Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator: Joanna Streck, PhD

Project Title: Switching Individuals in Treatment for Opioid Use Disorder Who Smoke Cigarettes to the SREC

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Version Name/Number: Version 10

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Opioid misuse and use disorder (OUD) have reached epidemic proportions in the United States (US) with a staggering death toll, economic costs exceeding $785 billion, and a public health crisis,[21–26] which has worsened during the coronavirus pandemic.[27–29] Methadone and buprenorphine are opioid agonist medications that are efficacious treatments for OUD, shown to dramatically reduce morbidity and mortality.[30,31] The number of patients receiving medication treatment for OUD (MOUD) has increased substantially in recent years particularly with the availability of office-based buprenorphine treatment.[32,33] However, tobacco use remains a significant problem for individuals receiving MOUD. While individuals in OUD treatment are less likely to die from their OUD, they face substantial negative health consequences because of their ongoing tobacco use. Indeed, the mortality rate of individuals who smoke with OUD is two to four-fold higher than nonsmokers with OUD, and mortality from tobacco use exceeds the mortality associated with other substance use in this population.[4,5,23,34] Tobacco treatment is critical for individuals receiving MOUD as evidence suggests that quitting tobacco increases the likelihood of long-term abstinence from alcohol and illicit drugs for patients in SUD treatment.[35]

Prevalence of combustible cigarette smoking among individuals receiving MOUD far exceeds that of the US adult general population, with estimates of smoking prevalence above 70% in individuals in OUD treatment compared to 13% in the general population.[1,2,7,36,37] Individuals in OUD treatment who smoke are aware of the health risks associated with smoking, express interest in quitting smoking,[38–42] but existing evidence-based FDA-approved smoking cessation pharmacotherapies are substantially less effective in patients with OUD compared to the general smoking population, with smoking abstinence rates less than one quarter that of rates seen in the general smoking population.[43,44] Several potential reasons for these increased rates of smoking and poor cessation outcomes in individuals receiving MOUD who smoke (MOUD-TUD) have been posited, including heightened nicotine withdrawal and intolerance of withdrawal discomfort, as well as the pro-smoking social norms including small social networks comprised of others who smoke.[7,45,46] Novel approaches to tobacco treatment, including harm

reduction paradigms, are urgently needed to reduce the burden of cigarette smoking in this vulnerable population.

There is ongoing debate about whether electronic cigarettes (e-cigarettes) may be a viable harm reduction strategy**.** E-cigarettes are non-combustible devices that heat a nicotine-containing liquid to produce an aerosol that users inhale or "vape."[8] Emerging data suggests that vaping may expose users to fewer toxins than cigarette smoking because e-cigarettes do not burn tobacco to generate smoke.[8] **E-cigarettes are unique and promising tools because unlike existing FDA-approved cessation pharmacotherapies, they provide sensorimotor stimuli that closely mimic smoking (e.g., hand to mouth motion, exhalation of vapor) in addition to replacing nicotine**.[47] These sensorimotor stimuli may be particularly important for MOUD-TUD who appear to have higher dependence and sensitivity to withdrawal discomfort, and continued use of nicotine in social situations.[45,46] Studies in the general smoking population show substantial interest in and use of e-cigarettes for smoking reduction and cessation, and clinical trials suggest that e-cigarettes are effective smoking cessation aids.[8,48–51] In an online survey of people who vape, participants rated e-cigarettes as more useful for quitting smoking, better at reducing tobacco cravings, less addictive, more convenient, more satisfying, and less expensive than nicotine replacement therapies (NRT).[52] Complete substitution of e-cigarettes for cigarettes has the potential to reduce tobacco-related health risks.[8] Indeed, promising studies in the general population have found that individuals who smoke who switch to e-cigarettes have decreased toxicant exposure and improvements in lung and vascular functioning.[53–58] However, continued use of cigarettes with e-cigarettes (i.e., dual use) remains a concern that could result in a level of exposure to toxicants equal to or higher than smoking alone and/or greater nicotine dependence.[47,59] Thus, more research is urgently needed to understand whether MOUD-TUD who are unable to quit smoking can switch to e-cigarettes to reduce cigarette use and toxicant exposure and ultimately reduce their devastating tobacco-related morbidity. Indeed, the FDA Center for Tobacco Products has regulatory authority over e-cigarettes and has called for more research on the safety of e-cigarettes in comparison to cigarette smoking and deemed individuals with SUDs as a priority population on whom more research is needed.[60,61]

Very little research has examined e-cigarette use among MOUD-TUD. In survey studies, MOUD-TUD report having tried e-cigarettes and report current use of these products (e.g., 73% lifetime use and 34% past 30 day use),[11,12] but very few studies have tested how e-cigarette use affects cigarette smoking behavior in this population.[13,14] Two small, brief pilot studies provided e-cigarettes to MOUD-TUD for 2 and 6 weeks, respectively, and reported that provision of e-cigarettes resulted in promising reductions in self-reported cigarettes smoked per day.[13,14] However, no prior studies of MOUD-TUD have tested provision of a pod-mod e-cigarette device type or biochemically-confirmed self-reported reductions in cigarette smoking using rigorous assessment of breath and urinary biomarkers.

Pod-mod device types have high appeal due to their high nicotine concentration, rapid nicotine delivery, and satisfying user experience.[15–17] Thus, these device types may be superior to earlier devices to serve as substitutes for combustible cigarettes in terms of nicotine delivery and withdrawal alleviation, but this has not been tested in MOUD-TUD. In August 2019, a concern about the safety of commercial e-cigarettes arose when cases of severe pulmonary illness associated with vaping (EVALI) were reported.[62,63] However, the primary cause of EVALI was vitamin E acetate, an adulterant in illicitly-obtained THC-containing vaping devices and not in commercial nicotine containing e-cigarettes. New EVALI cases have declined since September 2019.[64,65] Additionally, NIDA recently announced the availability of the standardized research e-cigarette (SREC), a pod-mod device (NJOY, LLC), designed to produce a consistent, well-characterized aerosol, to serve as a standardized device for clinical studies without concern of modifications being made to the device during the study course.[19]

Thus, the use of this standardized nicotine-only containing e-cigarette in a controlled experimental paradigm, with frequent safety monitoring,[66] is not expected to pose substantially elevated harm beyond the risk expected from smoking combustible cigarettes, though our research project will directly assess the effects of provision of SRECs on nicotine intake (see details of biomarker assessment below) and we will extensively monitor participant safety and changes in nicotine use (see Human Subjects attachments).

Objective assessment of nicotine and tobacco exposure is critical for assessing combustible cigarette reduction and increasing rigor. Established biomarkers of tobacco use include breath CO (a measure of recent combustible tobacco smoke exposure), urinary or salivary cotinine (a nicotine metabolite and measure of total exposure to nicotine from all combusted and non-combusted sources), and the urinary tobacco alkaloid anabasine that is structurally related to nicotine. Anabasine detects alkaloids from tobacco-derived products (e.g., cigarettes) and is not likely to be influenced by other sources of nicotine exposure (e.g., e-cigarettes only detected in trace amounts). Thus, anabasine can isolate changes in cigarette use and is a critical biomarker for assessment of cigarette reduction in studies where participants may use both cigarettes and e-cigarettes.[67,68] Together, these biomarkers can help determine whether participants are reducing cigarette smoking in response to e-cigarette provision, and if they are reducing vs. substituting or increasing their overall nicotine intake levels. However, this has not yet been investigated among MOUD-TUD and it is not clear if e-cigarette provision will reduce their tobacco toxicant exposure.

Office-based buprenorphine treatment provides an ideal setting for intervening on tobacco use. Unlike methadone, federal regulations allow for OUD treatment with buprenorphine in primary care settings.[69] Individuals in primary care clinic-based buprenorphine treatment are ideal candidates for tobacco harm reduction and treatment approaches as they are more likely to be stable in treatment compared to methadone treatment patients and the primary care setting permits more focus on non-OUD priorities such as tobacco.[70,71]

SUMMARY: This K23 project seeks to address gaps in e-cigarette research in MOUD-TUD, specifically those who are stable in their buprenorphine treatment, by testing the feasibility, acceptability, and preliminary effects of substituting the SREC for combusted cigarettes in individuals who smoke and are not yet ready to quit smoking. Specifically, using a randomized waitlist-controlled design, this project will rigorously assess the impact of provision of SRECs on tobacco use behavior (e.g., cigarettes per day, e-cigarette use), tobacco-related biomarkers, cigarette dependence and withdrawal, and short-term health effects and tolerability of e-cigarettes (e.g., respiratory and psychiatric symptoms, substance use). **This project is directly in line with NIDA's strategic plan and research priorities related to addressing real-world complexities (e.g., comorbidities such as polysubstance use) and accelerating development of treatments (e.g., defining alternative end points such as reductions in substance use).**[20] The data gathered from this project will prepare me with critical pilot data to inform a future R01-funded RCT. If supported by the data, that fully powered trial will investigate the durability, efficacy, and safety of substituting e-cigarettes for cigarettes to reduce cigarettes per day and tobacco toxicant exposure in this highly vulnerable population who have been unable to quit smoking with existing tools.

2. Specific Aims and Objectives

Aim 1: To assess the feasibility of an e-cigarette substitution intervention in 60 MOUD-TUD stable in OUD treatment with buprenorphine who are not yet ready to quit smoking. Outcome measures are enrollment and retention rates.

Hypotheses: *Hypothesis 1a*: 45% of those screened as eligible will enroll; *Hypothesis 1b:* >70% will complete the trial (i.e., attend final follow-up assessment and attend ≥50% of study visits). Hypotheses are based on my and my mentor's prior work recruiting from the same CHCs and based on a prior e-cigarette study in OUD treatment.[9,14,73]

Aim 2: To quantitatively examine the effects of SREC provision on changes in tobacco use behavior (cigarettes per day [primary outcome], SREC use), **exposure to tobacco-related biomarkers** (carbon monoxide, anabasine, cotinine), **cigarette dependence and withdrawal symptoms, and short-term health effects and tolerability** (respiratory and psychiatric symptoms, substance use, quantitative subjective effects of SREC use) during 8 weeks of SREC provision. Outcomes will also be assessed 4 weeks after SREC provision ends (at 12 weeks in the iSREC condition and at 20 weeks in WLC condition).

Hypothesis: The mean reduction in CPD from Baseline 2 to 8 weeks in the iSREC group will be greater than in the WLC group.
Secondary outcomes (Table 3): CPD: *Hypothesis:* The mean reduction in CPD across the 8 weeks of SREC provision will be at least 25% in an analysis combining randomized groups. Days of e-cigarette use: *Hypothesis:* During the 8 weeks of e-cigarette provision, patients will use e-cigarettes on at least 50% of the past 7 days measured at each assessment in an analysis combining randomized groups. Biomarkers*:* We anticipate that levels of CO and anabasine will decrease across the 8 weeks of SREC provision in a pre-post analysis combining randomized groups, corresponding with reduced cigarette consumption, and that biomarker levels in the iSREC group will be lower than WLC from Baseline 2 to Week 8. Cotinine levels may or may not change during SREC provision depending on the degree of substitution of e-cigarettes for cigarettes.

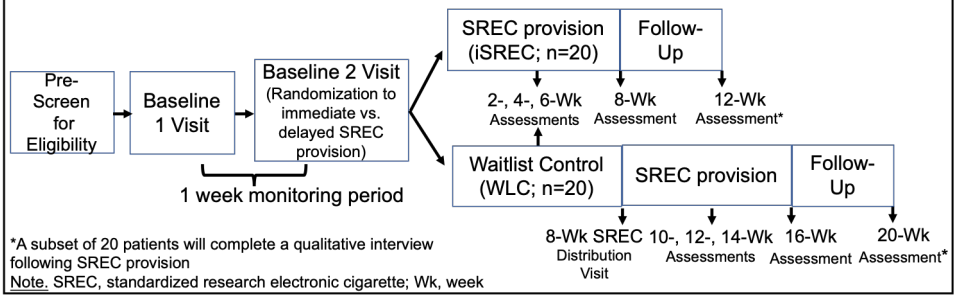
Aim 3: To qualitatively explore patient's experiences attempting to use the SREC to reduce combustible cigarette smoking, using individual in-depth exit interviews that occur at the end of the SREC provision in each group. I will examine barriers and facilitators of making a complete switch to e-cigarettes (e.g., impact of social-environmental factors), method of switching (e.g., gradual vs. immediate), and acceptability (e.g., positive/adverse effects of switching, desire to continue vs. quit e-cigarette use at trial end).

Proposition (Qualitative Hypothesis): Patients will describe e-cigarettes as acceptable and helpful for reducing cigarette use.

3. General Description of Study Design

Overall Strategy (Figure 1): I propose to conduct a randomized waitlist-controlled trial using a mixed-methods sequential explanatory design[74] to assess the feasibility, acceptability and effects of SREC provision on combusted cigarette use and biomarkers of tobacco product exposure in individuals receiving MOUD who smoke cigarettes daily. **N=60** patients will be randomized in a 1:1 ratio to 1 of 2 conditions for 8 weeks: 1) immediate standardized research e-cigarette provision (iSREC) or 2) delayed SREC provision waitlist control (WLC). Those randomized to the iSREC group will be provided a free 8-week supply of SRECs and asked to try to switch completely to the SREC. Those in the WLC condition will receive SREC provision after an 8-week delay.

Figure 1. Study design of the pilot randomized controlled trial (N=40)



4. Subject Selection

Inclusion Criteria

- Participants will be ≥18 years of age
- English Speaking
- Report daily cigarette smoking (≥5 cigarettes per day in the past week)
- Not be ready to quit smoking (not planning to quit in the next 30 days)
- Willing to try e-cigarettes
- In stable BUP treatment for OUD (in treatment for ≥3 months and planning to remain on current MOUD for ≥3 months) at an MGH-affiliated primary care community health center (CHC),MGH's hospital based Primary Care Adult Practice (Internal Medicine Associates), or MGH's West End or Bridge Clinic

Exclusion Criteria

- Participants who are pregnant or breastfeeding
- Using non-cigarette nicotine or tobacco products (e.g., e-cigarettes, cigarillos) recently (>3 days in past 30 days)
- Report past 30-day use of behavioral or pharmacologic smoking cessation aids
- Deemed inappropriate for participation by their provider
- Have an unstable psychiatric (e.g., past month suicidal ideation, active psychosis) or medical condition (e.g., life expectancy <1 year), as determined by the PI in consultation with her physician mentors
- Potential participants who indicate interest in quitting smoking in the next 30 days are ineligible for the study but will be offered an active referral to the Massachusetts State Quitline, consistent with best practices for smoking cessation.[79]

Recruitment Methods & Recruiting Diverse Populations

Massachusetts General Hospital (MGH) owns five Community Health Centers (CHCs) which are comprehensive adult primary care clinics located in diverse communities in the greater Boston area (e.g., Charlestown, Chelsea, Revere). We will also be recruiting at MGH's hospital based Primary Care Adult Practice (Internal Medicine Associates), and through MGH's West End and Bridge Clinic. Providers at these clinics provide buprenorphine (BUP) treatment to patients with opioid use disorder (OUD). We will employ the recruitment strategy used successfully in the PI's prior K12 pilot study.[71] MGH's electronic medical record contains a registry of patients receiving BUP treatment. Study staff will use the registry to identify potentially-eligible patients receiving BUP treatment at the primary care clinics; 520 patients were eligible for participation in my K12 survey study at the 5 CHC sites and 43% agreed to participate.[71] Patients will be mailed a letter that describes the study and provides a number to call to opt out of further contact from the study team. Research Invitations will be used for direct recruitment of any eligible subjects who have not opted out of receiving Research Invitations. Patients who opted out, will be filtered out of the recruitment list (e.g., from RPDR, Epic) and they will not be sent the Research Invitation. The PI will conduct ongoing monitoring of patient responses to ensure that selection criteria are identifying the right patients and that complaints about this method of recruitment are submitted to the IRB as an Other Event as needed. One week after the mailing, staff will call potentially eligible patients to describe the study, confirm eligibility, and offer enrollment into the trial. We will attempt to reach patients 3 times before assuming lack of interest in study. To the extent possible, research staff will be on site at the clinics during the specific weekdays when patients with OUD are seen for BUP treatment visits, allowing for in-person recruitment.

Methods to enhance recruitment of diverse populations: Individuals with OUD are a diverse and underserved population. Consistent with NIH policy, women and members of all minority groups will be eligible to participate in this study. We expect that the gender and minority composition in this project will largely match the composition of the clinical population at Massachusetts General Hospital's (MGH's) Community Health Centers (CHCs), and clinics where recruitment for the proposed project will take place. Based on my pilot work recruiting a similar patient population at the MGH CHCs in 2020, of the 111 participants reporting current exclusive cigarette smoking (not reporting using electronic cigarettes in the past 30 days) and stable on buprenorphine treatment at the CHCs, the demographic distribution of patients was: 43% women; 11% Hispanic, Latinx or Spanish ethnicity/origin; 82% white (non-Hispanic) race; 6% Black/African American; 1% Asian; 1% American Indian/Alaskan Native; 5% other race; 5% endorsed multiple races. We expect the clinical population of adults who smoke cigarettes stable in buprenorphine treatment (i.e., those eligible for this proposed study) to be similar to these gender and ethnic distributions. We will closely monitor the demographic and gender breakdown of our participant sample and plan to oversample certain racial or gender groups if necessary. Finally, while not considered a minority group per se, I will not exclude homeless individuals who meet inclusion criteria for the study; this is an important and marginalized population given the high prevalence of smoking and opioid use disorder in the homeless population.

5. Subject Enrollment

Study staff will call potentially eligible patients (who were not excluded by their provider and did not opt out). During the prescreening call, study stuff will describe the study, confirm eligibility, and offer enrollment into the trial. We will attempt to reach patients 3 times before assuming lack of interest in study. Patients who screen eligible via telephone (or in-person at the clinic if preferred) will be scheduled for an in-person or virtual Baseline 1 Visit.

If the screening visit is conducted virtually, informed consent will be obtained remotely. This will be done via electronic consent using an IRB approved-platform (e.g., MGB REDCap e-consent, Adobe eSign), or a remote consent process where the participant will be asked to sign the consent form and return back by email or mail. In either case, the consent discussion will occur identically to an in-person visit, but instead held over phone call or video conference.

Upon meeting study eligibility criteria through pre-screening, study patients will complete the informed consent process in-person, or electronically (if a remote visit) at the Baseline 1 assessment visit. A trained research assistant, or the PI, will obtain informed consent. Prior to consent, the PI or delegate will explain study procedures in detail, discuss potential risks and benefits of participation, and remind patients that the study is completely voluntary and that their choice to participate will not impact the care they are receiving currently at MGH, the CHCs, or care they may wish to seek in the future. They will be informed that they can choose to withdraw their participation at any time and may also choose not to answer any questions or submit any other data (e.g., urine samples) that they are not comfortable with. Patients will also be informed of the limits of confidentiality, including expressed risk of harm to self or others (see protocol below for details). They will receive the PI’s contact information and that of the MGH IRB to contact with any additional questions or concerns. The RA will assess participant’s ability to provide informed consent and route any questions about the participant’s capacity to the PI to weigh in on or assess further prior to enrolling the participant. The participant will be provided with a copy of their signed consent form to keep for their records. Patients’ signatures will be documented on our study consent log and all physical study consent forms will be kept separately from study data and will be locked in a filing cabinet in a locked office within the PI’s research office suite.

Because the PI's clinical service takes place in the MGH SUD Bridge Clinic, we will take several steps to minimize undue influence to enroll for any patients recruited from here. We will have a clinical research coordinator initially explain the study and screen patients, so the PI is not directly contacting her own patients. We will additionally offer patients the opportunity to take home the Consent Form, and call back if they wish to participate.

Once patients have been consented, they will be randomized in a 1:1 ratio to one of 2 study groups using the computer-generated randomization scheme created by the study statistician.

6. STUDY PROCEDURES

Visit Schedule SREC GROUP

		SREC Provision*					F/U
Visit Name	**BL1**	**BL2**	**V2**	**V4**	**V6**	**V8**	**V12**
Study Week for Immediate SREC Group	**W-1**	**0**	**W2**	**W4**	**W6**	**W8**	**W12**
Quantitative Measures							
Demographics, Tobacco, & OUD History	X						
MOUD Dose Questionnare		X	X	X	X	X	
# of Cigarettes Smoked/Day (CPD)							
Daily text messages	X	X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X	X
E-cigarette Use (Yes/No)							
Daily text messages		X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X	X
Pod collection/count			X	X	X	X	
E-cigarette Pos & Neg Subjective Effects				X		X	X
Cigarette Dependence & Withdrawal							
Dependence (FTCD)	X			X		X	X
E-cig Dependence (eFTND)	X			X		X	X
Withdrawal (MNWS)	X	X	X	X	X	X	X
Biomarkers of Exposure							
Breath Carbon Monoxide (CO)	X	X	X	X	X	X	X
Urinary Biomarkers (anabasine, cotinine)	X			X		X	X
Health Effects							
Adverse events	X	X	X	X	X	X	X
Respiratory Symptoms (SGRQ)	X	X	X	X	X	X	X
Non-Tobacco Substance use							
Urine Drug Toxicology	X			X		X	X
Addiction Severity Index (ASI-- only drugs/alcohol module)	X			X		X	X
Breath Alcohol	X	X	X	X	X	X	X
Alcohol (AUDIT-C)	X			X		X	X
Psychiatric Symptoms							
Depression (PHQ-9)	X			X		X	X
Anxiety (GAD-7)	X			X		X	X
Chart Review	X			X		X	X
Qualitative Interview							X
Domains: Barriers/facilitators of switching to SRECs (e.g., impact of social-environmental factors), method of switching, acceptability (e.g., positive/adverse effects of switching)							X

Note. SREC, standardized research electronic cigarette; F/U, follow-up; BL, Baseline; V, Visit; OUD, opioid use disorder; Pos & Neg, positive and negative

Key: *SRECs will be distributed to immediate SREC participants during BL2 (following randomization) and to WLC participants at their Week 8 visit (See Figure 1).

Visit Schedule WLC GROUP											
						SREC Provision*					F/U
Visit Name	**BL1**	**BL2**	**V2**	**V4**	**V6**	**V8**	**V10**	**V12**	**V14**	**V16**	**V20**
Study Week for WLC Group	**W-1**	**0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**
Quantitative Measures											
Demographics, Tobacco, & OUD History	X										
MOUD Dose Questionnare		X	X	X	X	X	X	X	X	X	
# of Cigarettes Smoked/Day (CPD)											
Daily text messages	X	X	X	X	X	X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X		X		X	X
E-cigarette Use (Yes/No)											
Daily text messages		X	X	X	X	X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X		X		X	X
Pod collection/count							X	X	X	X	
E-cigarette Pos & Neg Subjective Effects								X		X	X
Cigarette Dependence & Withdrawal											
Dependence (FTCD)	X			X				X		X	X
E-cig Dependence (eFTND)	X							X		X	X
Withdrawal (MNWS)	X	X	X	X	X	X	X	X	X	X	X
Biomarkers of Exposure											
Breath Carbon Monoxide (CO)	X	X	X	X	X	X	X	X	X	X	X
Urinary Biomarkers (anabasine, cotinine)	X			X				X		X	X
Health Effects											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Respiratory Symptoms (SGRQ)	X	X	X	X	X	X	X	X	X	X	X
Non-Tobacco Substance use											
Urine Drug Toxicology	X			X				X		X	X
Addiction Severity Index (ASI-- only drugs/alcohol module)	X			X				X		X	X
Breath Alcohol	X	X	X	X	X	X	X	X	X	X	X
Alcohol (AUDIT-C)	X			X				X		X	X
Psychiatric Symptoms											
Depression (PHQ-9)	X			X		X		X		X	X
Anxiety (GAD-7)	X			X		X		X		X	X
Chart Review	X			X		X		X		X	X
Qualitative Interview											X
Domains: Barriers/facilitators of switching to SRECs (e.g., impact of social-environmental factors), method of switching, acceptability (e.g., positive/adverse effects of switching)											X

Provision of Standardized Research E-cigarettes (SRECs): E-cigarettes provided will be NIDA's SREC (NJOY, LLC).[19] SREC pods (sealed and non-refillable) attach to the device and contain nicotinized e-liquid. We will provide devices with pods of 5% nicotine strength (each pod contains approximately 1.9 mL volume of liquid) in the Rich Tobacco flavor that is currently available. At the Baseline 2 Visit for iSREC patients (and Week 8 for WLC participants), each patient will receive a SREC device which includes a USB rechargeable battery, and a 2-week supply of pods. Research staff will provide written and verbal instructions and demonstrate how to use the device, recharge, and store the device safely, and reach on-call study staff for device-related issues. All participants will be also be provided with written educational materials designed to help vapers quit smoking (*"If You Vape: a Guide to Quitting Smoking"*) with modules such as keeping e-cigarettes handy and vaping when tempted to smoke.[80] Patients will be instructed to aim to switch completely to e-cigarettes by the end of the first week of provision and to try to use only the SREC during the remaining 7-weeks of provision. Patients will be given an initial e-cigarette pod supply equivalent to their average cigarette smoking rate measured during the week monitoring period between Baseline Visits 1 and 2, estimating that 1 SREC pod at 5% strength is equivalent to ~20 cigarettes per day.[81] The supply of pods provided

will be adjusted as needed to ensure that patients have the number needed to adequately substitute their cigarette use. Patients will attend assessment visits every two weeks during e-cigarette provision **(Figure 1**) to receive a new supply of pods, return their used and unused pods for inspection to measure e-cigarette use, report on respiratory and nicotine withdrawal symptoms, provide a breath CO sample, and troubleshoot any device or other study-related issues (**Table 2**). Patients will be instructed to contact on-call research staff between visits with any questions about the devices. At the end of the study (at 12 weeks for iSREC and 20 weeks for WLC), participants who express a desire for additional help with either smoking or vaping cessation will be provided with a referral to the state quitline. Participants expressing interest in continued e-cigarette use after the study will be briefly counseled on e-cigarette use, including how to purchase e-cigarettes, and best practices for staying tobacco free guided by the educational materials above.[80]

I. Schedule of Assessments (Table 2):

Immediate SREC Group Assessments: iSREC patients will complete full assessments at baseline (across 2 visits), and weeks 4, 8, and 12. At these visits, patients will complete a battery of questionnaires and provide urine and breath samples (**Table 2, Figure 1**). Additional brief visits to replenish e-cigarette supply and collect and count used and unused pods will occur at 2 and 6 weeks during SREC provision. To minimize respondent burden, only limited measures will be collected at these brief visits (CO, MNWS, respiratory symptoms, adverse events).

WLC Group Assessments: WLC patients will complete 2 baseline visits, and at weeks 4 and 8, WLC patients will complete the same assessments as the iSREC group to allow between randomized group comparisons and to monitor any changes in tobacco use across the WLC period (Figure 1). At Week 8, WLC patients will receive SRECs to begin SREC provision (Figure 1). WLC patients will then complete full assessments at weeks 12, 16, and 20 and brief SREC replenishment assessment visits at weeks 10 and 14 during their SREC provision.

Text Message Assessments: All patients will receive daily secure text messages (via Twilio, an MGH-approved secure messaging system) to assess their cigarette use on the prior day (cigarettes smoked per day; CPD) during the week between Baseline 1 and 2. Throughout the 8 weeks of e-cigarette provision (Baseline 2 to Week 8 for the iSREC group and Week 8 to Week 16 for WLC group), patients will also receive daily text messages to record the prior day's CPD (the number) and e-cigarette use (yes/no). WLC participants will also receive these daily texts during the WL period (Baseline 2 to Week 8) to serve as a comparison with the iSREC group. In the first week of e-cigarette provision, research staff will proactively reach out to any patients who do not respond to a daily text within 48 hours to check-in on switching, problem-solve any obstacles and answer any questions. We will provide study cell phones to patients who do not have a cell phone at enrollment or lose access to a personal cell phone during the course of the study. Text messages were an effective strategy for assessing e-cigarette use in a prior e-cigarette study in this population.[14]

Individual qualitative exit interviews: Under the guidance of Dr. Elyse Park (co-mentor), individual in-depth exit interviews using a semi-structured interview guide will be conducted following study completion (at 12 weeks for the iSREC group and 20 weeks for WLC) with a randomly selected subset of patients (n=20 total), stratified by cigarette reduction defined according to the quantitative text message data on daily cigarette use during the 8-weeks of SREC provision (Table 3). Specifically, stratification will be: mean CPD reduction from Baseline 2 to 8 weeks (Week 8 to Week 16 in WLC) $\geq$ 25% (n=10) vs. CPD reduction <25% (n=10). Interviews, administered primarily by the PI with assistance from a trained research assistant, will be conducted with each patient as soon as they complete the study. Interviews will last 30 minutes and explore patient's experience attempting to switch completely to e-cigarettes. The semi-structured interview guide will explore: 1) barriers and facilitators of making a complete

switch to e-cigarettes (i.e., complete substitution of e-cigarettes for cigarettes and no ongoing cigarette use) including impact of social-environmental factors (e.g., presence of others who smoke in home), 2) patient's method of switching (e.g., gradual vs. immediate and adherence to e-cigarettes) and, 3) acceptability (e.g., positive and adverse effects of switching, desire or plan to continue e-cigarette use at trial completion vs. quit use, nicotine withdrawal) **(Table 2**). The qualitative exit interview has two purposes: 1) to help explain the quantitative outcome data to understand patient's experiences and methods of switching to e-cigarettes and, 2) to inform future R01 intervention development and help identify an acceptable and effective switching protocol.

Quantitative Measures:
Demographics: age, sex, gender identity, race/ethnicity, education, marital status, housing stability (using items from the CDC's Behavioral Risk Factor Surveillance System[82]), health insurance.
Tobacco product use history: cigarette and e-cigarette use (ever, past 7-day, past 30-day), age at first use, flavor/brand, and nicotine level preference, quit and reduction attempts, use of cessation aids (past year, ever).
OUD history: primary opioid of abuse, age at first use, route of administration, length of time in current BUP treatment, and past 30-day use of substances (e.g., heroin, opioid analgesics, fentanyl, cannabis, stimulants, inhalants, sedatives, hallucinogens). Tobacco and OUD history will be assessed using an instrument developed and validated by collaborators.[72,83,84]
Daily cigarette consumption: Cigarettes smoked per day (CPD) will be assessed from baseline to Week 8 via daily text messages that ask patients to report the number of CPD on the prior day. Data from the 7 days prior to each outcome assessment (Baseline 2 and 2, 4, 6, and 8 weeks) will be averaged to create the outcome measures. The **primary outcome is change in mean CPD in the past 7 days at Baseline 2 vs. Week 8**. Because text messages end at 8 weeks when SREC provision ends, we will also collect CPD data using a 7-day timeline followback (TLFB[85]) method at Baseline 2 and at Weeks 4, 8, and 12 (Weeks 12, 16, 20, for WLC). This second method allows for comparison of change in CPD after e-cigarette provision ends using the same method of data collection across timepoints. We will also use CPD data to calculate # of days of smoking (smoking at least 1 CPD) in the past 7 days at each assessment to capture non-daily smoking.
Daily e-cigarette use: E-cigarette use will be assessed in the same two ways as CPD using both text messages and TLFB, but daily e-cigarette use will be reported as yes/no rather than as a quantity. The e-cigarette outcome measure is number of days of e-cigarette use in the past 7 days, rather than quantity of e-cigarettes because e-cigarette consumption is less easily quantified than a CPD count.[8,86,87] To explore ways to measure quantity of e-cigarette use, we will also inspect e-cigarette devices and count used and unused e-cigarette pods at each visit during provision to calculate number of pods used. The count of used pods is both a measure of adherence to the e-cigarette intervention and an exploratory measure of amount of e-cigarette use. If feasible, this exploratory assessment of amount of e-cigarette pod use could be used for future trials.
E-cigarette subjective effects: 11-item visual analogue scale (VAS) assessing positive subjective effects of e-cigarette use (e.g., satisfaction);[88] and a6-item VAS of e-cigarette sensory effects and appeal (e.g., "would you use it [e-cigarette] again")[90]
Cigarette dependence and withdrawal: Fagerstrom Test of Cigarette Dependence (FTCD[91]); Minnesota Nicotine Withdrawal Scale (MNWS) which assesses both desire to smoke and withdrawal symptoms[92]
Biomarkers of exposure: Expired air CO will be collected on site using a Covita Micropro Smokerlyzer. If participant is unable to attend in person visits when CO is scheduled to be

collected, we will send them an iCOquit Smokerlyzer, which will allow us to remotely measure participants breath CO levels.Cotinine (nicotine metabolite; urine) and anabasine (tobacco alkaloid to permit isolation of changes in cigarette use; urine) will be collected and stored at MGH and sent quarterly for analysis by Mayo Clinic laboratories.[68,93] For participants who attend all study visits remotely, we will ship urine drug testing materials to their home address to collect a urine sample during the visit, and we will provide a return label and packaging supplies and instructions for participants to send the sample back to our center. Levels of CO and anabasine reflect exposure to combustible tobacco products and should fall with corresponding reductions in CPD. Cotinine reflects nicotine exposure from all sources and may or may not change with CPD reduction depending on the extent of nicotine substitution achieved by e-cigarette use.
Respiratory Symptoms: A modified version of the St. George's Respiratory Questionnaire (SGRQ[94,95]) will be used to measure respiratory symptoms (e.g., wheezing, phlegm production, shortness of breath)
Non-tobacco substance use: Urine toxicology screen (12-panel CliaWaived FDA-approved test dipstick); The drugs/alcohol module of the Addiction Severity Index (ASI[96]) to examine past 30-day severity of 7 substance problem areas (e.g., drug, employment); Breath alcohol levels will be collected on site using an Alco-Sensor IV device; Alcohol Use Disorders Identification Test (AUDIT-C[97])
Depression symptoms: Patient Health Questionnaire-9 (PHQ-9[98]; See Human Subjects attachment for suicide risk and safety assessment protocol); Anxiety symptoms: Generalized Anxiety Disorder-7 scale (GAD-7[99])
Chart review of electronic medical record/BUP Registry: Urine drug screen results from patient's most recent clinical MOUD visit; total daily BUP dose and formulation of BUP; hospitalizations and emergency room visits since study enrollment.

Finally, in terms of safety monitoring, although not a proposed outcome measure per se, during all study visits, patients will be asked an open-ended question about new symptoms experienced since the last visit (adverse events [AEs]). Drs. Evins, Rigotti and I will review them to assess relatedness of symptoms to e-cigarette use. All AEs will be assessed using the FDA's definition of adverse events (See DSMP attachment).[100]

Visit Name	**BL1**	**BL2**	**V2**	**V4**	**V6**	**V8**	**V12**
Study Week for Immediate SREC Group	**-1**	**0**	**2**	**4**	**6**	**8**	**12**
Study Week for WLC Group	**-1**	**0**	**10**	**12**	**14**	**16**	**20**
Quantitative Measures							
Demographics, Tobacco, & OUD History	X						
# of Cigarettes Smoked/Day (CPD)							
Daily text messages	X	X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X	X
E-cigarette Use (Yes/No)							
Daily text messages		X	X	X	X	X	
Timeline Followback (past 7-days)		X		X		X	X
Pod collection/count			X	X	X	X	
E-cigarette Pos & Neg Subjective Effects				X		X	X
Cigarette Dependence & Withdrawal							
Dependence (FTCD)	X			X		X	X
E-cig Dependence (eFTND)	X			X		X	X
Withdrawal (MNWS)	X	X	X	X	X	X	X
Biomarkers of Exposure							
Breath Carbon Monoxide (CO)	X	X	X	X	X	X	X
Urinary Biomarkers (anabasine, cotinine)	X			X		X	X
Health Effects							
Adverse events	X	X	X	X	X	X	X
Respiratory Symptoms (SGRQ)	X	X	X	X	X	X	X
Non-Tobacco Substance use							
Urine Drug Toxicology	X			X		X	X
Addiction Severity Index-Lite (ASI)	X			X		X	X
Breath Alcohol	X	X	X	X	X	X	X
Alcohol (AUDIT-C)	X			X		X	X
Psychiatric Symptoms							
Depression (PHQ-9)	X			X		X	X
Anxiety (GAD-7)	X			X		X	X
Chart Review	X			X		X	X
Qualitative Interview							X
Domains: Barriers/facilitators of switching to SRECs (e.g., impact of social-environmental factors), method of switching, acceptability (e.g., positive/adverse effects of switching)							X

Note. SREC, standardized research electronic cigarette; F/U, follow-up; BL, Baseline; V, Visit; OUD, opioid use disorder; Pos & Neg, positive and negative

Key: *SRECs will be distributed to immediate SREC participants during BL2 (following randomization) and to WLC participants at their Week 8 visit (See Figure 1).

Table 3. Cigarette, E-cigarette and Biomarker Outcome Measures for Study Aim 2			
Outcome	**Type**	**Source**	**Definition**
Cigarette Use (past 7d)	**Primary**	**Daily texts (past 7d)**	**Change in mean number of CPD in the past 7 days from Baseline 2 to Week 8 between randomized groups***
	Secondary	Daily texts (past 7d)	Change in mean CPD in past 7 days from Baseline 2 to Week 4, and Week 4 to 8 (Weeks 8-12 and 12-16 in WLC)**
	Secondary	TLFB (past 7d)	Change in mean CPD in past 7 days from Baseline 2 to (1) Week 4 and (2) Week 8; and from Weeks 8 to 12 (Week 8-16 and 16-20 in WLC)**
	Secondary	Daily texts (past 7d)	Number of days of cigarette use (≥1 CPD) in the past 7 days from Baseline 2 to Weeks 2, 4, 6, and 8 (Weeks 8-16 in WLC)**
E-cigarette Use (past 7d)	Secondary	Daily texts (past 7d)	# of days of e-cigarette use in past 7 days at Weeks 2, 4, 6, and 8 between randomized groups*
	Secondary	TLFB (past 7d)	# of days used e-cigarettes in past 7 days at Weeks 4, 8, and 12 (Weeks 12, 16, 20 for WLC)**
	Exploratory	E-cigarette pod count	# of used e-cigarette pods at each assessment visit during e-cigarette provision (Weeks 2, 4, 6, 8 for iSREC and Weeks 10, 12, 14, 16 for WLC)**
Biomarkers			
Carbon monoxide (CO)	Secondary	Expired air	Change in CO (ppm) from Baseline to Weeks 4 and 8 between randomized groups*; from Baseline to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **
Anabasine	Secondary	Urine	Change in anabasine (ng/ml) from Baseline 1 to Weeks 4 and 8 between randomized groups;* from Baseline 1 to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **
Cotinine	Secondary	Urine	Change in cotinine (ng/ml) from Baseline 1 to Weeks 4 and 8 between randomized groups*; from Baseline 1 to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **
Note. E-cigarette, electronic cigarette; 7d, 7 days; CPD, cigarettes smoked per day; TLFB, timeline followback; Cigs, cigarettes; PPM, parts per million; ng/ml, nanograms per milliliter			
Key: *denotes a between randomized groups comparison (iSREC vs. WLC); **denotes a within-subjects comparison combining iSREC and WLC groups to examine changes across SREC provision and pre and post SREC provision			

Remuneration: Patients will be remunerated $50 for each visit they attend, and $50 for the qualitative interview. There are 7 total study visits if they are randomized to the SREC group, and 11 total study visits if randomized to the WLC. . Patients will receive $1 for each daily text message answered within 24 hours during the baseline period ($7 total), and $1 for each daily text answered during SREC provision with a $10 bonus for answering all 56 text messages. WLC patients will also be compensated $1 for each daily text answered during their 8-week delay period. Finally, all patients will receive a $50 bonus for completing all study visits including the follow-up assessment, excluding visits with excused absences. Payment will be via Advarra cards, a method that was acceptable in this population in my K12 study.[9]

For participants who need assistance with transportation to study visits, we will offer T-passes, parking vouchers, andreimbursement for parking garages up to $150. .

7. Risks and Discomforts

E-cigarette use: E-cigarettes are devices that heat nicotine to produce an aerosol that users “vape.” The health effects of e-cigarettes are still unclear, but preliminary data suggest that e-cigarettes appear to be less than harmful than tobacco cigarettes in that they expose users to fewer toxicants than cigarettes (NASEM, 2018), and emerging data suggest that

smokers who switch completely from conventional cigarettes to e-cigarettes will likely reduce their risk of tobacco-related health harms (the goal of the present study). Most exclusive e-cigarette users have lower nicotine levels than when they smoked regular combustible cigarettes. Some e-cigarette users, especially those who use both e-cigarettes and regular tobacco cigarettes, as well as youth and young adults, can have increased nicotine levels, though recent data suggests that on average, exclusive vapers, exclusive cigarette smokers and dual users of both products have similar levels of daily nicotine intake (Benowitz et al ., 2021). In some rare cases, these use patterns have been associated with seizures. Whether this would occur with individuals instructed to switch completely to e-cigarettes from cigarettes is unclear but based on prior data we would hypothesize highly unlikely to occur in the present study. E-cigarette users very often maintain addiction to nicotine, but this addiction appears to be somewhat less than that from tobacco cigarettes. Abruptly quitting e-cigarettes could cause withdrawal symptoms similar to those from quitting tobacco cigarettes but slightly less severe. The most common side effects include dry mouth, irritation of the throat and mouth, and mild cough. NIDA's standardized research electronic cigarette (SREC), that we will be providing to patients in the present study, appears to have fewer risks than other commercially available e-cigarettes because it produces a consistent, well-characterized aerosol, and was designed to serve as a standard for clinical studies without concern of modifications being made to the device during the course of a longitudinal study.

Patients may have heard that e-cigarettes, or "vapes," can explode and seriously injure people. Although this has not been reported with the SREC, study staff will instruct patients that although they appear rare, these explosions are dangerous. The exact causes of these incidents are not yet clear, but some evidence suggests that battery-related issues (reported with older device types not under investigation in the present study) may lead to vape explosions. In order to prevent e-cigarette related injuries, patients will be instructed to keep their e-cigarettes away from other metal objects, not charge the device with a phone or tablet charger, and not charge the e-cigarette overnight or leave it charging unattended, and to stop using the e-cigarette immediately if the batteries get damaged or wet. Patients will also be instructed to always keep e-cigarette liquid pods out of children's and pets' reach (although SREC pods are sealed and non-refillable thus e-liquid is not accessible) and sight after use. If the study staff learns about additional risks of e-cigarettes during the course of the study, patients will immediately be informed of these risks. Additionally, in August 2019, a new concern about the safety of commercial e-cigarettes arose when cases of severe pulmonary illness associated with vaping (EVALI) were reported. However, the Centers for Disease Control and Prevention (CDC) have since reported that: 1) vitamin E acetate, an additive in some THC-containing e-cigarettes, was strongly indicated as the primary cause of EVALI, 2) data suggests that most EVALI patients obtained these products from informal source such as friends, online, or in-person dealers, and, 3) there have been significant declines in new EVALI cases since September 2019 (CDC, 2020). Further, recently (4/26/22), the FDA approved a pod-mod e-cigarette device type (NJOY, LLC) which met the standard of being "appropriate for the protection of the public health." We propose to use NIDA's SREC (also manufactured by NJOY, LLC) as our e-cigarette product for the present study. The SREC will provide a device that produces a consistent, well-characterized aerosol as well as sealed pods to reduce concerns about device tampering during the study. Thus, use of the SREC is not expected to be harmful or elevate risk beyond the risk expected from smoking combustible cigarettes, and below we detail our plan for monitoring risks including any increases in nicotine use from baseline.

All patients will receive detailed verbal and written instructions (at Baseline 2 for iSREC and Week 8 for WLC participants) about how to properly use e-cigarettes, safely charge and store the devices, and instructions to reach out to study staff at any time during the study with any questions or concerns about e-cigarette use. To minimize the risks outlined in Section 1b.

above, I will also instruct patients on the nicotine content of the e-cigarettes compared to their regular daily cigarette and provide e-cigarette pod supplies using this calculation (adjusted as needed), as well as instruct patients on the signs/symptoms of too much or too little nicotine. Under the guidance of my physician mentors and collaborators, I will closely monitor for signs of nicotine increase from baseline, nicotine overdose or withdrawal, and respiratory symptoms at scheduled visits and in-between visits as necessary. I will advise patients to report all adverse events (assessed at each visit), and arrangements will be made for urgent visits with the patient's primary care provider, our study physicians, or the emergency department depending on the nature of the event. I will exclude individuals with severe medical complications as mentioned above and CHC providers may also chose to exclude any patients from participation. See Data Safety Monitoring Plan for additional details on safety monitoring and adverse event reporting.

Loss of confidentiality: Loss of confidentiality is another potential risk, though unlikely, for questionnaire items and/or for drug testing results. We have never had any confidentiality issues in any of our related trials and overall risks from loss of confidentiality are expected to be minimal.

We will ensure that maximal care is taken to preserve participant confidentiality to the highest extent possible. Questionnaire data will be collected and stored electronically using secure systems (e.g. REDCap; Research Electronic Data capture; http://project-redcap.org) and questionnaire data will not include any identifying information. Consent forms will be stored in a separate, locked filing cabinet within the PI's locked office on a locked floor at MGH. Additionally, access to patient identifiers will be limited to necessary study staff on a password-protected encrypted network drive on MGH's secure server. A separate file will link study ID with patient contact information. All digital audio recordings for the qualitative interviews will be immediately uploaded to the PI's MGH-encrypted computer and the file will then be deleted from the recording device.

All participant assessment visits that are held in-person will be in a standard confidential medical conference room at the MGH CHCs (see Dr. Wakeman's letter of support), or held at Dr. Evins' Center for Addiction Medicine To expand access to diverse populations, virtual visits may be conducted as necessary. Virtual visits will be conducted via MGB approved platforms (i.e., video calls over Zoom) and will mirror in-person visits with the identical personnel present on the call. All questionnaires typically collected during the in-person screening visit may be collected during the remote screening visit, as they are largely already completed on secure online platforms (i.e., REDCap).

The pre-screening visit and qualitative interview will be conducted via telephone and the RA will use confidential standard office space in in Dr. Evins' Center for Addiction Medicine and ensure that the patient is in a space that they are comfortable completing the interview. Only IRB approved study staff will have access to any research or personally identifying data.
REDCap: REDCap is a secure, web-based application that was developed by researchers at the Vanderbilt University. Locally hosted by Mass General Brigham/MGH Research Computing, REDCap allows for secure, electronic data collection and management of clinical research study data.

Urine biomarker analysis: Patient's urine samples will also be identified solely by patient's unique study ID and they will be kept in a secure MGH freezer until they are shipped in batches to the Mayo Clinic for analysis.

Emotional discomfort: There is minimal emotional discomfort or psychological risk associated from discussion of tobacco use and related symptoms proposed in this study. It is possible that patients may be uncomfortable answering questions about their tobacco use due to stigma associated with use, however these questions are not anticipated to cause significant embarrassment or emotional distress based on our prior work in this population. Tobacco use

is common among individuals with OUD, has been rated by participants as socially acceptable, and is also legal (like e-cigarette use), thus discussing use is not anticipated to cause significant emotional distress.

Study staff will instruct patients that they do not have to answer any questions or provide any samples that make them uncomfortable. If any patient during the pre-screening or any assessment visit endorses suicidality either spontaneously or via the Patient Health Questionnaire (PHQ-9) depression measure (i.e., PHQ-9 item 9 score > 0), the research assistant will follow a safety assessment protocol that our team has developed and used in several prior NIH-funded studies of vulnerable smoking populations. The protocol will involve further assessing safety risk through a series of structured questions, with specific instructions at each step based on the patients' response. It will begin by clarifying the response to PHQ-9 item 9 (i.e., determining passive versus active suicidality). If patients endorse active suicidality, the trained research assistant will further assess safety risk (e.g., plan, intent, past suicide attempts). The research assistant will notify the PI/ licensed psychologist (Dr. Streck) immediately, and patient's Community Health Center (CHC) provider about any active suicidal ideation and/or call 911 if necessary. In cases where the participant has active suicidal ideation, the research assistant will immediately page the PI and the PI will assess and triage the patient. In our team's previous work, it has been extremely rare for a patient to report active suicidality that requires immediate intervention.

Coronavirus (COVID-19) Infection: Although it is anticipated that all MGH staff and patients will be vaccinated and boosted by the anticipated start date for this K23 if funded, we will adhere to all state, national and MGH-specific COVID-19 infection control procedures to protect our study staff and patients from being at increased risk for infection.

Per MGH policies, all employees are required to receive all doses of the COVID-19 vaccine. Regardless, as mentioned above, we will adhere to all state, national and MGH-specific COVID-19 infection control procedures to protect our study staff and patients from being at increased risk for infection.

Adverse Events: As outlined in our Data Safety Monitoring Plan, in the event of any adverse or other serious events that require immediate medical, psychiatric, or other professional intervention, the research assistant, under the supervision of the PI, will triage the patient to the appropriate emergency services. Patients who present to study sessions intoxicated on substances or impaired in any way, will have their study visit rescheduled and they will need to present to that session not impaired in order to complete the session and be paid for participation. Patients who present to sessions intoxicated or impaired will be assessed for safety and transportation home will be provided if necessary. We will not exclude patients with positive non-buprenorphine drug screens during the trial. The PI (in consultation with her mentorship team), may exclude any patient from the trial if the patient becomes unable to complete study procedures for any reason.

8. Benefits

There is a possible direct benefit to participants. Patients will be instructed to reduce their combustible daily cigarette use and to substitute e-cigarette use for cigarette use which aims to facilitate reductions in cigarettes smoked per day, reduced tobacco exposure and eventual increased health benefits (e.g., improvement in dyspnea). Even if e-cigarettes are found to not reduce exposure to toxins, cigarettes per day, or if respiratory symptoms were to

worsen with their use (which is not anticipated), this study will still provide valuable data about the need for patients to avoid e-cigarette products. The data from this trial will be clinically informative and inform policies on regulating and marketing e-cigarettes. Preliminary data in the literature suggests e-cigarettes are likely to help reduce cigarette use in patients.

In the qualitative interview, patients will also have the opportunity to discuss their attempts to reduce their cigarette use and barriers and facilitators to e-cigarette substitution which may be useful for increasing patients' awareness of their cigarette use, what maintains use, and obstacles to stopping use which could be useful for eventual cessation of cigarette use.

9. Statistical Analysis

Specific Aim 1: **To assess the feasibility of an e-cigarette substitution intervention in 60 adults who smoke cigarettes daily and are stable on MOUD and not yet ready to quit smoking.**

Primary outcomes: Study enrollment (% screened of those identified via BUP registry, % eligible of those screened; % enrolled of those screened eligible); retention (% of patients who complete the trial, defined as completing the final follow-up assessment *and* ≥50% of the study visits). We will also document reasons for ineligibility and exclusion to inform future trial protocols.

Hypotheses: *Hypothesis 1a*: 45% of those screened as eligible will enroll; *Hypothesis 1b:* >70% will complete the trial (i.e., attend final follow-up assessment and attend ≥50% of study visits). Hypotheses are based on my and my mentor's prior work recruiting from the same CHCs and based on a prior e-cigarette study in OUD treatment.[9,14,73]

Analysis: Descriptive statistics using data from study recruitment and enrollment records will test hypotheses.

Specific Aim 2. To quantitatively examine the effects of SREC provision on changes in tobacco use behavior (cigarettes per day [primary outcome], e-cigarette use), exposure to tobacco-related biomarkers, cigarette dependence and withdrawal, and short-term health effects and tolerability of e-cigarettes during 8 weeks of e-cigarette provision.

Outcomes will also be assessed 4 weeks after e-cigarette provision ends (See **Table 3** for definitions of cigarette, e-cigarette and biomarker outcomes).

Primary outcome: **Change in mean cigarettes smoked per day (CPD) between baseline and 8 weeks comparing between randomized groups (iSREC group vs. WLC).**

Hypothesis: The mean reduction in CPD from Baseline 2 to 8 weeks in the iSREC group will be greater than in the WLC group.

Secondary outcomes (Table 3): CPD: *Hypothesis:* The mean reduction in CPD across the 8 weeks of SREC provision will be at least 25% in an analysis combining randomized groups. Days of e-cigarette use: *Hypothesis:* During the 8 weeks of e-cigarette provision, patients will use e-cigarettes on at least 50% of the past 7 days measured at each assessment in an analysis combining randomized groups. Biomarkers*:* We anticipate that levels of CO and anabasine will decrease across the 8 weeks of SREC provision in a pre-post analysis combining randomized groups, corresponding with reduced cigarette consumption, and that biomarker levels in the iSREC group will be lower than WLC from Baseline 2 to Week 8. Cotinine levels may or may not change during SREC provision depending on the degree of substitution of e-cigarettes for cigarettes.

Table 3. Cigarette, E-cigarette and Biomarker Outcome Measures for Study Aim 2

Outcome	Type	Source	Definition
Cigarette Use (past 7d)	**Primary**	**Daily texts (past 7d)**	**Change in mean number of CPD in the past 7 days from Baseline 2 to Week 8 between randomized groups***
	Secondary	Daily texts (past 7d)	Change in mean CPD in past 7 days from Baseline 2 to Week 4, and Week 4 to 8 (Weeks 8-12 and 12-16 in WLC)**
	Secondary	TLFB (past 7d)	Change in mean CPD in past 7 days from Baseline 2 to (1) Week 4 and (2) Week 8; and from Weeks 8 to 12 (Week 8-16 and 16-20 in WLC)**
	Secondary	Daily texts (past 7d)	Number of days of cigarette use (≥1 CPD) in the past 7 days from Baseline 2 to Weeks 2, 4, 6, and 8 (Weeks 8-16 in WLC)**
E-cigarette Use (past 7d)	Secondary	Daily texts (past 7d)	# of days of e-cigarette use in past 7 days at Weeks 2, 4, 6, and 8 between randomized groups*
	Secondary	TLFB (past 7d)	# of days used e-cigarettes in past 7 days at Weeks 4, 8, and 12 (Weeks 12, 16, 20 for WLC)**
	Exploratory	E-cigarette pod count	# of used e-cigarette pods at each assessment visit during e-cigarette provision (Weeks 2, 4, 6, 8 for iSREC and Weeks 10, 12, 14, 16 for WLC)**
Biomarkers			
Carbon monoxide (CO)	Secondary	Expired air	Change in CO (ppm) from Baseline to Weeks 4 and 8 between randomized groups*; from Baseline to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **
Anabasine	Secondary	Urine	Change in anabasine (ng/ml) from Baseline 1 to Weeks 4 and 8 between randomized groups;* from Baseline 1 to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **
Cotinine	Secondary	Urine	Change in cotinine (ng/ml) from Baseline 1 to Weeks 4 and 8 between randomized groups*; from Baseline 1 to Weeks 4, 8, and 12 (Weeks 8-20 in WLC) **

Note. E-cigarette, electronic cigarette; 7d, 7 days; CPD, cigarettes smoked per day; TLFB, timeline followback; Cigs, cigarettes; PPM, parts per million; ng/ml, nanograms per milliliter

Key: *denotes a between randomized groups comparison (iSREC vs. WLC); **denotes a within-subjects comparison combining iSREC and WLC groups to examine changes across SREC provision and pre and post SREC provision

Analysis Plan: CPD and number of days of e-cigarette use will be assessed in two ways at Baseline 2 and Weeks 4 and 8 (Weeks 8, 12, 16 for WLC): via daily text messages and by TLFB. I will use a past 7-day average to summarize the usage at each time point. For the primary outcome of change in CPD between baseline and Week 8, I will compare changes between the randomized groups (iSREC vs. WLC) using a two-sample test or a Wilcoxon rank test, whichever more appropriate. I will also conduct within-group comparisons (each patient serves as their own control) to examine changes in CPD during vs. after provision ends in a pre-post analysis that combines both randomized groups (i.e., change from 0 to 8 weeks in iSREC combined with 8-16 weeks in WLC, compared to 8-16 weeks in iSREC combined with 16-20 weeks in WLC) using one-sample t-tests or signed rank tests. The primary analysis will be limited to completers (patients who provided CPD data at Week 8). I will also perform sensitivity analyses with the following missing imputation methods of the Week 8 outcome measure: (1) Last value carried forward, (2) Trajectory from the available CPD at all previous time points, and (3) multiple imputation using all appropriate covariates. I will additionally employ repeated measures mixed effects models using data from all available time points to increase the power of the comparisons and investigate the group, time, and group x time interaction effects. I will perform an exploratory analysis on heterogeneity of treatment effect by examining whether any subgroup (e.g. age, gender, non-prescribed substance use in previous time point) achieves larger reductions of cigarette consumption during SREC provision. Number of days of e-cigarette use across the 8 weeks of provision and at post provision follow-up will be summarized at each assessment visit. For number of days of e-cigarette and cigarette use, biomarker outcomes (CO, cotinine, anabasine), and all other continuous measures assessed over time (i.e., FTCD, MNWS, subjective effect VAS ratings, SQRQ, PHQ-9, GAD-7, ASI, AUDIT-C), I will apply the same analytic approach as indicated above for CPD (i.e., both between randomized groups and within-subject comparisons). In addition, I will monitor the % of positive drug screens over the study period to evaluate whether substance use changes over time and between groups.

Power: The primary outcome is changes in cigarettes per day at baseline vs. 8 weeks between groups. Assuming α=0.05, 60 patients total and a 30% attrition rate, with a standard deviation

of 4.33 for change in cigarettes per day,[13] the study will have 80% power to detect a mean difference of 4.76 cigarettes per day in change from Baseline 2 to Week 8 between groups.
Deliverables: I plan to publish at least 3 manuscripts from this Aim: 1) "The feasibility, acceptability, and preliminary effects of substituting e-cigarettes for cigarettes in individuals who smoke receiving MOUD: a randomized waitlist-controlled trial" (target journal: *Addiction*), 2) "The impact of switching to e-cigarettes on longitudinal changes in psychiatric symptoms and substance use in patients with OUD" (target journal: *Drug and Alcohol Dependence* [DAD]) and, 3), Predictors and moderators of successful e-cigarette substitution in patients with OUD: A mixed-methods analysis (target journal: *Nicotine and Tobacco Research).*

Specific Aim 3. To qualitatively explore patient's experiences attempting to use the SREC to reduce combustible cigarette smoking, using individual in-depth exit interviews that occur at the end of SREC provision. Patients will report on barriers and facilitators of making a complete switch to e-cigarettes, their method of switching, as well as acceptability (e.g., desire to continue e-cigarette vs. stop use at trial end).
Proposition: Patients will describe e-cigarettes as acceptable and helpful for reducing cigarette use.
Analysis: Individual qualitative interviews will be audio-recorded, transcribed and iteratively analyzed using the framework method of content analysis (both inductive and deductive)[101] in Dedoose 8.3 qualitative software. With mentorship from Dr. Park, the trained research assistant and I will separately review each transcript and develop a coding framework. We will follow the steps of the framework method: 1) become familiar with the interview, 2) read a subset of initial transcripts to identify codes ("open coding"), 3) develop the coding framework, 4) assess the coding framework with additional transcripts and modify accordingly, 5) apply the coding framework

10. Monitoring and Quality Assurance

Training of all Study Personnel in the Responsible Conduct of Human Studies: Prior to recruiting subjects or handling study data, all study personnel will be required to pass the NIH approved course that reviews regulatory and informational documents on human subject protection and the responsible conduct of human studies. In addition, all study personnel will sign a statement of commitment to the protection of the rights and welfare of human subjects participating in research.

DATA SAFETY MONITORING PLAN

Overview: The PI will be responsible for monitoring safety throughout the trial and adhering to all reporting requirements. The PI will assume responsibility for reporting all adverse events that may arise to the IRB and/or federal funding agency, as required. Adverse events will be defined according to FDA's definition (i.e., any untoward consequence to study participants that may be related or possibly related to study procedures). Events may include, but are not limited to, worsening of psychiatric, emotional or physical symptoms; breaches in participant confidentiality, deviations from IRB-approved protocols (e.g., contacting participants to obtain survey data outside of IRB-approved time windows), or any participant safety concerns. Study recruitment, enrollment, and retention will be reviewed by the PI and research assistant (RA) weekly. Informed consents will also be reviewed weekly by the RA and PI, and monthly by the PI's mentors for the purposes of quality control. The RA will report on any issues or obstacles in recruitment, enrollment, survey administration, biospecimen collection, e-cigarette provision,

and follow-up to the PI during weekly research team meetings. The RA will review all questionnaire and collected biospecimens (e.g., breath, urine) in real time to ensure data completion.

Safety monitoring plan: In this proposal, I will provide e-cigarettes to individuals who smoke cigarettes with OUD who are not ready to quit smoking. I will collect safety information related to the following categories: (1) worsening of respiratory symptoms, (2) symptoms of nicotine toxicity, and (3) adverse events of e-cigarettes previously reported to the FDA. This includes regular monitoring (every 2 weeks for all participants and more if needed determined on a case-by-case basis) of dyspnea and open ended questions on any medical care (including hospitalizations or emergency room visits) since the last visit assessed at each study visit. While nicotine toxicity is rare in clinical trials, I will monitor breath CO levels at each study visit and also monitor for potential signs and symptoms of nicotine withdrawal. Adverse events related to e-cigarettes previously reported to the FDA include serious events such as hospitalization for pulmonary or cardiac causes, seizure, burns caused by e-cigarette devices/malfunction, and other adverse events such as headache, nausea/vomiting, dizziness, confusion, blurry vision, throat irritation, abdominal pain, and sleepiness. In consort with my physician mentors, I will advise participants to stop e-cigarette use if necessary. During the first week of e-cigarette use, patients will also be contacted if they don't respond to daily text messages within 48 hours and we will check in on their switch to e-cigarettes and assess any medical symptoms that may arise. I and/or a trained RA will collect all data. In the event of any adverse or other events that require immediate medical, psychiatric or other professional intervention, the RA will immediately page the PI who will triage the patient to the appropriate emergency services (e.g., 911 or emergency room).

Attribution of adverse events: Adverse events are any side effect that occurs in a participant, while serious adverse events are those that are life-threatening, resulting in hospitalization, disability, or death. I will attribute adverse events that arise in the study to e-cigarettes according to the following scale: definite (clearly related to e-cigarettes), probable (likely related to e-cigarettes), possible (may be related to e-cigarettes), unlikely (likely not related to e-cigarettes), and unrelated (clearly not related to e-cigarettes).

Reporting of adverse events: I will report all adverse events to the Mass General Brigham (MGB) IRB and the NIH funding agency. I will also report serious adverse events, and any events requiring the trial to be stopped, to the FDA. Any complications that are deemed to be related to the study will be immediately reported to the study PI (within 24 hours). Any serious adverse events that arise throughout the course of the award period will be reported to the Mass General Brigham IRB submitted within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. All adverse events will be submitted annually for review by the MGB IRB.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)

- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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