. Patients who are not making progress in the service (with at least 4 weeks of treatment) or determine that they no longer want to quit smoking can be referred for participation in the study, with agreement from both their Tobacco Treatment Service clinician and the patient. These patients will have to meet all required eligibility criteria for the study including no longer being treated by the providers in the service for the duration of the study and receiving standard tobacco cessation pharmacotherapies. However, if at any point during the study the patient indicates that they would like to quit smoking, participation will be ceased, and the patient will be referred back to the service for standard cessation treatment.

Justification for using smokers with no set plan to quit smoking: Based on ethical considerations, only smokers who have no set plan to quit smoking will be studied in a drug paradigm where smokers are given an opportunity to self-administer a nicotine-containing product. Most patients coming in for lung cancer screening and many other patients referred to the Tobacco Treatment Service do not currently have a plan for quitting smoking.
Individuals who express an interest in quitting smoking during the study will be provided with appropriate referrals for treatment at the Tobacco Treatment Service.
Switching to use of a Zyn product containing nicotine conveys minimal risk to an individual who is already a daily user of cigarettes. All participants will be able to self-titrate, meaning smoking and Zyn pouch use will be self-directed by the participant.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

(1) 21-77 years old (in line with NIH guidelines for 18+ being the age of consent in adults) (2008 PHS Guideline Update Panel)
(2) English literate
(3) Smoke at least 1 cigarette per day
(4) Not currently actively pursuing smoking cessation services or planning to use evidence-based cessation tools to quit in the next month
(5) Not interested in the use of existing FDA-approved tobacco pharmacotherapies (i.e., NRT, wellbutrin, varenicline) within the next month

Exclusion Criteria:

(1) Currently using any stop smoking treatments
(2008 PHS Guideline Update Panel)
(2) History of serious psychiatric condition (i.e., bipolar disorder, schizophrenia)
(3) Current uncontrolled medical condition
(4) Cardiac conditions that required a hospitalization or intensive treatment on an outpatient basis in the past year including: myocardial infarction, coronary artery disease, unstable angina, congestive heart failure, or tachyarrhythmias (including rapid atrial fibrillation, ventricular tachycardia, or ventricular fibrillation), as well as those with serious arrhythmias, those with serious or worsening angina pectoris, and those in the immediate (within 2 weeks) post myocardial infraction period.
(5) Female participants of child-bearing age will be excluded if they are currently pregnant or breastfeeding or report an unwillingness to use effective birth control (i.e., abstinence, IUD, implant, sterilization, pill, patch, ring, or barrier method such as condoms) for the duration of the study
(6) Planning to quit smoking with a set goal or time for quit attempt

9. How will **eligibility** be determined, and by whom? Write here

Interested participants will be provided with verbal information about the project. Interested participants will be initially screened by telephone or webscreener and will provide their name and contact information and provide answers to short screening questions to assess age, smoking status, and to ensure they are not currently seeking smoking cessation treatment. Upon speaking with patients from medical clinics or from the community, we will confirm final medical suitability with the patient's care team consistent with the protocol we currently use for patients who present for lung cancer screening as part of tobacco study (HIC#1608018181). In this other study, we review their medical status and suitability for nicotine replacement therapy with the advanced practice nurse who runs the screening clinic and oversees their care. Participants who meet initial eligibility screening will be invited to complete an intake session over the phone or video conference. During the intake session, participants will complete an informed consent form via RedCap link. Following this, a research assistant will obtain medical and substance use histories. The remote intake will include additional screening questionnaires and a detailed health interview. All research staff and research participants will be screened for COVID-19 symptoms prior to entry into CMHC. These include: fever of 99.9°F or higher, cough, shortness of breath/difficulty breathing, fatigue, repeated shaking with chills, muscle pain or body aches, chills, headache, sore throat, new loss of taste or smell, congestion or runny nose, nausea or vomiting, or diarrhea. Research staff and research participants must additionally affirm that they have not been in close proximity to anyone who is experiencing symptoms, or who have tested positive for COVID- 19, within 14 days of a scheduled in-person visit. Research staff and research participants will indicate whether they have traveled anywhere outside of Connecticut within 14 days prior to a scheduled in-person visit. Current Connecticut state guidance on quarantine requirements for those traveling into Connecticut from other states in the USA, or internationally, will be observed. Following this, the potential participants will be invited to come in or to meet at a convenient location for urine pregnancy tests, and breath CO levels. If study criteria are met, the participant will be scheduled for the subsequent sessions.

5. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

A detailed description of risks is provided below.

Breath and urine collections: All assays will be performed by appropriately trained research staff during the screening and all subsequent research visits. Breath screening and urine collections should add no risks other than those normally associated with these procedures. Breath screening involves blowing out through a tube. The precautions taken in light of COVID-19 are listed above under "collection of breath samples." Participants will collect a urine sample for a pregnancy test.

Rating Scales and Assessments: These are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. We have done our best to make the assessment schedule in this study as brief as possible. Also, our past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality will be made, as described below.

Use of cigarettes and oral nicotine pouch (Zyn): The risks of using the Zyn oral nicotine pouch are minimal and similar to oral nicotine replacement therapy (such as salivation, nausea, and dyspepsia). All nicotine pouch consumption will be self- directed by the participant in their normal every day environment.

There is the potential for nicotine overdose. Cigarette smokers titrate their cigarette use to adjust their nicotine levels. Subjects will determine how much they prefer to use the Zyn pouches to adjust their nicotine levels. Common symptoms of nicotine toxicity include the following: nausea, dizziness, headache, increased

heart rate or palpitations, tremor. However, current evidence in cigarette smokers who are dual users of other tobacco products indicates that this risk of nicotine toxicity is very low. We will advise participants of this potential risk and to reduce their use if they are taking in too much. This approach has parallels to the approach for recommending use of combination nicotine replacement therapy (i.e., patch + lozenge) in which we advise users of these symptoms and advise them to call us if they happen.

Smoking during pregnancy may be associated with increased risk for spontaneous abortion, increased perinatal mortality, and low infant birth weights. We will exclude females who are pregnant or nursing from this study.

Finally, we will provide a list of smoking cessation resources to participants at the end of the 4-week switching period. Any participants who indicate that they would like to quit smoking at any point before the end of the study will be discontinued from the Zyn switching protocol and provided a referral for treatment. We will closely monitor adverse events, and if participants experience adverse effects of nicotine (e.g., nausea, headache, vomiting), we will recommend that they cut back on their intake of nicotine. Dual use of cigarettes and Zyn pouches will be discouraged as participants will be instructed to switch to the Zyn pouches completely.

Risks will be minimized in several ways. Subjects can stop and withdraw from the study at any time. Participants self-administer the Zyn pouches, allowing them to change their dosage as they feel necessary, with a limit of 15 pouches per day. We will provide information to them about the potential risks of Zyn pouches, as well as use instructions, so they are more informed. All participants, especially those who are light/mild smokers, will be advised of the early signs of nicotine side effects and toxicities, and will be advised on what they should do if these symptoms do arise. Since self-reported signs and symptoms are most likely to identify health changes, baseline and ongoing monitoring of self-reported signs and symptoms of nicotine overdose will be done at each appointment. We will do a health questionnaire at baseline to monitor for any changes during exposure to the Zyn pouch. A movement in symptoms to severe will require physician review.
Positive findings of a change in symptom or single severe symptom would trigger clinical referral to the treating physician or ED. Additionally, participants will be asked to inform research staff of all prescription medications that they are taking. For any patients taking medications shown to interact with tobacco smoke, such as medications for depression or asthma, we will advise them that changes in their tobacco smoking or use of the oral nicotine pouch may alter the effectiveness of their medications, and that they should monitor themselves for any changes in addition to our regular monitoring. We will also suggest that they consult their physicians or pharmacists before using these pouches.

Participants will be recommended for clinical treatment including a CT/Chest CT X-ray based on recommendation from the study physician. This treatment will be coordinated for them, but they will be responsible for the cost.
Additional steps we will take to reduce risks associated with Zyn pouch use include:

1. Providing specific instructions to participants about how to use the products
2. Providing participants with instructions on nicotine overdose and what to do if they are experiencing nicotine overdose
3. Dr. Steve Baldassarri, a pulmonologist on the study team and will review subject eligibility and ongoing participation.
4. Weekly monitoring for adverse events including nicotine overdose
5. The study will be followed by the TCORS Data Safety Monitoring Board
6. We will perform an interim safety analysis to review adverse events

Loss of Confidentiality: Participants will be providing sensitive information, including their smoking, alcohol, and drug use behaviors. There are potential risks to subjects if such information were to be made public.

Several procedures will help reduce the risk of disclosure of sensitive information, described in detail below.

Limits to Confidentiality: Participants will be informed that we will aim to protect their confidentiality and not reveal any personal information collected as part of the research procedures, including their reported smoking and other substance use history. All personnel to be involved in this study are already or will be certified by the Yale Human Investigation Committee (HIC) as having completed training in the protection of the rights of human subjects who participate in research. However, participants will be informed that if they report any information to us about child abuse or homicidal/suicidal behavior, we will be required to report this information to the appropriate authorities.

Female subjects of childbearing potential will require urine pregnancy testing prior to enrollment in the protocol. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, women who would not be comfortable with pregnancy testing or the sharing of such testing results can “opt out” of the study at the time of the initial consent, without having to declare specific reasons.

These limits to confidentiality will be clearly stipulated in the consent form.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

The investigators are trained regarding proper guidelines for ethical human research, and they will ensure that all research activities are in full compliance. All research subjects will be competent adults who willingly provide their written agreement to participate prior to research participation during a formal informed consent process. A copy of the signed consent form will be provided to all subjects. All participants will be assured that research participation is voluntary, and that even after enrollment, they are free to discontinue without penalty at any point during the study. The investigative team has decades of clinical research experience with human subjects, including conducting similar study procedures in individuals with nicotine dependence and other substance use disorders.

Specific protections against risks include:

1. All personnel to be involved in this study are already or will be certified by the Yale Human Investigation Committee (HIC) as having completed training in the protection of the rights of human subjects who participate in research.

2. Inclusion and exclusion criteria and the use of trained research staff will help to avoid the enrollment of subjects into this study who are either ineligible or who would be at greater risk for complications because of uncontrolled psychiatric, or medical illnesses.

3. All patient interactions will be conducted in areas that are as private as possible in the clinic space of the Yale New Haven Hospital system or from remote locations.

4. Confidentiality of sensitive information will be accomplished by assigning unique numeric identifiers to each subject, and exclusively using these numbers on all paper and electronic data records which contain sensitive information. All identifying information will be maintained in a separate locked file. Paper data files will be maintained in secure filing cabinets in a locked office. Electronic data files will be stored on password-protected, encrypted computers. No reports will identify specific subjects, and only aggregate data will be used in all reports. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996.

5. Any identifiable information that is obtained in connection with this study will be disclosed only with subject permission or as required by U.S. or State law. Individually identifiable health information will be

protected in accordance with the Health Insurance Portability and Accountability Act of 1996. We will clearly explain our mandated obligation to report incidents, including suspicion of child or elder abuse or neglect, threats of harm to self and others. Data will only be reported in aggregate. During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data but will strictly adhere to the rules of confidentiality. Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the Project Director, until they are destroyed, after all analyses are complete and after the federal requisite waiting period (7 years) to maintain records. Any information published as a result of the study will be such that it will not permit identification of any subject.

6. Protection of health-related information collected via RedCap: Participants will be able to access the secure survey administered through the Yale RedCap program through their phone internet browser or computer. These survey forms will only include the subjects' unique numeric identifiers, which are assigned to the subject at the time of enrollment. A file linking subjects' name to unique numeric identifiers will be kept in a separate locked file to which only study researchers will have access.

Data and Safety Monitoring Plan:

a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
Greater than minimal risk

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB, or Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

The potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by Dr. Fucito according to the following categories:
a.) Definite: Adverse event is clearly related to investigational agent/participation. b.) Probable: Adverse event is likely related to investigational agent/participation. c.) Possible: Adverse event may be related to investigational agent/participation.
d.) Unlikely: Adverse event is likely not to be related to the investigational agent/participation. e.) Unrelated: Adverse event is clearly not related to investigational agent/participation.

The following scale will be used in grading the severity of adverse events noted during the study:
1 Mild adverse event
2 Moderate adverse event
3 Severe

In addition to grading the adverse event, Dr. Fucito and the study team will determine whether the adverse

event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:
1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
   The study team will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent form are needed. Subjects will be closely monitored for safety throughout the research trial. Although in our experience this is a very rare event, subjects who show significant deterioration (e.g., increased substance use or psychiatric symptoms, including significant suicidal or homicidal ideation), will be withdrawn from the study and referred for appropriate treatment.

At any point if the investigator feels that subjects' health or well-being may be threatened by continuation in the study, subjects will be withdrawn from the study. If participants have a medical emergency, they will be instructed to call 911. Subjects who experience a significant psychiatric or medical problem that requires overnight hospitalization at an acute care facility will be considered to have experienced an SAE.

The Principal Investigator, Dr. Fucito, will report the following types of events to the IRB: Any incident, experience or outcome that meets ALL 3 of the following criteria:
1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied;AND
2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known orrecognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non- medical in nature and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects.

These adverse events meeting the criteria for unanticipated problems involving risks to subjects or others will be reported to the Yale HIC within 5 days of it becoming known to Dr. Fucito. The procedures for SAE reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Communication of recommendations and decisions from all parties (Yale Human Investigation Committee) will be made back to Dr. Fucito in a timely manner.

i. What provisions are in place for management of interim results?

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator and the Institutional Review Board have the authority to stop or suspend the study or require modifications. (Osei et al.)

ii. What will the multi-site process be for protocol modifications? N/A this is a single-sitestudy

2. Statistical Considerations: Describe the statistical analyses that support the study design.

Data analyses will be conducted with SPSS software. Effect size estimates with 95% confidence intervals will be constructed for each aim to inform future studies. In Part One, we will use descriptive statistics to characterize responses to survey items about smokers' interest in switching to an e-cigarette device compared to other non-combustible tobacco products (e.g., smokeless tobacco/snus) and/or pharmaceutical nicotine (i.e., nicotine replacement therapy). We will examine whether cigarette smokers' interest in using these products may vary by: (1) demographic characteristics, (2008 PHS Guideline Update Panel) tobacco use variables and smoking-related characteristics, and/or (3) smokers' perceptions of these products/medications. In Part Two, we will conduct a pilot study in which current cigarette smokers are switched to using a Zyn pouch. A sample size of 30 for the Zyn switching protocol (15 randomized to 6mg nicotine concentration pouches and 15 randomized to 3mg nicotine concentration pouches) was determined to test the feasibility and acceptability of the Zyn pouch and to estimate effect sizes to inform the optimal sample size for a larger follow-up study. The primary statistical analyses will evaluate between-group differences in cigarette smoking and Zyn pouch use over the 4-week period. We will also evaluate changes in biomarkers of tobacco exposure from baseline to the end of the 4-week period switching to the Zyn product.

Data Monitoring**:** Procedures for data collection, data management, monitoring of data quality and data analysis have been developed and refined in our previous tobacco studies. An experienced data analyst and the PI will supervise these procedures which include use of a computerized database to monitor research activities, screening and enrollment, compliance with protocol, completion of scheduled assessments, and data retrieval. Data quality will be ensured by: 1) extensive training/supervision of research staff in data collection; 2) preliminary review of all assessment instruments prior to data entry and checks for completeness and coding errors; 3) double data entry of written assessment instruments; 4) error-checking statistical programs.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS,

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS / tobacco products ☐ N/A

We will be providing participants with a Zyn nicotine pouch. . Participants will be provided either the 3mg or 6mg nicotine strength Zyn pouches and will be asked to select two flavors (i.e., unflavored, mint, cinnamon, coffee, citrus) to try at the first visit. We have contacted the FDA to determine whether an IND is required. We are evaluating behavioral responses to using the Zyn pouches and are not using the Zyn pouches for purposes of treatment or smoking cessation. This research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks associated with the use of the drug product. No other nicotine or tobacco products will be distributed to participants.

The TCORS core lab will analyze the chemical makeup of the Zyn pouches to be sure what chemicals are present and to assure consistency of the products under study We will take 4 oral nicotine pouches in 3mg and 6mg nicotine concentrations in different flavors to evaluate their chemical makeup.

B. DEVICES ☒N/A See above under tobacco products.

a)

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 100 for part one survey; 30 for part two Zyn pilot
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrials.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

Describe how potential subjects will be identified. Potential subjects will be identified through Tobacco Treatment Service at Yale New Haven Hospital as well as other clinics in Yale-New Haven Hospital. In addition, potential subjects will be identified by responses to community-based advertisements.

a. Describe how potential subjects are contacted.

The Tobacco Treatment team is available for patient consultation at Yale New Haven Hospital. We will recruit current smokers to complete the anonymous survey. We will recruit current smokers for the Zyn pilot study who express that they are not currently interested in quitting smoking when they are approached by the Tobacco Treatment Team or physicians and their support staff during medical appointments or if they contact us after seeing community-based advertisements. There is no link between subjects completing the anonymous survey and those completing the pilot study.

b. Who is recruiting potential subjects? The PI and research staff will recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☐ Yes, some of the subjects

☒ No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: We request a waiver of signed authorization for part one, for participants to complete an anonymous survey. Participants will receive an information sheet indicating the purpose of the survey, that the survey is voluntary and anonymous, and they will be told that their answers will not impact their relationship with the clinic or healthcare provider. We request a waiver of signed authorization for part two, for the pilot study, only for initial participant recruitment/screening purposes to obtain interested participants' phone numbers and/or email for voice and text communication to make initial contact with the research team. At the first phone contact with the research team, participants will provide verbal consent for the screening process. Participants who see community-based advertisements will be invited to complete a

webscreener to assess potential eligibility. On the webscreener, participants will click yes or no to consent to completing the survey. Participants in both the phone screen and

webscreen will be asked to provide brief demographic information and smoking status information to determine initial eligibility prior to setting up a remote intake appointment where informed consent will be obtained via a RedCap link where participants will electronically sign the document.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

After the screening process is complete and the participant is found to be eligible, the RA/PI will schedule them for a remote intake. During this intake, all eligible participants will be asked for electronic written consent using the Yale HIC approved combined consent/HIPAA form that will be sent to them via a RedCap link. The entire consent form will be reviewed in detail with the participant over the phone or video conference during the first intake appointment. All risks and potential benefits will be described. Any questions the participant may have will be addressed. If the participant wishes, they may review the consent form and consider it further before signing. They may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the participant has signed the consent, they may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. All participants will automatically receive a signed copy of the consent form to their emails to retain for their records. All eligible participants will also be asked to provide contact information in the following manner. In addition to providing their own personal contact information, participants will be asked to give the names of two friends or relatives whom we can contact to obtain this information. We will contact these individuals only if we are unable to contact the participant directly and then only for the purpose of obtaining a forwarding address and phone number. Participants will be made aware of this information and potential reason for contacting the listed friends/relatives. We will inform the person that the participant has authorized us to contact them, and they will be asked if they are willing to give out this information. If they decline, they will not be contacted again.

7.Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

We will not be enrolling participants with limited decision-making capacity. We plan to exclude individuals with current serious psychiatric or medical illnesses. During the consenting process, the research assistant will read and review the consent form over the phone or video conference with the prospective participant. The research assistant will then ask the potential participant various questions about the consent form and study protocol to ensure the prospective participant sufficiently understands the study and the nature of their consent to participate. If concerns arise that a potential individual does not have sufficient capacity to provide informed consent, we will have a clinical member of the team conduct a mini mental status exam to verify capacity.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

6. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ Not Requesting any consent waivers

☒ Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO ☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?

  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒
- Why would the research be impracticable to conduct without the waiver? We request a waiver of signed authorization for part one, for participants to complete an anonymous survey. We request a waiver of signed authorization for part two, for the pilot study, only for initial participant recruitment/screening purposes to obtain interested participants' phone numbers and/or email for voice and text communication to make initial contact with the research team.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? At the first phone contact with the research team, participants will provide verbal consent for the screening process. Participants who see community-based advertisements will be invited to complete a webscreener to assess potential eligibility. On the webscreener, participants will click yes or no to consent to completing the survey. Participants in both the phone screen and webscreen who meet initial eligibility during the screening process will be invited for a remote meeting to learn more about the study, ask any questions, and provide electronic written informed consent before beginning research activities.

SECTION IV: PROTECTION OF RESEARCH

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? We will collect names and demographic information. Identifiable information will be collected and used to enroll and contact participants. It will only be used for this purpose. All collected information will be stored in locked cabinet apart from the research records.
2. How will the research data be collected, recorded and stored? Research data will be collected using phone interviews, survey assessments, urine specimens, and self-reports. All identifiable information (names and demographic information) will be stored in a locked file cabinet. All participants will be assigned a study participant ID made up of numbers and letters. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number (e.g., CM24). A list of IDs and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet. All other research data (interviews, survey assessments, urine specimen results, and self- reports) will not contain identifiable information and will be labeled only with the subjects' unique numerical indicator. Participants' results will not be recorded.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☒Desktop Computer ☐Other

   Digital data with PHI will be stored on a secured server. Digital data without PHI may be stored and analyzed on a laptop or desktop computer.

   What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Several steps will be taken to safeguard the confidentiality of subjects and their data. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. All research data that is collected will be assigned a study participant number and that number will be the only link between participant names/identifying information and the digital

databases. The names of participants will not be associated with these data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept in a locked file cabinet where it can only be accessed by senior level project staff. Any information published as a result of the study will be in aggregate and such that it will not permit identification of any participant.

We are not directly assessing incidents of child abuse or elderly abuse. However, if this information is disclosed by a participant or volunteer in the context of this research, a report will be made to the Department of Child and Families Services or other agency as required by law. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document.

All investigators and key personnel have taken the required Yale University HIPAA training. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. A list of numbers and the corresponding names will be maintained by the Principal Investigator in a locked research cabinet.

Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 and by additional protections of substance abuse treatment records afforded under Code of Federal Regulations (CFR) Part 2, Subpart E. All research personnel will be trained on human subjects protection and HIPAA procedures.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

1. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. The data will be stored in a locked room for 7 years after the final data is collected. After this point, the Data Manager and Principal Investigator will oversee the process in which data is destroyed or de-identified.

2. If appropriate, has a Certificate of Confidentiality been obtained?

   A certificate will not be requested.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There is a need to investigate harm reduction approaches for smokers who are not interested in quitting smoking, given the high rates of use among cigarette smokers and negative impact on morbidity and mortality. The purpose of this study is to evaluate whether switching cigarette smokers to a non-combustible product is an acceptable and feasible alternative to continued smoking of cigarettes and to evaluate whether it reduces exposure to harm via repeated biomarker assessments. This study may help to inform federal policy regulations of these products by the FDA.

SECTION VI: RESEARCH ALTERNATIVES AND

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   This is not a treatment study. Most patients coming in for lung screening or Tobacco Treatment Service indicate that they are not interested in quitting smoking. Anyone interested in quitting smoking will be provided with a treatment referral and will not be eligible to participate in this study.

All participants will receive information about available smoking cessation services at the end of the study.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants will be paid $40 for each visit: intake, week 4, week 8, total=$120. Participants will also receive parking reimbursement ($4/visit) as needed (total=$8). We will use a Bank of America pre-paid debit card to provide the payment for taking part in the study. We will have to share participant name, address, and telephone number with Bank of America for ePayments and this information is communicated in the consent form. The participant will receive a card in the mail with the first payment. Each additional payment will be automatically added to the card.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   There are no costs for participation.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   a. Will medical treatment be available if research-related injury occurs? *Write here*
   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

   (a-e) If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No ☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?

Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered “no” to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

2008 PHS Guideline Update Panel, L. a., and Staff. (2008). Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respir Care, 53(9), 1217-1222.

Cappelleri, J. C., Bushmakin, A. G., Baker, C. L., Merikle, E., Olufade, A. O., & Gilbert, D. G. (2007). Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addictive Behaviors, 32(5), 912-923.

Cella, D., Lai, J.-S., Jensen, S. E., Christodoulou, C., Junghaenel, D. U., Reeve, B. B., & Stone, A. A. (2016). PROMIS Fatigue Item Bank had Clinical Validity across Diverse Chronic Conditions. Journal of Clinical Epidemiology, 73, 128-134. doi: https://doi.org/10.1016/j.jclinepi.2015.08.037

Chang, C. M., Edwards, S., Arab, A., Del Valle-Pinero, A., Yang, L., & Hatsukami, D. K. (2016). Biomarkers of tobacco exposure: summary of an FDA-sponsored public workshop. Cancer Epidemiology and Prevention Biomarkers, cebp. 0675.2016.

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res, 3(1), 7-16. doi: 10.1080/14622200020032051

Ericksen, A. B., Smokin’ Smokeless Sales. CStore Decisions, 2020. https://cstoredecisions.com/2020/08/25/smokin-smokeless-sales/ Accessed September 28, 2020.Foulds, J.,

Hughes, J., Hyland, A., Le Houezec, J., McNeill, A., Melvin, C., Okuyemi, K., Shiffman, S., Wassum, K., Williams, L., Zeller, M. Barriers to use of FDA-approved smoking cessation medications: implications for policy action. Society for Research on Nicotine and Tobacco. March,

2009.

Hajek, P., Phillips-Waller, A., Przulj, D., Pesola, F., Myers Smith, K., Bisal, N., . . . McRobbie, H. J. (2019). A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med, 380(7), 629-637. doi: 10.1056/NEJMoa1808779

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict, 86(9), 1119-1127.

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry, 43(3), 289-294.

Humphrey, L., Deffebach, M., Pappas, M., Baumann, C., Artis, K., Mitchell, J. P., . . . Slatore, C. (2013) Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Rockville (MD).

Irwin, D. E., Atwood, C. A., Jr., Hays, R. D., Spritzer, K., Liu, H., Donohue, J. F., . . . DeWalt, D. A. (2015). Correlation of PROMIS scales and clinical measures among chronic obstructive pulmonary disease patients with and without exacerbations. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, 24(4), 999- 1009. doi: 10.1007/s11136-014-0818-1

Jarvis, M. J., & Sutherland, G. (2001). Tobacco smoking. In D. W. Johnston, M. Johnston, A. S. Bellack, & M. Hersen (Eds.), Health psychology, Vol. 8. Comprehensive clinical psychology (p. 645–674). Elsevier Science Publishers B.V.

McNeill, A., et al., Vaping in England: an evidence update including mental health and pregnancy, March 2020. Public Health England: London, UK, 2020.

Morean, M., Krishnan-Sarin, S., Sussman, S., Foulds, J., Fishbein, H., Grana, R., & O'malley, S. S. (2018). Psychometric evaluation of the Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for use with electronic cigarettes. Nicotine & Tobacco Research.

Mushtaq, N., & Beebe, L. (2020). Evaluating the Psychometric Properties of the Severson 7-Item Smokeless Tobacco Dependence Scale (SSTDS), Nicotine & Tobacco Research.

National Academies of Sciences, Engineering. and Medicine, Public Health Consequences of E- Cigarettes, ed. K. Stratton, L.Y. Kwan, and D.L. Eaton. 2018, Washington, DC: The National Academies Press. 774.

Osei, A. D., Mirbolouk, M., Orimoloye, O. A., Dzaye, O., Uddin, S. M. I., Benjamin, E. J., . . . Blaha,
L. J. (2019). Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. The American Journal of Medicine. doi: https://doi.org/10.1016/j.amjmed.2019.02.016

Patel, T., et al., Patient Perception of Vaping in the Midst of the Electronic
Cigarette and Vaping Product Associated Lung Injury (EVALI) Epidemic. Missouri Medicine, 2020. 117(3): p. 265-270.

Plurphanswat, N., Hughes, J.R., Fagerstrom, K., Rodu, B. Initial information on a novel nicotine product.
The American Journal on Addictions, 2020. 29: p. 279-286.

Rose, M., Bjorner, J. B., Gandek, B., Bruce, B., Fries, J. F., & Ware, J. E. (2014). The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. Journal of Clinical Epidemiology, 67(5), 516-526. doi: https://doi.org/10.1016/j.jclinepi.2013.10.024

Russell, C., McKeganey, N., Haseen, F. Transitions in cigarette smoking associated with use of the

JUUL vaping device among 18,779 adults in the United States. 2018.Shadel, W. G., Edelen, M. O., Tucker, J. S., Stucky, B. D., Hansen, M., & Cai, L. (2014). Development of the PrOMis® nicotine Dependence item Banks. Nicotine & Tobacco Research, 16(Suppl 3), S190-S201.

Smith, S. S., Piper, M. E., Bolt, D. M., Fiore, M. C., Wetter, D. W., Cinciripini, P. M., & Baker, T. B. (2010). Development of the Brief Wisconsin Inventory of Smoking Dependence Motives.
Nicotine & Tobacco Research, 12(5), 489-499. doi: 10.1093/ntr/ntq032

Sobell, L., & Sobell, M. (1995). Alcohol consumption measures. In J. Allen & M. Columbus (Eds.), Assessing alcohol problems: A guide for clinicians and researcher (pp. 55-73). Bethesda, MD: National Institute on Alcohol Abuse & Alcoholism.

Sobell, L., & Sobell, M. (2003). Alcohol consumption measures. In J. P. A. a. V. B. & Wilson (Eds.), Assessing alcohol problems: A guide for clinicians and researchers. (pp. 75-99). Bethesda, MD: National Institute on

Alcohol Abuse & Alcoholism.
U.S. Department of Health and Human Services. Smoking Cessation. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2020.
Vickerman, K.A., et al., Use of Electronic Cigarettes Among State Tobacco Cessation Quitline Callers. Nicotine & Tobacco Research, 2013. 15(10): p. 1787-1791.
Walker, N., Verbiest, M., Kurdziel, T., Laking, G., Laugesen, M., Parag, V., & Bullen, C. (2019). Effectiveness and safety of nicotine patches combined with e-cigarettes (with and without nicotine) for smoking cessation: study protocol for a randomised controlled trial. BMJ Open, 9(2), e023659. doi: 10.1136/bmjopen-2018-023659
Wang, J. B., Olgin, J. E., Nah, G., Vittinghoff, E., Cataldo, J. K., Pletcher, M. J., & Marcus, G. M. (2018). Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. PloS one, 13(7), e0198681-e0198681. doi: 10.1371/journal.pone.0198681
Welz, C., Canis, M., Schwenk-Zieger, S., Becker, S., Stucke, V., Ihler, F., & Baumeister, P. (2016). Cytotoxic and Genotoxic Effects of Electronic Cigarette Liquids on Human Mucosal Tissue Cultures of the Oropharynx. 35(4), 343-354. doi: 10.1615/JEnvironPatholToxicolOncol.20160166

APPROVED BY THE YALE UNIVERSITY IRB 2/28/2023