

eSupplement 1

eSupplement 1 was prepared by the authors to provide interested readers additional protocol and statistical-analysis details on the three randomized, controlled trials reported in Higgins ST, Sigmon SC, Tidey JW, et al. *Reduced Nicotine Cigarettes and E-Cigarettes in High-Risk Populations: 3 Randomized Clinical Trials*

Protocols for each of the three trials are detailed separately below followed by the Statistical Analysis Plan for those trials at the end of each protocol.

The protocol information provided below is what local Institutional Review Boards at each research site approved.

Summary of Protocol Modifications:

10-2-20 Two modifications were made across the three trials. (1) We stipulated that individuals must have access to the technology necessary to complete the initial study eligibility assessment. (2) Deleted mention of a debit card and an e-cigarette sampling session and associated questionnaire which were carried over from the original in-person protocol.

10-12-20 Made three protocol modifications across the three trials. (1) Moved to salivary rather than urine drug toxicology testing to allow observed specimen collection. Urine specimens were retained as a back-up should someone be able to provide adequate saliva for valid testing. (2) Stipulated that should a participant fail to provide a first void urine specimen, arrangements to get that specimen on another day will be made rather than substituting a spot urine specimen. (3) Added an e-cigarette flavor rating questionnaire.

11-30-20 Modified curbside assessments to include a lab option for inclement weather.

2-2-21 Modified protocols to allow increases in weekly supply of e-liquid pods if a participant consistently uses more than their baseline determined amount.

3-17-21 Substituted breath CO for a urine specimen to confirm abstinence in the assessments completed 30 days after trial completion.

5-11-21 Increased maximal participant compensation to more equitably compensate participants for the considerable time commitment the trials require.

6-27-22 (1) Provided greater detail to the protocols regarding study policy on contraception use. (2) Updated the Data Safety Monitoring Board roster.

1-23-23 Increased maximal participant compensation to include bonuses for every two consecutive study visits completed on schedule.

47 **Reduced Nicotine Cigarettes and E-Cigarettes in High-Risk Populations: 3 Randomized Clinical**
48 **Trials**

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97 **STUDY PROTOCOL: SMOKERS WITH AFFECTIVE DISORDERS**

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Abbreviations

- 173 • 3HC: 3-hydroxycotinine
- 174 • BAL: Breath alcohol levels
- 175 • BDI: Beck's Depression Inventory
- 176 • BMI: Body Mass Index
- 177 • BP: Blood pressure
- 178 • BPM: Beats per minute
- 179 • BRIEF-A: Behavioral Rating Inventory of Executive Function
- 180 • CES: Cigarette Evaluation Scale
- 181 • CO: Carbon monoxide
- 182 • COT: Cotinine
- 183 • CPD: Cigarettes per day
- 184 • CPT: Cigarette Purchase Task
- 185 • CPT: Continuous Performance Task
- 186 • DAST: Drug Abuse Screening Test
- 187 • DDT: Delay Discounting Task
- 188 • D-KEFS: Delis-Kaplan Executive Function System
- 189 • EDC: Electronic Data Capture
- 190 • EQ-5D: Euro-Qol
- 191 • FSPTCA: Family Smoking Prevention and Tobacco Control Act
- 192 • FTND: Fagerström Test for Nicotine Dependence
- 193 • GAD: Generalized Anxiety Disorder
- 194 • HR: Heart rate
- 195 • IVR: Interactive Voice Response
- 196 • MDD: Major Depressive Disorder
- 197 • MINI: Mini International Neuropsychiatric Interview
- 198 • MNWS: Minnesota Nicotine Withdrawal Scale
- 199 • NMR: Nicotine metabolite ratio
- 200 • NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
- 201 • NNC: Normal nicotine content
- 202 • NNN: *N*-nitrosonornicotine
- 203 • OASIS: Overall Anxiety Severity and Impairment Scale
- 204 • OUD: Opioid Use Disorder
- 205 • PANAS: Positive and Negative Affect Schedule
- 206 • PHQ: Patient Health Questionnaire
- 207 • PSS: Perceived Stress Scale
- 208 • QSU: Questionnaire of Smoking Urges
- 209 • RNC: Reduced nicotine content
- 210 • TLFB: Timeline Follow Back
- 211 • VLNC: Very low nicotine content
- 212 • WISDM: Wisconsin Index of Smoking Dependence Motives

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215
216 **PROTOCOL**
217

218 **1. OBJECTIVE**
219

220 While the prevalence of smoking in the US general population has declined over the past 50
221 years, there has been little to no decline among people with mental health conditions. Affective
222 disorders (ADs) are the most common mental health conditions in the US, and over 40% of
223 people with ADs are current smokers.¹ A national policy of reducing the nicotine content of
224 cigarettes has the potential to reduce tobacco use, dependence, and related adverse health
225 outcomes.²⁻⁴ Controlled trials in psychiatrically stable smokers have shown that extended use of
226 very low nicotine content cigarettes (VLNCCs) results in reductions in cigarettes per day (CPD),
227 cigarette dependence, and tobacco toxicant exposure, with few adverse consequences.⁵⁻⁸
228 Furthermore, our research during UVM TCORS Phase 1 funding indicates that smokers with
229 ADs respond to reductions in cigarette nicotine content with reductions in cigarette demand.⁹⁻¹⁰
230 However, tobacco market conditions are likely to exert considerable influence over the extent to
231 which that potential is realized. In particular, we hypothesize that the following conditions are
232 likely to exert considerable influence over the potential effectiveness of a national nicotine
233 reduction policy for cigarettes, particularly in smokers with ADs and other vulnerabilities to
234 tobacco addiction: (1) whether alternative sources of non-combusted nicotine are readily
235 available, and (2) whether these alternatives are available under conditions that optimize their
236 appeal.

237 The goal of the proposed trial is to experimentally model whether increasing the availability
238 and appeal of an alternative, non-combusted source of nicotine (e-cigarettes) enhances the
239 effects of reduced-nicotine cigarettes in smokers with ADs. Daily smokers with current ADs,
240 recruited at University of Vermont and Brown University, will be randomized to one of the
241 following four conditions: (1) normal nicotine content cigarettes (NNCCs) alone, serving as the
242 control condition, (2) VLNCCs alone, (3) VLNCCs + nicotine e-cigarettes in only tobacco flavors
243 (TF e-cigs), or (4) VLNCCs + nicotine e-cigarettes in preferred flavors (PF e-cigs). Participants
244 will be asked to use only their assigned study products for 16 weeks. Outcome measures
245 include total CPD, cigarette demand assessed by behavioral economics-based purchase tasks,
246 craving, withdrawal, psychiatric symptoms, breath carbon monoxide (CO) and biomarkers of
247 tobacco toxicant exposure. In Week 17, participants will receive incentives to abstain from
248 cigarettes during a three-hour laboratory test session and we will assess the effects of study
249 conditions on cigarette demand, craving and withdrawal.

250 This research will address the following specific aims: Aim 1 (Primary): Compare the effects
251 of (1) NNCCs alone, (2) VLNCCs alone, (3) VLNCCs + TF e-cigs and (4) VLNCCs + PF e-cigs
252 on total CPD in smokers with ADs. We hypothesize that at Week 16, total CPD will be reduced
253 in a linear, graded manner (condition 4 > 3 > 2 > 1), with the largest reduction in the VLNCC +
254 PF e-cig condition. Aim 2 (Secondary): Compare the effects of the four study conditions on
255 cigarette demand, psychiatric symptoms, and biomarkers of smoke and tobacco toxicant
256 exposure (CO, NNAL, PAHs) in smokers with ADs. We hypothesize that at Week 16, cigarette
257 demand, CO, and toxicant biomarkers will have decreased in a linear, graded manner, with the
258 largest reduction in the VLNCC + PF e-cig condition. We will characterize effects on psychiatric
259 symptoms but are not testing specific hypotheses on these symptoms. Aim 3 (Exploratory): To
260 explore the effects of the four study conditions on cigarette demand, craving, and withdrawal in
261 smokers with ADs during the abstinence assessment period.

262 The integrative theme of this TCORS is vulnerable populations. The proposed research is
263 highly relevant to the CTP's scientific domains of Addiction and Behavior because it will address
264 whether reducing the nicotine content of cigarettes reduces cigarette use, dependence, and
265 product appeal, and whether these effects are enhanced by the availability of an appealing
266 alternative source of non-combusted nicotine. It will address the Health Effects domain by
267 assessing the effects of these conditions on tobacco toxicant exposure and a respiratory
268 biomarker. The proposed study is significant and innovative because it will model how

269 availability and appeal of e-cigs may moderate the effectiveness of a national reduced- nicotine
270 policy for cigarettes in this understudied population. Finally, it is programmatic as it will build
271 upon and extend the work that our team accomplished on VLNCCs in those with ADs during
272 phase 1 of UVM TCORS funding.

273 274 **2. SIGNIFICANCE**

275 276 **2.1. Affective Disorders (AD) and Smoking**

277 Each year, cigarette smoking kills almost half a million Americans and costs the US almost
278 \$300 billion in medical costs and lost productivity.¹¹ While smoking rates in the general US
279 population have declined over the past 50 years, there has been little to no decline among people
280 with mental health conditions (MHCs), indicating that current tobacco control policies and
281 treatments are not benefiting these smokers.^{1,12} Affective disorders (ADs), which include major
282 depressive disorder and anxiety disorders, are the most common MHCs in the US; in 2015, 7%
283 of US adults reported past-year major depressive disorder and 18% reported a past-year anxiety
284 disorder.¹³ Over 40% of people with ADs are current smokers.¹ Stated conversely, 22% of
285 nicotine-dependent smokers report having a mood disorder and 23% report an anxiety disorder.¹⁴
286 Smokers with ADs make as many cessation attempts as those without MHCs, but are more likely
287 to relapse when they try to quit.¹⁵⁻¹⁸ Hence, ADs are associated with disproportionately high rates
288 of tobacco-related disease and death.^{19, 20}

289 Similar transdiagnostic factors appear to underlie the low cessation rates in people with
290 depression and anxiety disorders.²¹ Negative mood is a prominent feature of major depression
291 and anxiety disorders²². Although long-term cessation is associated with improvements in mood,²³
292 smoking abstinence produces transient increases in negative mood that are reversed by
293 smoking.²⁴ Smokers with ADs report more severe effects of abstinence on negative mood than
294 those without MHCs,²⁵ and have stronger expectancies that smoking will reduce negative mood.²⁶⁻
295 ²⁸ Anhedonia (reduced capacity to experience pleasure from rewarding stimuli) may also
296 contribute to smoking persistence in people with ADs. Anhedonia is a key symptom of depression
297 and anxiety disorders and is associated with increased responsiveness to pharmacological
298 reinforcers that potently release mesolimbic dopamine (DA).²⁹ Consistent with this hypothesis,
299 smokers with a history of major depression have greater smoking-induced DA release than those
300 without depression,³⁰ and overvalue cigarette reinforcement.^{31,32} Furthermore, nicotine can
301 enhance the reinforcing effects of environmental stimuli.^{33,34} This may contribute to low cessation
302 rates in smokers with ADs, as smokers with depression, but not those without MHCs, report
303 greater enjoyment of activities in their natural environments while smoking.³¹

304 A national nicotine reduction policy for cigarettes may be an effective regulatory approach to
305 reducing cigarette dependence in smokers with ADs. The 2009 Family Smoking Prevention and
306 Tobacco Control Act gave the Food and Drug Administration (FDA) the authority to regulate
307 tobacco products as appropriate to protect public health, including limiting the nicotine content of
308 cigarettes.³⁵ An FDA-mandated reduction in the nicotine content of cigarettes to a minimally-
309 addictive level could reduce tobacco reinforcement and dependence.^{3,36} This approach could be
310 particularly beneficial to subpopulations of smokers who have less success with currently-
311 available cessation treatments, such as people with ADs. Our work during the UVM TCORS
312 phase 1 funding period, indicates that smokers with ADs, like smokers without MHCs, respond to
313 reductions in the nicotine content of cigarettes with reductions in cigarette demand and other
314 measures of addiction potential. However, tobacco market conditions are likely to exert
315 considerable influence over the extent to which the effects of reduced-nicotine cigarettes are
316 realized in the natural environment. This may be particularly true of smokers with ADs, who are
317 more sensitive to the effects of nicotine withdrawal than those without MHCs.³⁷ Use of electronic
318 cigarettes (e-cigs) is increasing sharply in the US, and it is important to consider the potential
319 moderating effects of e-cig use on a reduced-nicotine policy for cigarettes. By providing an
320 alternative source of nicotine, we believe that the availability of nicotine e-cigs, and
321 manipulations that increase their appeal (flavors), will enhance the ability of a national cigarette
322 nicotine-reduction policy to decrease cigarette smoking, dependence and toxin exposure among

323 smokers with ADs.

324
325 **2.2. Relevance of the project to the integrative theme and goals of the TCORS**

326 The integrative theme of the UVM TCORS is vulnerable populations, and its goals are to
327 model the potential effects of tobacco product standards on product use in vulnerable populations,
328 with the goal of reducing the risks of product use, dependence, and product-related adverse
329 health outcomes. For the FDA to effectively execute its tobacco regulatory responsibilities, it must
330 have sound scientific evidence on how product standards impact tobacco use in populations with
331 high rates of tobacco dependence. This project will provide the FDA with evidence on the effects
332 of a reduced-nicotine standard for cigarettes, alone and combined with another FDA-regulated
333 product (e-cigs), on measures of cigarette use, demand, dependence, tobacco toxicant exposure
334 and psychiatric symptoms in this vulnerable population.

335
336 **2.3. Relevance to the scientific domains and priorities of the FDA CTP**

337 The proposed research is highly relevant to the CTP's scientific domains of Addiction and
338 Behavior because it will address whether reducing the nicotine content of cigarettes reduces
339 cigarette use, dependence, and product appeal, and whether these effects are enhanced by the
340 availability of appealing alternative sources of non-combusted nicotine. It will address the **Health**
341 **Effects** domain by assessing the effects of these conditions on tobacco toxicant exposure and a
342 respiratory biomarker.

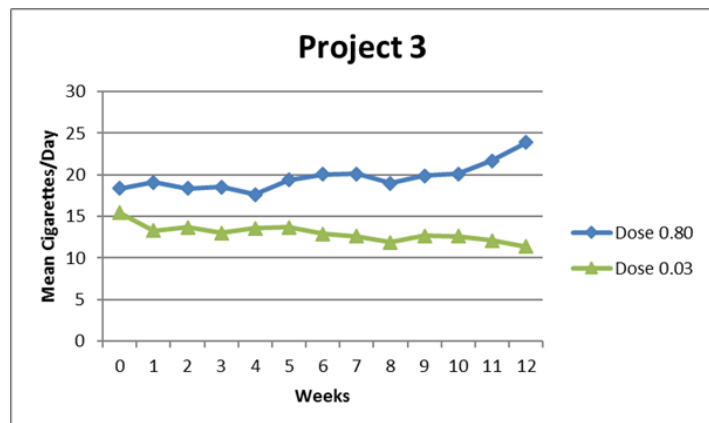
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344 **2.4. How study outcomes will improve scientific knowledge related to the manufacture,**
345 **distribution and marketing of tobacco products**

346 Study outcomes will directly inform scientific knowledge concerning the manufacture of
347 tobacco products by demonstrating whether a reduction in the maximum nicotine content of
348 cigarettes sold in the US to ≤ 0.4 mg nicotine/g tobacco would reduce smoking in this vulnerable
349 population. The outcomes will also indicate whether continuing to allow the sale of e-cigs in
350 characterizing flavors improves the efficacy of a reduced-nicotine standard for cigarettes on
351 smoking reduction in this population.

352
353 **3. RATIONALE**

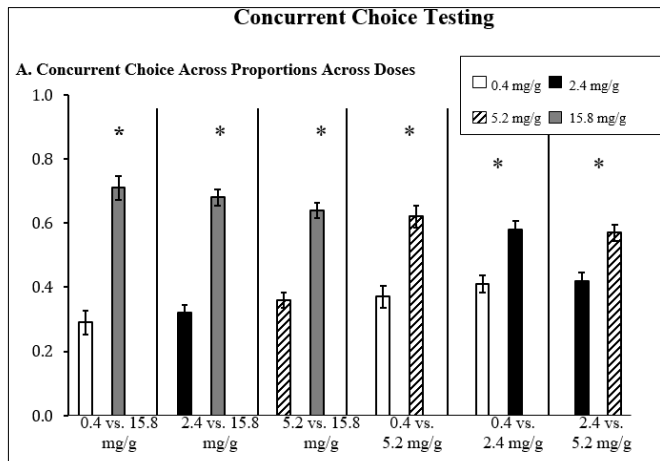
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355 **3.1. Effects of Nicotine Reduction in Smokers with AD**

356 Controlled trials of research cigarettes differing in nicotine content in general population
357 samples have demonstrated that those who are switched to VLNCCs reduce their daily cigarette
358 use, nicotine exposure, cigarette dependence, and tobacco toxicant exposure, with few adverse
359 consequences.⁵⁻⁸ Given the low smoking cessation rates in smokers with ADs, it is important to
360 consider whether these smokers experience benefits or negative consequences of nicotine
361 reduction. Prior to the work accomplished by this TCORS during Phase 1 funding, few studies
362 had examined effects of VLNCCs in smokers with ADs. Several laboratory studies in smokers
363 with elevated depression or anxiety symptoms found that both VLNCCs and normal-nicotine
364 cigarettes reduce craving and withdrawal and do not exacerbate depression or anxiety (reviewed
365 by Gaalema et al.³⁸). We recently conducted a secondary analysis of a large randomized clinical
366 trial that examined the effects of
367 cigarettes varying in nicotine content
368 over a 6-week period in non-treatment-
369 seeking smokers, in which we
370 examined whether those with higher vs.
371 lower depressive symptoms at baseline
372 differed with regard to their responses
373 to cigarettes varying in nicotine
374 content.³⁹ We found that after 6 weeks
375 of use, those who had used VLNCCs
376 had lower smoking rates, nicotine
377 dependence and craving than those



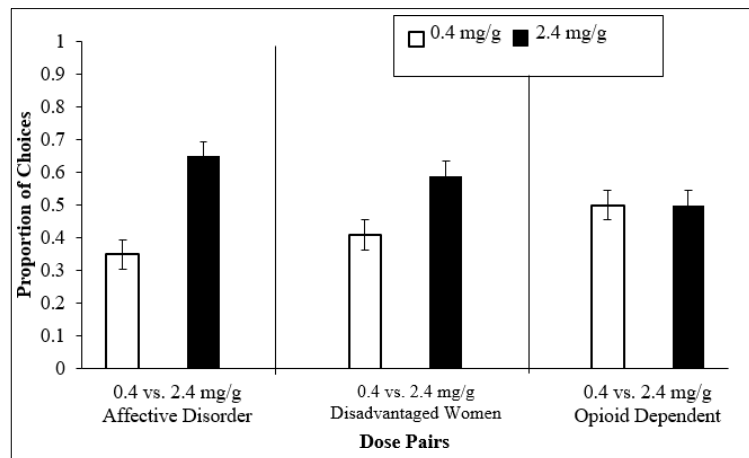
378 who had used NNCCs, regardless of baseline depressive symptom score. Furthermore, those
 379 with elevated depressive symptoms at baseline who had been assigned to VLNCCs had lower
 380 depressive symptoms at Week 6 than those who had used NNC cigarettes. Importantly,
 381 biochemically-confirmed VLNCC compliance also did not differ by group. These findings provide
 382 support for the idea that a reduced-nicotine standard for cigarettes may reduce smoking, without
 383 worsening depressive symptoms, in smokers with elevated depressive symptoms. However,
 384 that study examined VLNCC effects in a non-clinical sample with elevated depressive
 385 symptoms, not those with diagnosed depression or anxiety disorders.

386 To our knowledge, we are the first to report the effects of reduced-nicotine cigarettes on
 387 measures of cigarette reinforcement in smokers with ADs. In Study 1, we examined the acute
 388 subjective and behavioral effects of cigarettes varying in nicotine content (15.8, 5.2, 2.4 and 0.4
 389 mg nicotine/g tobacco) in smokers with ADs.^{9,10} In concurrent choice testing with the cigarettes



available at an equal response effort, participants chose the higher over the lower nicotine content cigarettes across each of the six dose pairs consistent with reduced nicotine content cigarettes having lower addiction potential (below, left). The only difference between populations was at the 0.4 versus 2.4 mg/g dose pair, where smokers with affective disorders chose the higher dose more often ($p < .001$), while disadvantaged women ($p = .06$) and those with opioid dependence ($p = .91$) did not exhibit a significant preference

404 between those two doses (below, right). All doses decreased craving and withdrawal symptoms
 405 with no evidence of compensatory smoking. While the higher nicotine cigarettes were rated as
 406 more satisfying, increasing the response requirement to obtain these cigarettes reversed that
 407 preference. This observation has considerable tobacco regulatory implications. For example, allowing
 408 VLNCCs to be sold in common retail outlets while restricting sale of higher content cigarettes to more regulated
 409 stores would be predicted to shift preference towards the former. This same concept may also extend to
 410 regulatory efforts to shift preference from harmful combusted to less harmful non-combusted tobacco
 411 products. Overall, our results indicate that reducing the nicotine content of cigarettes reduces the
 412 relative reinforcing effects of smoking, and hence addiction potential, in smokers with ADs and
 413 other vulnerabilities to tobacco addiction. The 0.4 mg/g most robustly differed from the 15.8
 414 mg/g dose in this population, supporting prior hypotheses about reducing nicotine content below
 415 0.7 mg/g³.



426 In Study 2, we are examining effects of cigarettes varying in nicotine content in smokers with
 427 ADs over a 12-week period. Preliminary results from 35 participants indicate that VLNCCs reduce
 428 smoking rates by >40% relative to NNCCs in Weeks 9-12 (see figure at right). However, while
 429 smokers with ADs reduce their smoking rates, few quit completely, similar to results seen in
 430 general population samples.⁷ These findings set the stage for examining whether providing an
 431 alternative, non-combusted source of nicotine (e-cigs) enhances the efficacy of reduced-nicotine

432 cigarettes in this population.

434 3.2. E-Cig Use

435 E-cigs consist of a cartridge containing an e-liquid solution of nicotine, propylene glycol (PG),
436 vegetable glycerin (VG), flavoring, and other additives, which is heated with an atomizer that
437 vaporizes the solution. First generation e-cigs resemble cigarettes (“cigalikes”) and are disposable
438 or rechargeable, second generation products (such as the product that will be used in this study)
439 often resemble pens and have refillable e-liquid reservoirs, and third generation devices have
440 larger batteries, adjustable power delivery and replacement heating coils and wicks.⁴⁰ Nicotine
441 levels from e-cigs can be comparable to those from cigarettes, depending on e-cig characteristics,
442 e-liquid nicotine content and user topography.⁴¹⁻⁴⁴ Potential risks of e-cig use include exposure to
443 low levels of carcinogens, toxicants, metals in the vapor, and cytotoxic effects of flavors.^{45,46}
444 However, toxin and carcinogen levels from e-cigs appear to be far lower than those from
445 cigarettes. Hecht et al.⁴⁷ reported that former smokers who had switched to e-cigs had 59-99%
446 lower levels of 6 tobacco toxicant and carcinogen metabolites than ongoing smokers, comparable
447 to reductions seen in smokers who had switched to nicotine lozenges.⁸ Another study found that
448 NNAL, a metabolite of the tobacco carcinogen NNK, was reduced by 64% in smokers who had
449 switched to e-cigs for two weeks, as was chest tightness.⁴⁸

450 E-cig use has increased sharply in the US, particularly among people with MHCs. A 2012
451 national probability survey in >10,000 US adults found that people with MHCs (including ADs)
452 were twice as likely to have ever used or to currently use e-cigs than those without MHCs.⁴⁹
453 Survey data from 2015 indicate a doubling of use since the Cummins et al. survey, and people
454 with MHCs were still twice as likely to use e-cigs as those without MHCs (24.4% ever use, 11.4%
455 current use).⁵⁰ Of those with depression and anxiety disorders, 24-30% reported ever use and 11-
456 13% reported current use.⁵⁰ Two surveys also reported that likelihood of e-cig use was associated
457 with psychiatric symptom severity or number of MHCs endorsed, suggesting a systematic
458 relationship.^{50,51} Smokers in general report that their reasons for e-cig use are to quit or reduce
459 smoking, to reduce cigarette craving and nicotine withdrawal, because e-cigs bother other people
460 less than cigarettes, and because they can use e-cigs in places where smoking is forbidden.⁵¹⁻⁵⁵
461 Smokers with MHCs report similar reasons for use.⁵⁶⁻⁵⁹

463 3.3. E-cig effects on smoking

464 To date, clinical trials indicate effects of e-cigs on smoking reduction, but little effect on
465 quitting.⁶⁰⁻⁶² Modest effects on cigarette abstinence in these trials may have been due to use of
466 first generation e-cigs that provided variable nicotine delivery and were subject to battery failure.⁶³
467 A trial using second generation e-cigs found cigarette abstinence rates of 34% after 8 weeks and
468 21% 6 months later, with an overall 60% reduction in CPD.⁶⁴ Few studies have examined the
469 effects of e-cigs in smokers with ADs. Among hospitalized smokers with serious mental illness
470 enrolled in a cessation trial, e-cig use increased during the trial but was not associated with
471 smoking abstinence.⁶⁵ Likewise, a survey in veterans found a strong association between MHCs
472 and e-cig use, but no association with quitting.⁵⁶ A secondary analysis of the Bullen et al. ASCEND
473 trial⁶⁰ found that mental health status did not moderate the effect of e-cigs on quitting.⁶⁶ A pilot
474 study in 21 smokers with psychotic disorders found that e-cig use decreased CPD.⁵⁹ Both of the
475 latter studies reported high rates of e-cig acceptability among smokers with MHCs.^{59,66}

476 We recently completed a pilot study in 18 smokers who were asked to switch to a second-
477 generation e-cig with 18 mg/ml nicotine e-liquid for 6 weeks.⁶⁷ All of those enrolled completed the
478 study. Participants significantly reduced their CPD, breath CO levels, Fagerström Test for
479 Cigarette Dependence scores, and increased their readiness to quit, all with large effect sizes
480 (Cohen’s *d*’s ranging from 0.88 to 1.3). At a follow-up visit 4 weeks later, changes from baseline
481 had been maintained with large effects sizes on all measures (Cohen’s *d*’s ranging from 0.8 –
482 1.1). This work demonstrates our experience and success with testing an e-cig similar to that
483 which will be used in this study over a multi-week period.

485 3.4. Mechanisms of e-cig effects

486 E-cigs reduce cigarette craving and nicotine withdrawal symptoms.⁶⁸ Although early studies

487 found that e-cigs were less effective than cigarettes at reducing cigarette craving and
488 withdrawal,^{60,69,70} second-generation e-cigs more effectively reduce craving and withdrawal under
489 natural *ad lib* use conditions.^{41,64,71} E-cig effects on craving and withdrawal symptoms are
490 determined by the extent to which e-cig are used by smokers; in turn, determinants of e-cig use
491 include product appeal and reinforcing effects.^{72,73}
492

493 **3.5. Importance of e-cig flavors**

494 More than two-thirds of adult e-cig users in 2013-2014 used a flavored e-cig.^{74,75} Flavors have
495 been shown to substantially enhance the appeal and relative reinforcing effects of e-cigs^{76,77} and
496 have been cited as a key feature of e-cigs affecting use among adults.^{75,78,79} Experimental studies
497 show that flavors increase demand for e-cigs among cigarette smokers,^{80,81} particularly smokers
498 who are not current e-cig users.⁸¹ Studies of e-cig users also highlight that flavors play an
499 important role in their experience of the product⁸²⁻⁸⁴ and in reducing cigarette consumption and
500 craving.^{83,85} Although a recent review on e-cigs and mental illness reported one study of flavors,
501 which found no differential appeal in young adult smokers with mental illness in the VA,⁵⁷ flavored
502 (menthol) cigarette use is preferentially used among individuals with severe psychological
503 distress⁸⁶ and is associated with greater prevalence of both depression and anxiety in US young
504 adults.⁸⁷ Therefore, it warrants investigation whether providing e-cigs in preferred flavors
505 increases e-cig use and the ability of e-cigs to substitute for cigarettes in smokers with ADs.
506

507 **3.6 Products to be tested**

508 Cigarettes to be assessed

509 The cigarettes to be used in this study were made under an NIH contract with production being
510 overseen by the Research Triangle Institute (referred to as “Spectrum cigarettes”). NIH currently
511 has approximately 10 million of these cigarettes (of varying types) for research purposes. The
512 cigarettes selected for the study span the range of yields likely to produce the hypothesized
513 effects, as described above. Spectrum cigarettes are not currently commercially available,
514 although they are similar in many ways to marketed cigarettes (e.g., similar manufacturing, filter,
515 paper, etc.).
516

517 E-cigarettes to be assessed

518 Both the JUUL and the Vuse Solo will be used and assessed in this study. While JUUL will be
519 offered to all participants, participants that are unwilling to use JUUL will be offered the Vuse
520 Solo.

521 JUUL is a commercially available closed system containing two components. One component
522 contains a lithium-ion battery (200 mAh), nichrome coil heater, silica wick, and stainless steel
523 vapor path. The other component is the prefilled e-liquid container that also serves as the
524 mouthpiece. Each commercially available cartridge holds approximately 0.7 mL of e-liquid
525 containing approximately 40 mg of nicotine or 5% nicotine by weight (NBW). A lower dose
526 containing approximately 23 mg of nicotine per cartridge or 3% NBW is also marketed but will
527 not be used in this study. All containers contain glycerol, propylene glycol, natural oils, extracts
528 and flavors, nicotine, benzoic acid. We will not alter the e-liquid in any way. The research staff
529 will distribute the e-liquid containers as purchased from the manufacturer. The JUUL apparatus
530 and 5% NBW e-liquids that will be used are legally purchasable and have been as of August 8,
531 2016. We will not alter them in any way.

532 Vuse Solo is a commercially available closed system containing two components. The
533 power/heating device includes a 270 mAh battery, silica wick, microchips, and sensor. The other
534 component is the prefilled e-liquid container. Each commercially available cartridge holds
535 approximately 1 mL of liquid containing 48 mg of nicotine or 4.8% NBW. All containers contain
536 vegetable glycerin, propylene glycol, reverse-osmosis water, glycerin, flavorings, and nicotine.
537 The research staff will distribute the e-liquid containers as purchased from the manufacturer.
538 The Vuse apparatus and e-liquid cartridges that will be used are legally purchasable and have
539 been as of August 8, 2016. We will not alter them in any way.
540

541 **3.7. Summary**

542 Although smoking rates have declined in the overall US population, there has been little to no
543 decline among people with ADs. A nicotine reduction strategy for combustible tobacco combined
544 with e-cigarette availability may have complementary effects on smoking reductions and
545 consequent tobacco-related health effects in this vulnerable population. This research is highly
546 significant because it will model how the availability of e-cigs, a non-combusted nicotine product
547 that is rapidly increasing in use among US smokers, impacts the effectiveness of a reduced-
548 nicotine policy for cigarettes in this vulnerable population. It is responsive to the goals of the FDA
549 in that the study conditions are designed to model real-world scenarios of possible harm reduction
550 policies in a population that is vulnerable to smoking persistence.
551

552 **4. Project Study Methods**

553 This study will use a four-condition, parallel-groups research design. After a baseline period
554 in which daily smoking rate and other baseline assessments are completed, participants will be
555 randomly assigned to one of the following four conditions for a 16-week experimental period: (1)
556 normal nicotine content cigarettes (NNCCs, 15.8 mg/g) alone, which serves as the control
557 condition; (2) very low nicotine content cigarettes (VLNCCs, 0.4 mg/g) alone; (3) VLNCCs +
558 tobacco-flavored nicotinized e-cigs (TF e-cig, 4.8 - 5.0% nicotine by weight, NBW, if they choose
559 to use the Vuse or JULL device, respectively); or (4) VLNCCs + preferred-flavor nicotinized e-
560 cigarette (PF e-cig).
561

562 **5. Study Screening Procedures**

563 **5.1. Participants**

564 Participants will be men and women, ages 21 – 70 years, with a current diagnosis of an
565 affective disorder, defined as a major depressive disorder, dysthymic disorder, generalized
566 anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, or panic disorder
567 with or without agoraphobia based on the Mini Neuropsychiatric Interview (MINI) which uses
568 DSM-5 criteria, OR Lifetime diagnosis of one of the above based on MINI with a self-report of
569 currently receiving treatment for one of these disorders prescribed psychoactive medication,
570 behavioral therapy, etc.). Additionally, they must be sufficiently literate to complete the research
571 tasks, be in good physical health without serious illness or change in health in past three months,
572 and have the technological capabilities to complete weekly face-to-face video assessments and
573 the compatibility to use ico Smartphone Smokerlyzers for assessing breath carbon monoxide
574 (CO) levels. Study inclusion and exclusion criteria are detailed below.
575
576
577

578 **5.2. Recruitment**

579 Using an intent-to-treat analysis approach, we require 53 randomized per condition (212 total)
580 to test our primary aims. We estimate 10% attrition between enrollment and randomization based
581 on UVM TCORS Phase 1 research, and will therefore enroll up to 59 per condition (236 total). In
582 addition, we will pilot test with up to 20 participants (10/site) for a total of 256 participants (90 at
583 Brown, 166 at UVM). Potential participants will respond to community advertisements (local
584 newspapers, community bulletin boards, lab Facebook page, Facebook ads, lab website, center
585 website, behavioral health centers, Craigslist, city buses, etc.) that contain a study description,
586 link to an online survey and the name and phone number of the Research Assistant. Participants
587 can choose to complete the pre-screening questionnaire online or by phone. At UVM, individuals
588 recruited from online sources will be directed to a UVM-hosted recruitment website where they
589 will have the opportunity to select which research studies interest them. They will then be
590 redirected to a brief online screener to assess eligibility. The Patient Health Questionnaire-4⁸⁸
591 will be used to screen for probable mood or anxiety disorder. This 4-item instrument, which
592 comprises the first 2 items of the Patient Health Questionnaire 9-item (PHQ-9) scale⁸⁹ and the first
593 2 items of the Generalized Anxiety Disorder 7-item (GAD-7) scale⁹⁰ measures the two core DSM-
594 IV criteria for major depressive disorder and generalized anxiety disorder, respectively. The
595 PHQ-4 begins with the stem question: "Over the last 2 weeks, how often have you been bothered

596 by the following problems?” and each item is scored from 0 (“not at all”), 1 (“several days”), 2
597 (“more than half the days”), or 3 (“nearly every day”). Therefore, the total score on this composite
598 measure ranges from 0 to 12. A total score of 3 for the 2 anxiety items or the 2 depression items,
599 plus questions querying past treatment for depression or anxiety, will be used to identify probable
600 cases. If deemed eligible, those who complete the online questionnaire will be called by the
601 Research Assistant to further discuss the study. The RA will read a script briefly explaining the
602 study. Participants will be informed that this is not a smoking cessation program, and that smoking
603 cessation services are available in the community independent of their decision to participate in
604 this study. If interested, they will be invited to participate in the first portion of the screening
605 interview. Research assistants will inform eligible participants that the screening will occur over
606 video chat, and will assist the participant with setting up an appropriately secure video
607 platform. Those who call into the laboratory will be read a script briefly explaining the study. After
608 verbal informed consent is received, the participants will be asked questions over the phone to
609 determine initial eligibility.

610 During this first portion of the screening, the participant will complete questionnaires through
611 REDCap online while the research assistant is present over video chat or phone to deliver
612 instructions and to answer any questions. The participant will then answer interviewer-
613 administered questionnaires over video chat. Participants who did not yet set up their video
614 platforms will do so with the research assistant before beginning any questionnaires. Participants
615 will be instructed to have picture identification (e.g. driver’s license) available to show the staff. If
616 participants anticipate not having acceptable ID, staff should consult with the project coordinator
617 or study PI. Initial study eligibility will be determined after data are collected from this visit.
618 Participants who meet initial study eligibility will be scheduled for the second portion of the
619 screening.

620 Before the second portion of the screening occurs, eligible participants will receive the
621 equipment necessary to use for collecting physiological measurements. Participants will be
622 asked to pick up this equipment via curbside pickup at our clinic (UVM University Health Center,
623 UHC), which will consist of participants calling staff once they arrive at UHC and staff coming out
624 to give participants a bag/box containing the following equipment: a Smokerlyzer; an audio jack
625 adapter for the Smokerlyzer if necessary; a blood pressure cuff; an oximeter; a thermometer; a
626 urinary cotinine dipstick; urine cups with attached temperature test strips; a pregnancy test strip
627 (if applicable) and urine toxicology test strips or a saliva toxicology test. Participants (and staff)
628 will be asked to use cloth face coverings when exchanging product. If participants arrive via car,
629 staff will drop this bag on the hood of the participant’s car while the participant remains in the car
630 Participants may be invited to come inside to pick up this equipment if the participant is asked to
631 wait for this exchange. All participants must pass a COVID19 screening before entering the
632 building. If there is any waiting that needs to occur inside the building, the participant will wait
633 inside one of our five highly ventilated smoking chambers. If there happens to be no space in
634 the smoking chambers, the participant will be told that they cannot come up to the clinic until
635 space is available. After each use, the all of the surfaces in the smoking chambers will be cleaned
636 with 70% or greater of alcohol solution by staff wearing a mask and gloves, as well as all of the
637 door handles. If the participant uses the bathroom while they are in the clinic, the bathroom
638 surfaces and handles will be wiped down after use by staff while masks and gloves are worn.
639 Participants who are using the smoking chambers at any point in the study to wait for product or
640 equipment exchange will remain in the chambers until a staff member comes to knock on the
641 door to let them out. In this way, we can avoid people coming into close contact with each other
642 in the larger room that contains the smoking chambers. A minimum of 6 feet of distance will be
643 maintained for all staff and participants at all times. For participants who come to the clinic, a
644 commercial courier will deliver this equipment to them before the second portion of the screening.

645 If at any point the Smokerlyzers are not available for distribution, we will conduct the CO test
646 curbside before or after participants are invited inside and the courier service will not be
647 available. Research Assistants will bring down the CO monitor when they bring the rest of the
648 equipment to the participant. While maintaining 10 feet of distance and wearing gloves, staff will
649 explain how the CO monitor works. Once the participant is ready, staff will press the button to

650 obtain the measurement and will set the CO monitor down and will back away 10 feet. The
651 participant will then come to pick up the device and will blow into the monitor. After the participant
652 completes the test, they will set down the monitor and back up 10 feet and staff will retrieve the
653 monitor. After every use, staff will wipe down the CO monitor with disinfectant wipes and
654 hydrogen peroxide wipes. When using the monitor, a D-piece (a portable valve filter) must be
655 placed into the monitor and then the single use plastic mouthpiece is placed into the D-piece.
656 The monitor has built in SteriTouch technology to ensure optimum infection control, and the D-
657 pieces filter out 99.9% of airborne bacteria and greater than 97% of viruses for excellent infection
658 control. Each participant will be assigned their own D-piece to use throughout the study, and no
659 D-piece will ever be shared among participants. Participants will gently exhale into the D-piece for
660 the breath carbon monoxide reading. Participants will be instructed only to exhale through the
661 device, not to inhale. D-piece technology also includes a one-way valve that prevents air from
662 being drawn back from the monitor. D-pieces will also be wiped down after each use with
663 disinfectant wipes and hydrogen peroxide wipes and stored in a container at the lab.

664 Once participants have received the necessary equipment to complete the physiological
665 portion of the screening, the research assistant will initiate a video call with the participant. During
666 this call, the participant will be instructed on how to use the equipment and then will be asked to
667 use the equipment to obtain the following physiological readings: blood pressure, heart rate,
668 oxygen saturation, temperature, and breath CO levels. Participants will also be asked to collect a
669 urine or saliva sample during the visit. If a saliva sample is collected, the participant you will
670 provide the saliva sample over video chat while the staff observes. If a urine sample is collected,
671 staff will ask participant to bring this urine sample to the video screen after collection to perform a
672 urine toxicology test and a pregnancy test (if applicable). These urine cups will have temperature
673 strips affixed to ensure that the sample is valid. Participants who have a carbon monoxide level
674 of less than or equal to 8 will also be asked to use the urinary cotinine dipstick to determine
675 whether they are positive for cotinine. The participant will obtain the physiological readings and
676 perform the tests and then will hold the results of the test up to the camera so that the research
677 assistant can interpret and record the readings on REDCap. Potential participants will also be
678 instructed to have handy a pack of their usual brand cigarettes, all prescription medications they
679 are currently taking and identification (example, driver's license) during this second portion of
680 screening visit. If participants anticipate not having acceptable ID site staff should consult with
681 the project coordinator or study PI.

682 A participant must complete his/her two-part screening session within 30 days of completing
683 the pre-screening questionnaire. If the participant is not able to complete the two-part screening
684 visit in that timeframe, he/she will need to complete the pre-screening questionnaire again.

686 **5.3. Informed Consent Process:**

687 Before beginning the informed consent process, potential participants will need to produce
688 identification as described above. The interviewer will confirm the age and identity of the
689 participant. If the participant is not between the ages of 21 and 70, he/she will be dismissed
690 without payment. During the first portion of the screening session, study information will be
691 presented and documentation of the participant's informed consent via electronic signature on
692 REDCap will be required prior to participating in the screening session. In order to ensure
693 adequate informed consent, participants will be asked to read the first several lines aloud (to
694 determine literacy) and will then be given ample time to read the consent document. If the
695 interviewer suspects the participant is not literate, he or she will have them continue reading
696 further to confirm. Inability to read and comprehend written study materials will result in ineligibility
697 and the interviewer will inform the participant that they are not eligible. Only after the participant
698 and the researcher are fully satisfied that the participant understands the purpose of the study,
699 the confidentiality of the data, the procedures, the risks/benefits and his/her rights as a research
700 participant will the consent form be signed and the participant undergo screening procedures.

702 **5.4. Screening Measures**

703 **Those who consent will be screened for eligibility using the following measures:**

704 **The following physiological measures will be collected and entered directly into REDCap**
705 **by the interviewer:**

- 706
- 707 1) Expired breath carbon monoxide (CO) levels will be assessed using an ico Smokerlyzer
708 Smartphone Monitor (Covita -for remote collection) or a Bedfont CO monitor (for curbside
709 collection), a reliable and valid measure of recent smoking.
 - 710 a. Urinary cotinine test strips will be used to asses cotinine levels if a participant's
711 carbon monoxide reading is less than or equal to 8 ppm.
 - 712 2) A urine or saliva toxicological screen will be performed to assess the presence of illicit
713 drugs including up to the following drugs: marijuana, cocaine, opiates, oxycodone,
714 benzodiazepines, barbiturates, amphetamines, methadone, buprenorphine,
715 methamphetamines, MDMA and PCP. Participants who fail the drug screen for drugs
716 other than marijuana or their prescribed opioid medication may reschedule the interview
717 but will need to be re-consented to ensure they have received adequate informed consent.
718 They will be excluded if they are positive for drugs (other than marijuana or prescribed
719 medications as determined by PI on a case-by-case basis) the second time.
 - 720 3) Urine Pregnancy Test (HCG detection) will be performed for all participants.
 - 721 4) Blood pressure and heart rate will be measured using an automated blood pressure
722 monitor and a finger pulse oximeter to help the licensed medical professional determine
723 final participant eligibility. Participants will be told if their blood pressure is in an abnormal
724 range and advised to see a doctor by research staff. The research staff will also submit a
725 medical event form for the LMP to review along with a Blood Pressure and Heart Rate
726 Symptom Checklist form to ascertain details of the symptomatology for the LMP to review.
727 In severe cases, the LMP may also choose to call the participant to follow-up and/or
728 withdraw the participant from the study if necessary. All of these procedures are
729 documented in our Blood Pressure/Heart Rate Collection: Standard Operating Procedure
730 form which we can submit to the IRB if the Committee deems necessary.
 - 731 5) Body temperature, respiratory rate and oxygen saturation will be added as physiological
732 measures based on the CDC recommendations and those of Dr. David Kaminsky.
733 [https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)
734 [disease/healthcare-providers/index.html](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)
735

736 **The following screening assessment will be administered on paper as an interview:**

- 737 1) The Mini International Neuropsychiatric Interview (MINI) 7.0⁷⁰
738

739 The following screening assessments will be administered as an interview and then will be
740 entered directly into REDCap by the interviewer:

- 741 1) The MINI Plus Modules
- 742 2) The MINI suicide subscale⁹⁴ to evaluate suicide risk.
- 743 3) MINI Follow-up Questionnaire (if applicable)
- 744 4) Tobacco Use History and Exposure Questionnaire, which measures variables such as
745 smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts,
746 duration of quit attempts and duration of smoking.
- 747 5) Smoking Cessation Therapy Use Questionnaire
- 748 6) Time Since Last Cigarette Questionnaire
- 749 7) Medical History Questionnaire to assess current diagnoses, symptoms and past health
750 problems.
 - 751 a. Medications will be recorded directly onto the Concomitant Medications form in
752 REDCap.
- 753 8) Drug Abuse Screening Test (DAST-10), which assesses quantity and frequency of
754 alcohol and drug use (12 month and 1 month version)

755 **The following screening assessments will be completed by the participant directly in**
756 **REDCap, except where noted otherwise:**
757

- 1) Demographic History Questionnaire, which will assess age, gender, ethnicity, race, education, income, marital status, and employment history.
- 2) Alcohol Use Questionnaire---based on the Alcohol Use Disorders Identification Test⁹⁵ (12 month and 1 month version)
- 3) Drug Use Questionnaire---based on the Drug Abuse Screening Test⁹⁶ (12 month and 1 month version)
- 4) Fagerström Test for Nicotine Dependence (FTND)⁹⁷;
- 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM)⁹⁷ will be administered to assess nicotine dependence severity.
- 6) Penn State Electronic Cigarette Dependence Index⁹⁹; -
- 7) Smoking Stages of Change Algorithm¹⁰⁰;
- 8) Identifying Information Form will include the participant's REDCap Subject Identifier, name, address (including the county of residence), email address, phone number, age, date of birth, and social security number (if applicable).
 - a. This form will be entered into the 'Identifying Information Access Database'.
 - Each site will have a separate 'Identifying Information Access Database'.
 - Identifying information will not be shared with other sites. Each site is responsible for maintaining confidentiality of this information.
 - Identifying information will be kept in a locked file cabinet (source document) and in a password protected Access Database (electronic version) separate from all other study data.
- 9) Beck Depression Inventory (BDI-II)⁹¹, to assess depressive symptoms.
(This form has been updated on 1.29.20 so as to use the BDI-II. The BDI-II will be used instead of the BDI so that the data collected will be directly comparable to other projects using the BDI-II).
- 10) Overall Anxiety Severity and Impairment Scale⁹²(OASIS); to assess frequency and severity of anxiety symptoms.
- 11) COVID19 Symptom Questionnaire
- 12) Respiratory Symptom Questionnaire will be administered to assess respiratory health

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be recorded securely. The interviewer will enter the data into REDCap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form'.

5.5. Suicidality/Mental Health Monitoring

Participants who endorse suicidal intention in the past month or a suicide attempt in the past 6 months as indicated on the BDI (score > 1 on question 9) or MINI suicide subscale (endorse question 4 and/or 5 on the MINI suicide subscale or question 6 on the MINI suicide subscale with suicide attempt in the past 6 months) or answer "yes" to question A3g on the MINI Neuropsychiatric interview and symptoms have occurred in the past two weeks will be assessed by a clinician for eligibility and possible intervention. The research staff member will contact a licensed clinician for evaluation. In the event that no clinician is available, staff will put the participant in contact with the National Suicide Prevention Lifeline at 1-800-273- 8255. They will also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible. Additionally, they will contact the Project Coordinator to inform her of the situation. The participant will be paid \$25 (+\$25 bonus if applicable) and provided with local mental health resources. Post enrollment, any report of suicidal ideation or attempt by a participant will be grounds for immediate withdrawal from the study.

5.6 Inclusion/Exclusion Criteria

Inclusion Criteria:

- 1) Men and women ages 21-70,
- 2) Past-year: MDD, dysthymic disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, or panic disorder with or without agoraphobia,

- 813 based on MINI structured interview, OR Lifetime diagnosis of one of the above based on
814 MINI with a self-report of currently receiving treatment (prescribed psychoactive
815 medication, behavioral therapy, etc.),
- 816 3) Report smoking ≥ 5 cigarettes per day for the past year,
 - 817 4) Provide an intake breath CO sample >8 ppm, (if ≤ 8 ppm, then urinary-cotinine strip must
818 be positive)
 - 819 5) Be without current substance abuse/dependence other than nicotine,
 - 820 6) Be sufficiently literate to complete the research-related tasks,
 - 821 7) Be in good physical health without serious illness or change in health in the past three
822 months as determined by the licensed medical professional at each site,
 - 823 8) Have appropriate equipment to complete face-to-face video assessments and use ico
824 Smartphone Smokerlyzer Monitors. For those who do not have a Smartphone, staff will
825 explore potential alternate plans (e.g., project-provided inexpensive Android phone)

826
827 Exclusion Criteria:

- 829 1) Exclusive use of roll-your-own cigarettes,
- 830 2) Planning to quit smoking in the next 30 days,
- 831 3) A quit attempt in the past 30 days resulting in greater than 3 days of abstinence,
- 832 4) Significant use of other tobacco or nicotine products within the past month (more than 9
833 days in the past 30).
- 834 5) Positive toxicology screen for any of the following drugs: cocaine, opiates, methadone,
835 oxycodone, buprenorphine, benzodiazepines, barbiturates, amphetamines,
836 methamphetamines, MDMA and PCP
 - 837 a. Marijuana will be tested for but will not be an exclusionary criterion. Participants
838 will be discouraged from smoking marijuana during the study.
 - 839 b. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, or
840 amphetamines will not necessarily be excluded.
 - 841 c. Participants failing the toxicology screen will be allowed to re-screen once. These
842 participants will need to be re-consented before being rescreened to ensure they
843 have received adequate informed consent.
- 844 6) Self-report of binge drinking alcohol (more than 9 days in the past 30 days, 4/5 drinks in a
845 2 hour period in females/males),
- 846 7) Systolic blood pressure < 90 or ≥ 160 mmHg
 - 847 a. Participants failing for blood pressure will be allowed to re-screen once.
- 848 8) Diastolic blood pressure < 50 or ≥ 100 mmHg
 - 849 a. Participants failing for blood pressure will be allowed to re-screen once.
- 850 9) Breath CO > 80 ppm,
- 851 10) Heart rate is greater than or equal to 115 bpm or less than 45 bpm
 - 852 a. Participants failing for heart rate will be allowed to re-screen once.
- 853 11) Currently seeking treatment for smoking cessation,
- 854 12) Being pregnant, trying to become pregnant, or nursing, or not report using a form of
855 approved birth control if applicable determined by the Project Medical Director
- 856 13) Have used nicotine replacement, bupropion or other pharmacotherapies as cessation aids
857 in the past month (bupropion will be allowed for treatment of depression),
- 858 14) Unstable psychiatric conditions (psychiatric medication changes in the past 4 weeks),
- 859 15) Symptoms of psychosis, dementia or mania,
- 860 16) Suicidal ideation in the past month (score > 1 on the BDI question 9 or endorse question
861 4 and/or 5 on the MINI suicide subscale),
- 862 17) Reporting a plan or attempt to commit suicide, which is assessed on question A3g of the
863 MINI Neuropsychiatric Interview Major Depressive Episode Module. Thoughts of suicide
864 without an intent or plan is not an exclusion criteria,
- 865 18) Suicide attempt in the past 6 months (endorse question 6 on the MINI suicide subscale
866 with suicide attempt in the past 6 months),

- 867 19) Participation in another research study in the past 30 days,
- 868 20) Co- habitation with any research participant who has or is participating in the current
- 869 study,
- 870 21) Daily use of e-cigarettes in the past month (defined as 6 – 7 days per week).__
- 871 22) Oxygen saturation of < 90%
- 872 23) Reporting positive symptoms for COVID19
- 873

874 Individuals under age 21 are excluded because they cannot legally buy cigarettes. Those with
875 unstable medical, psychiatric, or medication conditions (as determined by the licensed medical
876 professional) are excluded as these symptoms could affect a participant's ability to complete the
877 study. Examples include but are not limited to the following: angina, stroke, heart attack which
878 occurred since phone screening, blood clots in the arms or legs for which the individual is
879 undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy,
880 severe shortness of breath caused by conditions such as uncontrolled asthma, COPD, or
881 arrhythmia, active untreated infection such as pneumonia, active untreated endocrine disorder
882 such as hyperthyroidism. We will exclude those currently seeking smoking treatment and those
883 who plan to quit in the next 30 days, as participation in this study may not lead to reductions in
884 smoking. We will exclude pregnant or nursing women and women of reproductive potential who
885 are unwilling to use acceptable forms of birth control throughout the study if applicable determined
886 by the Project Medical Director. We will also exclude anyone with current or recent alcohol or drug
887 abuse problems as these factors could independently affect smoking behavior during the study.
888 Individuals with baseline CO readings greater than 80 ppm, those with heart rate or blood
889 pressure readings that are out of range (systolic: 90-159 mmHg; diastolic: 50-99 mmHg; HR: 45-
890 114 bpm) and anyone who has attempted suicide in the past six months will be excluded from the
891 study for safety concerns. Individuals who smoke 'roll your own' cigarettes exclusively will be
892 excluded from the study because we will be unable to standardize their baseline smoking
893 behavior. Individuals who have reported daily use of e-cigarettes in the past 30 days will be
894 excluded as they may not be compliant with experimenter-provided e-cigarettes. Individuals who
895 have recently participated in a research study will be excluded as participation may have changed
896 their smoking patterns, which may preclude a stable smoking baseline. Because participants are
897 required to complete portions of the protocol independently, they will need to be able to
898 independently read and comprehend the study materials.

900 **5.7. Eligibility Determination:**

901 The research assistant will review the entire screening assessment battery for initial eligibility
902 determination, confirming the participant meets the above described inclusion/exclusion criteria.
903 All eligibility criteria that are not related to physiological measurements will be assessed during
904 the first portion of the screening visit, and all criteria related to physiological measurements will
905 be determined during the second portion of the screening. The final eligibility of the participant
906 will be determined by a licensed medical professional (MD,DO, NP, PA, Master's prepared RN
907 or CRN) at each site after reviewing the Medical History Questionnaire, BDI, Mini Neuropsychiatric
908 Interview, and the MINI suicide subscale. The licensed medical professional may meet with a
909 participant if available and think it necessary for eligibility determination. He/she will sign off on
910 eligibility prior to the first baseline visit. If the licensed medical professional determines the
911 participant is not medically eligible to participate in the study, has current symptomatology that
912 would interfere with interpretation of the data, or is unlikely to complete the study he/she will inform
913 the research assistants who will contact the participant prior to the first baseline visit. The licensed
914 medical professional will not need to review the medical history forms of participants who are
915 ineligible for other, non-medical reasons.

916 If a participant fails the urine or saliva toxicology screen due to a prescription medication
917 he/she is taking, then he/she will not be automatically excluded. The interviewer will make note of
918 this when he/she submits the forms to the licensed medical professional for final eligibility
919 determination.

920 Once all the screening procedures have been completed, researchers will pay participants
921 \$25 (+\$25 bonus if applicable) for their time as long as they pass the drug tests and meet the

922 minimum requirements for carbon monoxide or urinary cotinine levels. Participants will be paid
923 after the completion of the study visit. If participants are deemed ineligible at any point in the
924 screening, the participant will be paid after determined ineligible. Marijuana will be tested for but
925 will not be an exclusionary criterion. If a participant does not pass the drug test but has a current,
926 valid prescription that would explain the failed test he/she will not be automatically excluded and
927 will still receive the visit payment. Participants who meet all other eligibility criteria, sans the
928 medical criteria, will be scheduled for the first baseline visit.

929 At the end of the screening session, the researcher will complete the End of Visit Evaluation
930 Form. This will allow the researcher to make note of any problems encountered during the visit
931 and to assess the truthfulness of the participant in regards to self-report of tobacco use.
932

933 **6. Study Baseline Procedures**

934
935 This study will use a one-week, two-session baseline period to collect baseline individual
936 difference measures and monitor daily usual-brand smoking behavior. At Baseline 1 or within 1
937 business day of the Baseline 1 visit, participants will be provided their usual brand cigarettes to
938 smoke, equivalent to 150% of their daily smoking rate. Participants will be encouraged to come to
939 the lab to pick up their usual brand cigarettes in a curbside exchange after they complete the
940 questionnaires and physio for the BL1 visit. Those who cannot come to the lab will receive product
941 via a commercial courier. A time line follow back (TLFB) will be used during the period between
942 Baseline 1 and Baseline 2 to assess the daily cigarette use for the first 7 days the participant has
943 product. The participant must have received their UB cigarettes from the lab before the 7-day
944 assessment period starts, and Baseline 2 must occur at least 7 days after the participant receives
945 their usual brand cigarettes from the lab. If the baseline period extends past seven days and if the
946 participant has run out of product, participants will need to purchase their own usual brand cigarettes.
947 Use of a two session baseline period will ensure stability of daily smoking reports, reduce reactivity
948 to the daily cigarette monitoring, and reduce participant burden. During the two baseline sessions,
949 participants will complete subjective questionnaires. Each visit will last approximately two to four
950 hours. At the end of each baseline session, the researcher will complete the End of Visit Evaluation
951 Form,. This will allow the researcher to make note of any problems encountered during the visit and
952 to assess the truthfulness of the participant in regards to self-report of tobacco use. Participants will
953 also be supplied with saliva test equipment and urine collection equipment during the Baseline 1
954 product exchange so that they can collect saliva and first void urine samples during the Baseline
955 2 visit.

956 For the Baseline 1 visit and all subsequent visits, the participant will be sent a REDCap link
957 within 15 minutes of the start of the scheduled visit to complete all of the non-interviewer
958 administered questionnaires. The participant will complete these questionnaires on their own but
959 can have the research assistant present on a video call if they desire. Before beginning the
960 physiological assessment portion of the visit over video call, the research assistant must review
961 the participant's questionnaire responses for that visit. Participants will be compensated after the
962 completion of the study visit and when the participant has received their new product.

963 At Baseline 2 and all subsequent visits, after the participant has answered the questionnaires
964 and has completed the physiological portion of the visit over video call, participants will be asked
965 to come to the lab for exchange of product and biological samples. Participants will bring in their
966 used and unused product from the previous visit as well as a first-void urine sample for assessing
967 tobacco- related toxin exposure and a salivary sample for assessing nicotine metabolism rate on
968 applicable visits (BL2, Week 8 and Week 16) using equipment that was provided at the previous
969 visit. Participants will be instructed to call the RA at the office when they get to the clinic to ensure
970 that there is enough space in the smoking chambers to house all participants while abiding by
971 safety guidelines as detailed on page 14 of the protocol. All participants must pass a COVID19
972 screening before entering the building. When invited into the lab, the participant will be shown to a
973 smoking chamber and will instructed to place their bag of product outside of the chamber. The
974 participant will wait here while the RA processes and returns product through the randomization
975 database. Then the RA will dispense new product and bring the bag back to the participant. When

976 the RA deems it safe for the participant to exit the chamber, the RA will instruct the participant
977 that they can leave. The RA will instruct the participant to observe social distancing measures
978 during this exchange, providing clarification if necessary. If a participant forgets their first-void
979 urine sample at the Baseline 2 visit, staff will ask participant to come back to the clinic with their
980 first void urine sample before exchange of product occurs. If participant is unable to return to the
981 clinic with their first void sample, staff can arrange to meet the participant off campus to pick up
982 their urine sample and to give participant their study product. Distancing and safety measures as
983 described above must be observed. For participants who cannot make it to UHC, special
984 arrangements will be made to enable use of the randomization database and product
985 return/distribution procedures to the extent possible. Each week, during - or scheduled as nearly
986 as possible to – a virtual visit, a complete accounting of the participant's product inventory will be
987 taken and processed remotely through the randomization database. The participant will separate
988 product based on its type (e-cigarette or combustible inventory) and status (used/unused), and
989 the RA will process return characteristics through the database accordingly. The RA will clarify
990 barcode characteristics with the participant when legibility is compromised. The participant will be
991 instructed to keep unused product in their possession, but to exchange any used product with the
992 courier who will deliver newly dispensed replacement products within 48 hours.

993 Product that will be given to participants for the Baseline 2 visit cannot be given/sent to
994 participants until 7 days have passed following completion of the Baseline 1 visit. We will need to
995 calculate baseline smoking rate during this 7-day period and so participants cannot have access
996 to any blinded study product or e-cigarettes before this 7-day period has ended.

998 **6.1. Visit scheduling requirements for baseline period:**

999 Participants will be required to schedule the Baseline 1 visit within 30 days of the completion
1000 of their screening visit. If a participant still wants to be in the study after 30 days, he/she will need
1001 to be re-screened. The participant will need to be re-consented but will maintain the original
1002 REDCap Subject Identifier. The ideal target window separating Baseline 1 and Baseline 2 is
1003 between 7 and 12 days. The minimum is 7 days and the maximum is 21 days. If the participant
1004 does not complete the visit within 21 days, then he/she will not be rescheduled and will be
1005 discontinued from the study.

1007 **6.2. Measures/Assessments**

1009 **The following physiological measures will be collected and recorded directly into REDCap
1010 by the interviewer:**

- 1011 1) CO
- 1012 2) Blood Pressure
- 1013 3) Heart Rate
- 1014 4) Body temperature
- 1015 5) Oxygen saturation
- 1016 6) Respiratory rate
- 1017 7) Urine or Saliva Toxicology
- 1018 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

1020 **The following assessments will be administered as an interview at Baseline 1 and entered
1021 directly into REDCap by the interviewer at the end of the visit:**

- 1022 1) Concomitant Medications Form
- 1023 2) Health Changes Questionnaire, which will assess any weekly health changes,
- 1024 3) Time Since Last Cigarette Questionnaire

1026 **The following assessments will be administered at Baseline 1 and completed by the
1027 participant directly in REDCap:**

- 1028 1) BDI

- 2) OASIS
- 3) Respiratory Symptom Questionnaire
- 4) COVID19 Symptom Questionnaire
- 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM) will be administered to assess nicotine dependence severity.
- 6) Perceived Health Risks Rating¹⁰¹, a measure of the perceived addictive potential and other health risks associated with cigarettes;
- 7) Perceived Stress Scale (PSS)¹⁰¹, assessing the degree to which life situations are perceived as stressful;
- 8) Positive and Negative Affect Scales (PANAS)¹⁰², a measure of changes in positive and negative mood;
- 9) Respiratory Health Questionnaire, a UVM measure of cough, shortness of breath and other respiratory symptoms;
- 10) Minnesota Nicotine Withdrawal Scale (MNWS)¹⁰³, a measure of nicotine withdrawal;
- 11) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU)¹⁰⁴, which measures the urge to smoke;
- 12) Vaping Craving Questionnaire¹⁰⁵, which measures the urge to vape;
- 13) Cigarette Evaluation Scale – Usual Cigarette (CES)¹⁰⁶, which measures responses to cigarettes (e.g., reward, satisfaction);
- 14) Vaping Evaluation Scale (VES), which measures responses to taping (e.g. reward, satisfaction)
- 15) Cigarette Purchase Task – Usual Brand Version (CPT)¹⁰⁷, a self-report analogue of a progressive-ratio schedule that measures the relative reinforcing efficacy of cigarettes by querying how many of that day’s cigarette they would consume in a day at varying prices. This task will indicate whether prolonged VLNC cigarette use reduces cigarette demand and increases sensitivity to increases in cigarette costs;
- 16) Snaith-Hamilton Pleasure Scale (SHAPS)¹¹⁰.

All participants will also be asked to select their top three flavors of e-cigarette liquid from a list read to them by the RA. This question will be asked in preparation for giving flavored pods to participants who are randomized into the flavored e-cigarette condition. This information will be recorded directly into REDCap. Participants will be asked to rate these top three flavors based on either previous experience with these flavors or to indicate how much they believe that they will like or dislike the flavors.

Physiological measures collected at Baseline 2 will be entered directly into REDCap by the interviewer:

- 1) CO
- 2) Blood Pressure
- 3) Heart Rate
- 4) Body temperature
- 5) Oxygen saturation
- 6) Respiratory rate
- 7) Urine or Saliva Toxicology
- 8) Urine Pregnancy (if applicable; to be performed every two weeks)
- 9)

The following assessments will be administered as an interview at Baseline 2 and then entered directly into REDCap by the interviewer:

- 1) Concomitant Medications Form
- 2) Health Changes Questionnaire
- 3) Time Since Last Cigarette Questionnaire

1082
1083 **The following assessments will be administered at Baseline 2 and completed by the**
1084 **participant directly in REDCap:**

- 1085 1) BDI
- 1086 2) OASIS
- 1087 3) COVID19 Symptom Questionnaire
- 1088 4) Respiratory Symptom Questionnaire
- 1089 5) MNWS
- 1090 6) WISDM
- 1091 7) PANAS
- 1092 8) QSU (usual brand)
- 1093 9) Vaping Craving Questionnaire
- 1094 10) CES (usual brand)
- 1095 11) Vaping Evaluation Scale
- 1096 12) CPT (usual brand)
- 1097 13) Snaith-Hamilton Pleasure Scale (SHAPS)
- 1098 14) E-Cigarette flavor rating questionnaire
 - 1099 a. Participants will rate only the flavors that they received from staff for this visit

1100
1101 In the event that the REDCap website is not functioning, the assessments will be administered
1102 aloud and participant answers will be recorded securely. The interviewer will enter the data into
1103 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
1104 Visit Evaluation Form'.

- 1105 1) for each picture as they appear on the screen.

1106 1107 **6.3 E-cigarette Training Session (Baseline 2):**

1108 Participants assigned to an e-cig condition will be told that they will be provided with a JUUL. If a
1109 participant indicates an unwillingness to use the JUUL device, the research assistants will offer
1110 the participant the Vuse Solo as alternative device. If the participants does not wish to use either
1111 device, he or she would be ineligible for the study.

1112 Participants in the e-cigarette conditions will be given e-cigarette pods BEFORE the training
1113 session occurs. These pods will be either picked up at the lab (preferred) or delivered to the
1114 participant 1 to 2 days before their Baseline 2 visit occurs. Participants randomized to the e-
1115 cigarette conditions will be notified before their Baseline 2 visit (but after the 7-day period
1116 following Baseline 1) and informed of their e-cigarette condition. Participants randomized to the
1117 flavored condition will be given pods of up to three flavors of their choice. Staff will calculate how
1118 many total pods participants will be given at this time based on their smoking rate, and
1119 participants will be able to choose the proportion of each flavor that they would like to receive.

1120 The e-cigarette training session will occur over video chat after the physiological
1121 measurements have been collected. The first 30 minutes of the training session will consist of
1122 the participant being taught how to use, charge, and replace pods/cartridges for their e-
1123 cigarette of choice. Participants will first try their JUUL using the tobacco flavor, and then decide
1124 which device they would like to use for the duration of the study. If desired, participants are able
1125 to choose a preferred device to use without testing both e-cigarettes. At this point, participants
1126 who are in the tobacco-only flavor condition will conclude their training session.

1127 For all visits following Baseline 2, participants in the preferred flavor condition are permitted
1128 to take up to three flavors home per week, but can choose to take less than three flavors if
1129 desired. Participants will take home their chosen pods or cartridges of up to three flavors until
1130 next visit. Participants will be able to change their flavors at only one point in the study if they
1131 desire. Participants will only be allowed to take home three flavors at one time. Participants will
1132 be given an E-cigarette instructional manual that reviews the e-cigarette training done at this
1133 visit. Participants will be encouraged to call with any device issues.

1134 1135 **6.4. Interactive Voice Response System:**

At the end of the first baseline visit, participants will be trained to use the Interactive Voice Response (IVR) System, which will contact participants each day throughout the study and ask about their smoking behavior as well as withdrawal symptoms the week before and after Baseline 2. We will also review the IVR adherence incentive program, which consists of \$1 per call plus a \$10 bonus for seven consecutive calls.

The IVR system is operated by TeleSage (<https://telesage.com/about/>). To be enrolled in the IVR system, research staff will enter the participant's initials, telephone number, subject identifier, and visit dates into the IVR TCORS website. Identifying information (initials and telephone numbers) will not be extracted as part of the data by the bioinformatics group. Please refer to TeleSage's privacy statement and HIPAA compliance form for additional information.

Baseline 2 biological specimens:

1) Urine sample for smoking biomarker assessment:

Participants will be asked to provide a urine sample (first void of the day) at the second baseline session and to post-randomization weeks 8 and 16 for biomarker assessment. Biomarker analysis will provide nicotine and carcinogen exposure outcome measures and verify compliance with VLNC cigarettes. Samples will be stored at -80C. Urine samples will be analyzed for total nicotine (cotinine plus its glucuronide conjugate, a useful measure of daily nicotine exposure), the tobacco-specific nitrosamine 4-methylnitrosamine-1-(3-pyridyl)-1-butanol (NNAL), and metabolites of 4 polycyclic aromatic hydrocarbons (PAHs), which are biomarkers of tobacco smoke carcinogens and decrease upon tobacco cessation or reduction. Anatabine is a minor alkaloid that is reduced in users of VLNC cigarettes and e-cigs. Therefore, anatabine levels in samples from those assigned to the VLNCC, VLNCC +TF e-cig and VLNCC+PF e-cig conditions should be lower than levels from those in the NNCC condition. These analyses will be performed by the Murphy lab at the University of Minnesota.

2) Saliva Samples for smoking biomarker assessment:

We will collect a saliva sample at the second baseline session and post-randomization weeks 8 and 16 for analysis of nicotine metabolite ratio (NMR; ratio of 3-hydroxycotinine [3 HC] to cotinine [COT]), a phenotypic marker of nicotine metabolic rate. Analyses of these samples will be performed by the Tyndale lab.

Biomarker shipping and storage:

Biomarkers will be shipped quarterly to the University of Vermont Laboratory for Clinical Biochemistry Research (Tracy Lab). The Tracy Lab will serve as a central repository for all biomarker specimens and will be responsible for distributing specimens to the appropriate labs on a quarterly basis. Urine samples will be analyzed and stored at the University of Minnesota Murphy Lab. The saliva samples will be analyzed and stored at the University of Toronto Tyndale Lab.

7. Study Experimental Procedures

7.1 Experimental Period:

Participants will be seen weekly throughout the 16-week experimental period. Weeks 4, 8, 12, 16 and the abstinence visit will take approximately 2-4 hours each. All other sessions will last approximately 2 hours. If a participant has a positive urine or saliva toxicology test or is visibly intoxicated as determined by slurred speech, swaying, or stumbling, the session will be rescheduled until a negative test result is obtained and intoxication is not present. As a part of each experimental visit, participants will be asked to come to UHC for a product exchange. All participants must pass a COVID19 screening before entering the building. Participants will be instructed to contact the RA at the office when they get to the clinic to ensure that there is enough space in the smoking chambers to house all participants while abiding by safety guidelines as detailed on page 14 of the protocol. All participants must pass a COVID19 screening before entering the building. When invited into the lab, the participant will be shown to a smoking

1190 chamber and will be instructed to place their bag of product outside of the chamber. The participant
1191 will wait here while the RA processes and returns product through the randomization database.
1192 Then the RA will dispense new product and bring the bag back to the participant's smoking
1193 chamber and leave it on the ground in front of the chamber. When the RA deems it safe for the
1194 participant to exit the chamber, the RA will instruct the participant that they can leave. The RA will
1195 instruct the participant to observe social distancing measures during this exchange, providing
1196 clarification if necessary. At the end of each experimental session, the researcher will complete
1197 the End of Visit Evaluation Form, which will be filed in the participant's binder. This will allow the
1198 researcher to make note of any problems encountered during the visit and to assess the
1199 truthfulness of the participant in regards to self-report of tobacco use and compliance to study
1200 procedures.

1201 1202 **Visit scheduling requirements for experimental period:**

1203 The ideal scheduling window between each visit is 7 days based on the date of the Baseline
1204 2 Visit. For additional scheduling requirements, refer to the '*Scheduling Visits SOP*'. If a participant
1205 misses a visit and is unable to reschedule during the window (± 3 days), that visit will not be
1206 'made-up' in the future. All measures that were not completed will be considered missing data
1207 and will not be collected during future visits. If a visit mistakenly occurs outside of the designated
1208 window, this is a protocol deviation. A 'Non-Medical Event Form' will need to be completed.
1209 Additionally, each visit should occur at approximately the same time of day ± 2 hours.

1210 If a participant is not able to attend his/her Week 16 visit, then it should be rescheduled even
1211 if it is outside of the scheduling window. This will be documented as a protocol deviation.

1212 1213 **7.2 Experimental Visits Weeks 1, 3, 5, 7, 9, 11, 13, and 15 Procedures**

1214 1215 **7.2.A. Measures/Assessments**

1216 **Physiological Measures Collected and entered directly into REDCap by the interviewer:**

- 1217 1) CO
- 1218 2) Blood Pressure
- 1219 3) Heart Rate
- 1220 4) Body temperature
- 1221 5) Oxygen saturation
- 1222 6) Respiratory rate
- 1223 7) Urine or Saliva Toxicology
- 1224 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

1225 1226 **The following assessments will be administered as an interview and will be entered** 1227 **directly into REDCap by the interviewer:**

- 1228 1) Concomitant Medications
- 1229 2) Medical Event Form, if applicable
- 1230 3) Health Changes Questionnaire
- 1231 4) Time Since Last Cigarette Questionnaire

1232 1233 **The following assessments will be completed by the participant directly in REDCap:**

- 1234 1) BDI
- 1235 2) OASIS
- 1236 3) COVID19 Symptom Questionnaire
- 1237 4) Respiratory Symptom Questionnaire
- 1238 5) MNWS
- 1239 6) Snaith-Hamilton Pleasure Scale (SHAPS)

1240 In the event that the REDCap website is not functioning, the assessments will be administered
1241 aloud and participant answers will be recorded securely. The interviewer will enter the data into
1242 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
1243 Visit Evaluation Form'.

1245 **7.3 Experimental Visits Weeks 2, 4, 6, 8, 10, 12, 14, and 16 Procedures:**

1246
1247 **7.3.A Measures/Assessments**

1248 **Physiological measures collected and entered directly into REDCap by interviewer:**

- 1249 1) CO
1250 2) Blood Pressure
1251 3) Heart Rate
1252 4) Body temperature
1253 5) Oxygen saturation
1254 6) Respiratory rate
1255 7) Urine or Saliva Toxicology
1256 8) Urine Pregnancy test (if applicable)
1257

1258 **The following assessments will be administered as an interview and will be entered into REDCap by the interviewer at the end of the visit:**

- 1259 1) Concomitant Medications
1261 2) Medical Event Form, if applicable
1262 3) Health Changes Questionnaire
1263 4) Time Since Last Cigarette Questionnaire
1264

1265 **The following assessments will be completed by the participant directly in REDCap:**

- 1266 1) BDI
1267 2) OASIS
1268 3) COVID19 Symptom Questionnaire
1269 4) Respiratory Symptom Questionnaire
1270 5) MNWS
1271 6) QSU (usual brand)
1272 7) QSU (study cigarette)
1273 8) Vaping Craving Questionnaire
1274 9) CES (usual brand)
1275 10) CES (study cigarette)
1276 11) Vaping Evaluation Scale
1277 12) PANAS
1278 13) Cigarette Purchase Task - Usual Brand Cigarette Version (weeks 4, 8, 12 and 16 only)
1279 14) Cigarette Purchase Task – Study Cigarette Version (weeks 4, 8, 12 and 16 only)
1280 15) Cross-price Elasticity Task¹⁰⁹- e-cigarettes and combustible cigarettes (weeks 4, 8, 12
1281 and 16 only) (for e-cigarette experimental conditions only)
1282 16) Penn State Electronic Cigarette Dependence Index (weeks 8 and 16 only)
1283 17) Respiratory Health Questionnaire (weeks 8 and 16 only)
1284 18) FTND (weeks 8 and 16 only)
1285 19) Perceived Health Risks Questionnaire (weeks 8 and 16 only)
1286 20) Smoking Stages of Change Algorithm and Contemplation Ladder (weeks 8 and 16 only)
1287 21) WISDM – Brief Scale
1288 22) Snaith-Hamilton Pleasure Scale (SHAPS)
1289 23) Drug Use Questionnaire – 1 month version (weeks 8 and 16 only)
1290 24) Perceived Stress Scale (weeks 8 and 16 only)
1291 25) Alcohol Use Questionnaire – 1 month version (weeks 8 and 16 only)
1292 26) E-cigarette flavor rating questionnaire (weeks 4, 8, 12 and 16 only)
1293

1294 In the event that the REDCap website is not functioning, the assessments will be administered
1295 aloud and participant answers will be recorded securely. The interviewer will enter the data into
1296 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
1297 Visit Evaluation Form'.

1298 **Biological Samples to be collected:**
1299

- 1300 1) First void urine sample (Weeks 8 and 16 only)
1301 2) Saliva sample (Weeks 8 and 16 only)
1302

1303 **7.4 Interactive Voice Response System:**

1304 Participants will continue to use the IVR system on a daily basis throughout the
1305 experimental period to record the number of study cigarettes smoked per day, measurement of
1306 e-cig use and use of non-study cigarettes or other tobacco products. Measurement of e-cig use
1307 will be collected by asking two questions: how many daily e-cigarette episodes occurred, where
1308 one episode consists of around 10-15 puffs or up to approximately 10 minutes, and what
1309 proportion of pods and/or cartridges were used per day. Participants will also be asked to log
1310 how many flavors of e- cigs they used per day. During the first week after Baseline 1, the IVR
1311 system will collect information about mood and withdrawal symptoms.
1312

1313 **7.5 Variable Incentive Program:**

1314 An incentive program has been developed with the goal of improving attendance at
1315 scheduled assessment sessions, compliance with using only study-provided tobacco products,
1316 and encouraging honest self-reports regarding all nicotine/tobacco use.

1317 Briefly, participants will receive a total of seven tickets for each weekly visit they attend after
1318 randomization (Visits 03-18, weeks 1-16). In total, participants could earn 112 valid tickets
1319 across the 16 visits. Participants will be instructed that these tickets correspond to attendance
1320 (one ticket), honest reporting (one ticket), compliance in bringing back used and unused
1321 pods/cartridges (two tickets) and adherence to using only the assigned study product (three
1322 tickets). Participants who do not bring back all of their unused study product and used
1323 packaging will be told that they may not be eligible to earn the two compliance tickets.

1324 Participants will be further instructed that all of the tickets that they receive “could” be eligible
1325 for entry into a monthly drawing for prizes, but that only tickets that are “validated” will be eligible
1326 for prizes.

1327 Since it is prohibitively expensive to test urine samples each week for each participant and
1328 because it is currently not feasible to detect with reasonable precision non-compliance based on
1329 biomarkers in the two higher nicotine group, we plan to only validate the attendance tickets.
1330 Hence, each participant who attends their regularly scheduled weekly session will have a total of
1331 seven validated tickets entered into the monthly drawing.

1332 To convey the message that we may be validating honest reporting and use of only study-
1333 provided products, a bogus pipeline of sorts, we will tell the participants that a composite
1334 assessment of the measures that we collect MAY be used to validate the amount of nicotine
1335 and tobacco products that they are using. So there is some minor deception involved, but
1336 technically we could conduct urine toxicology testing for both purposes. Hence, if the urine
1337 toxicology testing is presented as something that MAY be done for validation purposes, we feel
1338 that any deception is relatively minor. For scientific/economic reasons we are just electing to
1339 restrict validation to attendance.

1340 Nevertheless, we will debrief all participants upon the completion of the trial. We will inform
1341 them that the incentive program was based exclusively on attendance due to the relatively high
1342 cost of urine toxicology testing and other practical problems with shipping the urines for prompt
1343 testing.

1344 Drawings will be conducted on the 1st of each month. Validation will be performed by staff
1345 who have no participant interaction and are not blind to condition. Any ticket drawn will be
1346 eligible for an incentive as the only true contingency is for attendance. There will be no mention
1347 of the basis for earning incentives (i.e., whether the ticket was for attendance, honesty,
1348 adherence). Participants will simply be informed that he or she earned an incentive from the
1349 drawing.

1350 Each drawing will be independent (without replacement); consequently, some participants will
1351 not win a prize and others may win more than one during the study if more than one of their
1352 tickets is drawn. After confirming winners, the remaining tickets from each month will be
1353 discarded (i.e., tickets will only be entered into one drawing). The monthly prize amounts are

1354 detailed below.

1355 We estimate based on the 2 ½ years we think it will take to complete this study, that
1356 participants will win an average of approximately \$65 in prizes or an additional \$5.50 per week
1357 per participant.

1358
1359 Grand Prize (1): \$500 cash Second Prize (1): \$200 cash Third Prize (5): \$10 cash

1360 1361 **7.6 Product and Procedures Compliance Review Sessions:**

1362 At each visit, Baseline 2 through Week 16, participants will be counseled about their use of
1363 the study cigarettes and assigned e-cigarette (if applicable). Participants will be asked about any
1364 concerns or obstacles associated with use of the study cigarettes and assigned e-cigarette (if
1365 applicable). The importance of honest self-reporting will be stressed. Participants will be told that
1366 they will not be penalized for use of other nicotine or tobacco products and that it is crucial for
1367 them to report any use of these products. If difficulties are encountered, participants will be asked
1368 why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to
1369 problem-solve how to deal with these difficulties in order to meet the protocol requirements.
1370 Additionally, participants will be counseled about their IVR completion, visit attendance, task
1371 engagement and product accountability. Refer to the '*Product and Procedures Compliance
1372 Review Sessions SOP*' for more information.

1373 1374 **7.7 Quit Attempts During the Study Protocol:**

1375 At each weekly session, we will ask each participant if s/he is currently abstaining from
1376 smoking with the intention of quitting and whether s/he is planning to quit smoking prior to
1377 his/her next scheduled visit. If a participant is currently abstaining from smoking with the
1378 intention to quit, we will encourage the participant to continue abstaining, schedule them for
1379 weekly visits, and provide them with NCI's Clearing the Air manual and local smoking cessation
1380 resources. We will give them the option of taking study product(s) home but not require that they
1381 take them, and if they do take the product(s) home we will suggest that they put the product(s)
1382 away at home so as to remove these cues from view. We will ask the participant to contact staff
1383 if they lapse and would like to receive study product(s) prior to his/her next visit. If a participant
1384 is planning to quit but has not initiated a quit attempt, we will ask if s/he has identified a quit date
1385 and if so what the date is, provide them with the Clearing the Air manual and local smoking
1386 cessation resources, provide them with the study product(s), and recommend that they put the
1387 product(s) away out of view on the quit date.

1388 For those in a condition including e-cigarettes, we will defer to the participant's interests in
1389 continuing to use e-cigarettes as part of their quit attempt. Those who indicate that they will
1390 continue to use them will be given their same weekly supplies base on their baseline smoking
1391 rate. Those who indicate that they are planning to abstain from both combusted and non-
1392 combusted tobacco, we will honor that request. As we state above about combusted cigarettes,
1393 if participant changes his or her mind about resuming e-cigarette use, they can contact us and
1394 obtain their weekly supply.

1395 1396 **7.7.A. If a participant is currently abstaining from smoking with the intention to quit:**

- 1397 • Encourage participant to continue abstaining from smoking
- 1398 • Schedule the participant for normal weekly visits, but no puff topography
- 1399 • Provide the participant with the '*Clearing the Air*' manual and local smoking cessation
1400 resources
- 1401 • Give the participant the option to receive study product rather than require him/her to take
1402 the product
- 1403 • If the participant choses to receive the study product have him/her sign a form
1404 acknowledging that cigarette availability could be detrimental to the quit attempt.
1405 Recommend that he/she put the product "away" at home as to avoid unwanted cues to
1406 smoke.
- 1407 • If the participant chooses not to receive the study product, have him/her contact the lab if

1408 he/she lapses and would like to pick up or be mailed the study product prior to his/her next
1409 visit.

1410
1411 **7.7.B. If a participant is planning to quit smoking, but has not initiated the quit attempt:**

- 1412 • Ask if he/she has identified a target quit date and, if so, what that target date is
- 1413 • Provide the participant with the 'Clearing the Air' manual and local smoking cessation
1414 resources
- 1415 • Provide the participant with the study product as usual. Recommend that on the target
1416 date he/she put the product "away" at home as to avoid unwanted cues to smoke.
1417

1418 **7.8 Abstinence Assessment Session:**

1419 After the week 16 visit, participants will be required to attend one additional visit the
1420 following day. During this visit, participants will have been encouraged to abstain from smoking
1421 until their next scheduled visit (approximately 24 hours later). The abstinence assessment
1422 session should be scheduled no less than 18 hours and no more than 30 hours after the Week
1423 16 visit. Abstinence will be verified by an expired breath carbon monoxide level of less than or
1424 equal to 6 parts per million (ppm). This session will allow us to determine whether the
1425 experimental cigarettes and e-cigarette use (for the e- cigarette conditions) have reduced the
1426 effects of abstinence on these measures relative to the control conditions. If the participant
1427 does NOT meet abstinence criteria, he/she will only receive \$20 for the visit. Those who do
1428 meet abstinence criterion will do concurrent choice session detailed below.
1429

1430 **7.8.A Participants Who Meet Criteria for Abstinence**

1431
1432 **7.8.A.1 Measures/Assessments**

1433 **Physiological measures collected and entered directly into REDCap by the interviewer at**
1434 **the end of the visit:**

- 1435 1) CO
- 1436 2) Blood Pressure
- 1437 3) Heart Rate
- 1438 4) Body temperature
- 1439 5) Oxygen saturation
- 1440 6) Respiratory rate
- 1441 7) Urine or Saliva Toxicology
1442

1443 **The following assessments will be administered as an interview and will be entered**
1444 **directly into REDCap by the interviewer:**

- 1445 1) Concomitant Medications
- 1446 2) Medical Event Form, if applicable
- 1447 3) Health Changes Questionnaire
- 1448 4) Time Since Last Cigarette Questionnaire
1449

1450 **The following assessments will be completed by the participant directly in REDCap:**

- 1451 1) BDI
- 1452 2) OASIS
- 1453 3) COVID19 Symptom Questionnaire
- 1454 4) Respiratory Symptom Questionnaire
- 1455 5) MNWS
- 1456 6) PANAS
- 1457 7) QSU-brief - Usual Cigarette
- 1458 8) QSU-brief - Study Cigarette
- 1459 9) Vaping Craving Questionnaire
- 1460 10) Cigarette Purchase Task - Usual Brand Cigarette Version
- 1461 11) Cigarette Purchase Task - Study Cigarette Version
- 1462 12) E-cigarette Purchase Task- E-cigarette Version

1463 13) Snaith-Hamilton Pleasure Scale (SHAPS)
1464

1465 In the event that the REDCap website is not functioning, the assessments will be administered
1466 aloud and participant answers will be recorded securely. The interviewer will enter the data into
1467 REDCap when it resumes functioning properly. This information should be recorded in the 'End
1468 of Visit Evaluation Form'.

1469
1470 **7.8.B. Participants Who Do Not Meet Criteria for Abstinence**
1471

1472 **7.8.B.1 Measures/Assessments**

1473 **Participants who do NOT meet abstinence criteria will be required to complete the**
1474 **following assessments:**

- 1475 1) CO
1476 2) Blood Pressure
1477 3) Heart Rate
1478 4) Body temperature
1479 5) Oxygen saturation
1480 6) Respiratory rate
1481 7) Urine or Saliva Toxicology
1482

1483 **The following assessments will be administered as an interview and entered directly into**
1484 **REDCap by the interviewer:**

- 1485 1) Concomitant Medications
1486 2) Health Changes Questionnaire
1487 3) Medical Event Form, if applicable
1488 4) TLFB
1489

1490 **The following assessments will be completed by the participant directly in REDCap:**

- 1491 1) BDI
1492 2) OASIS
1493 3) COVID19 Symptom Questionnaire
1494 4) Respiratory Symptom Questionnaire
1495

1496 **7.9 Participant Compensation:**

1497 Participants will receive \$25 plus a \$25 bonus for completing each screening visit on time as
1498 scheduled. Payment for the first screening session will be made upon its completion. Payment
1499 for the second screening session will be made regardless of enrollment as long as the
1500 participant passes the drug test and meets the minimum requirements for carbon monoxide or
1501 urinary cotinine levels. Participants who do not pass the drug test or who are visibly intoxicated
1502 as determined by slurred speech, swaying, or stumbling will not be able to complete the visit
1503 and will be asked to take another test several days after the first positive. If they are negative for
1504 the second test, they will be eligible to participate, and if they are positive the for the second text
1505 they will be excluded. Participants will receive \$100 for each study visit from Baseline 1 to Week
1506 16. Participants will also have a chance to earn an additional \$20 bonus for every study visit that
1507 is completed on time as scheduled starting at Week 1 and ending at Week 15.

1508 Participants can receive up to \$120.00 for the abstinence session (\$20 if participant does
1509 not achieve abstinence, \$120 if participant reaches abstinence), \$40 for biochemical verification
1510 of abstinence at 30 day follow up visit, and up to \$306 for completing daily IVR reports of study
1511 cigarette and other nicotine and tobacco use. There will also be a \$150 bonus distributed at
1512 Week 16 for completing the study. Participants who do not complete the entire study will receive
1513 compensation for the sessions that they do complete. Total compensation for completing Study
1514 3, including study visit payments, daily IVR calls and end of study bonus is \$2816. As
1515 mentioned above, participants will have a chance to earn additional incentives for compliance,
1516 honesty and attendance through urine testing. Participants will be given a debit card at the
1517 beginning of the study (during the second portion of the screening visit) and compensation for

1518 each visit will be automatically transferred to the card after they complete that visit. If debit cards
1519 are unavailable, participants will be paid via an alternate method (i.e. cash or check).

1520
1521 **7.10 End of Study:**

1522 After a participant has completed all study procedures and has been paid for participation the
1523 research assistant will read the following script and give the participant the *Clearing the Air*

1524 *Manual.*

1525 *“If you’ve reduced your smoking during this study, we encourage you to continue these reductions*
1526 *or even consider quitting. We would like to provide you with some resources should you decide*
1527 *to try to abstain from smoking (give “Clearing the Air” and hotline information). Please also feel*
1528 *free to consult with your physician and use any medications he/she deems appropriate. We will*
1529 *call you in approximately 30 days to ask about your smoking since leaving the study. There is no*
1530 *right answer and we know how difficult quitting can be. Please just answer honestly. The call will*
1531 *take less than 5 minutes. Thanks again for your participation.”*

1532 The following assessments will be administered using REDCap:

- 1533 1) End of Study Questionnaire
1534

1535 **7.11 30 Day Follow up Phone Call:**

1536 Participants will receive a follow-up phone call between 25 and 35 days after the abstinence
1537 assessment session to assess their smoking patterns. The phone questionnaire will last less
1538 than five minutes. The questionnaire will ask if the participant is still smoking, how much and
1539 whether he/she has attempted to quit smoking since the end of the study. Participants will
1540 receive 5 variable incentive program lottery tickets for completing the call as compensation.

1541 Those who report abstinence will be invited to complete biochemical verification and be
1542 compensated \$40 for doing so. Abstinence will be achieved by a carbon monoxide reading of 6
1543 parts per million (ppm) or under. A urine sample may also be collected to be sent to the lab for
1544 analysis. Additionally, any Medical Event Forms that remain open from the last session will be
1545 discussed. If the participant became pregnant during the study, this would have been recorded
1546 as a medical event. During this phone call, the research assistant will confirm her due date.

1547 This event will remain open until delivery. At that time the licensed medical professional will
1548 contact the participant to ask a few questions about the baby’s health and will update the
1549 Medical Event Form.

1550 Once a participant has completed all study procedures and all open events have been
1551 closed, the PI or Project Manager will review the participant’s record and sign a form indicating
1552 study completion for that participant.

1554 **8.0 Study Randomization**

1556 **8.1 Randomization Process**

1557 The lead statistician will create a randomization schedule for each of the two sites,
1558 amounting to 150% of expected enrollment at each site. The excess randomization codes will be
1559 used in the event that a site will have to enroll extra participants due to unexpectedly slow
1560 enrollment at another site. The nicotine doses will be identified by letter code and only
1561 Administrative Core personnel with no participant contact will have the link between the
1562 statistician’s letter code and dose assignments. There will be no blinding of e-cigarette
1563 conditions. The Administrative Core will maintain the randomization schedule and the link
1564 between the alphabetic code and treatment assignment securely. A second sealed copy will be
1565 secured in a separate building to protect against loss related to fire or other unforeseen events.

1566 The University of Vermont will be responsible for removing all identifying information from
1567 cigarettes received from the Research Triangle Institute (RTI), labeling each carton with a blind
1568 code, assigning product using this blind code based on the randomization schedule being
1569 provided by the UVM Biostatistics Core, and shipping cigarettes and e-cigarettes to each site as
1570 needed based on recruitment. Each site will be responsible for tracking product received and
1571 distributed to participants, collecting unused product from participants, and returning unused
1572 cigarettes and e-cigarettes to UVM. The participants, investigators and study staff will not have
1573 knowledge of which product is given to a participant or whether different participants received
1574 the same or different product.

1576 **8.2 Study Product Administration**

1577 During the experimental period, participants will be provided with a 14-day supply of research
1578 cigarettes equivalent to 150% of their daily smoking rate. Those in the e-cigarette conditions will

1579 also be provided with a 14-day supply of e-cigarettes equivalent to their daily smoking rate. This
1580 rate will be calculated at Baseline 2 and will be an average daily smoking rate based on the IVR
1581 data that reports on the usage for the first seven days following the day of the first baseline visit.
1582 This will ensure adequate availability of cigarettes in the numerous locations participants may
1583 typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if
1584 they miss a scheduled visit. Participants will be instructed to use the research cigarettes for 12
1585 weeks, at which point they are to discontinue product use.

1586 If there is prior knowledge a participant will be missing a visit (i.e. planned vacation, laboratory
1587 closure, etc.), then the participant will be provided with an adequate supply of cigarettes to make
1588 up for the missed visit(s). The participant will be given a 21-day supply if one visit is going to be
1589 missed and a 28-day supply if two visits are going to be missed.

1591 **8.3 Guidelines for Reporting other Nicotine Product Use**

1592 Participants will be asked to refrain from use of other non-study cigarettes during the study
1593 period. If participants have to use another nicotine product, they will be told to use a non-
1594 combustible product (gum, patch, etc.). Additionally, they will be told there is not a penalty for use
1595 of non-study products, and that it is crucial for them to report any use of non-study tobacco
1596 products. Throughout the baseline and experimental periods, an Interactive Voice Response
1597 (IVR) system will be used on a daily basis to record the number of study cigarettes and non-study
1598 cigarettes used the previous day. During the baseline and first experimental week, participants
1599 will also answer daily IVR questions about their mood. Participants will be seen weekly for
1600 assessments. Brief standardized review sessions focusing on compliance with the study
1601 cigarettes and other study procedures will be provided at each visit.

1603 **8.4 Product Accountability:**

1604 Participants will be required to keep track of all the products provided to them. Therefore, they
1605 will be instructed to return all unused products and empty cigarette packs e-liquid pods/cartridges
1606 to the laboratory each week. Research staff will complete the 'Product Accountability Log' as they
1607 process participants' product. Any discrepancies in the product dispensed versus product
1608 returned will be discussed and recorded in the log. Research staff will weigh all opened e-cigarette
1609 pods/ cartridges that the participant returns at all visits to determine how much e-liquid was used
1610 since the participant was last seen. Empty cigarette packs and e-liquid pods/cartridges will not be
1611 saved. Unused cigarette packs and e-liquid pods/cartridges will be re-distributed to the
1612 participants during Weeks 1-15. During Week 16, remaining unused cigarettes and e-cigarette
1613 pods/cartridges returned by the participants will be collected by the research staff.

1614 Participants who report running out of cigarettes or e-liquid pods/cartridges prior to a
1615 scheduled weekly visit will be allowed to come in for an unscheduled visit to obtain more
1616 research cigarettes. To determine whether a rate change for cigarettes is necessary, we will
1617 look at the past two CO levels as compared to the Baseline 2 CO. If the CO trend is consistent
1618 with the self-report of smoking all of the allotted cigarettes then a rate increase will be granted.
1619 The participant will then receive cigarettes at a rate of 175% of their daily smoking rate. The
1620 maximum increase is 200% of their daily smoking rate. To determine whether a rate change for
1621 e-cigarettes is necessary, we will monitor the amount of e-cigarette use the participant is
1622 reporting and showing through product return along with any unscheduled visits. The
1623 investigator may grant an e-cigarette rate increase in increments of 25%. The maximum increase
1624 for e-cigarettes will be 200% of their baseline weekly e-cigarette dispensation rate.

1625 If participants lose more than two packs of cigarettes and/or pods/cartridges and require an
1626 unscheduled visit to the laboratory to supplement their supply, they will be told the next time
1627 they lose more than two packs they will have to wait until their next scheduled appointment to
1628 receive more cigarettes.

1630 **9. Study 3 Statistical Methods and Sample Size**

1631 **9.1 Statistical Methods**

Continuous outcomes will be summarized by mean, standard deviation, median and range. Categorical outcomes will be summarized by frequencies and percentages. Skewed continuous outcomes will be log- or square-root transformed as appropriate. Variables measured at each baseline visit will be averaged and the average will be used as the baseline measurement. As we expect conditions to be balanced on important baseline characteristics due to randomization, our primary analysis for all endpoints will not be adjusted for potential confounders. However, a secondary analysis will be completed for all outcomes adjusting for demographic characteristics (e.g., age), that we have found to be important in prior studies. Potential moderators (e.g., SSRI vs. non-SSRI antidepressant, depression vs. anxiety disorders, BMI above or below 30) will be explored by adding that term and the moderator-by-condition term to the model. We will examine age group and gender as potential moderators in a similar fashion.

Participants will be randomized in equal probability to one of the four conditions, with randomization stratified by site and menthol cigarette status. All analyses will follow the intent-to-treat principle (i.e. subjects will be analyzed according to condition assignment, regardless of compliance). The Primary Aim will examine the effects of condition on total CPD (study product and non-study product). CPD will be analyzed by week (mean over all days in a seven-day period) using a mixed model to account for repeated measures from the same individual.

Models will include baseline CPD as a covariate. Using a mixed model also allows us to include the effect of study site as a random effect. Additional analyses conducted using data collected at the end of the study will use orthogonal comparisons to test for a linear trend in the decrease in CPD, such that VLNCC + PF e-cig > VLNCC + TO e-cig > VLNCC > NNCC, with the largest reduction in the VLNCC + PF e-cig condition. As we expect that differences among conditions for some of the outcomes may not follow a linear pattern, we will use related planned comparisons to test for threshold effects, specifically contrasting the NNCC condition to all three VLNCC conditions, and NNCC to the two VLNCC + e-cigarette conditions.. Analysis of cigarette demand, smoke exposure and tobacco carcinogens (Aim 2) as well as additional outcomes, including subjective effects, will be analyzed in a similar manner. Because Exploratory Aim 3 is based on abstinence-induced effects and will be examined using data collected at a single visit at Week 17, analysis will be based on an analysis of co-variance model. In addition to the effect of condition, we will include important covariates noted above. Exploratory analyses will also be conducted combining data collected from three of the vulnerable populations (disadvantaged women of childbearing age, opioid dependent individuals, individuals with AD) to explore potential differences in effects of study condition across these populations. This will be done with the addition of the effects of population and population-by-condition terms to the models described above. Study staff will make every effort to minimize missing data, and results of our ongoing trial suggest that this will be minimal. We will examine the missing data pattern, and if it is missing at random, will use all data available, without imputation.

permutation tests.¹²¹

9.2 Sample Size

Sample size was determined using NQuery Advisor based on hypothesis tests related to Aim 1, specifically to detect a significant difference between the study conditions (NNCC, VLNCC, VLNCC + TO e-cigs, VLNCC + PF e-cigs) on total cigarettes per day (CPD). The primary statistical approach will be repeated measures ANOVAs but required sample sizes were calculated focusing on expected outcomes at Week 16. This sample size estimate is intentionally conservative and calculated based on one outcome at one time point; however, given the repeated measures nature of our data, we will have correlated observations within subjects. Thus, with the given sample sizes we will achieve the stated power to detect differences of even lesser magnitude than stated or planned. Our sample size determination is based on preliminary results from our current trial and results from a large randomized clinical trial of

Table 2. Observed effect sizes

Outcome	Observed between-group ES (15.2 vs. 0.4 mg/g)
CPD	0.81
Craving	0.20
FTND	0.42
Breath CO	0.33

1687 cigarettes varying in nicotine content.⁷ Note that the between-group effect size is defined as the
1688 difference of study condition means divided by the common standard deviation. A sample size of
1689 53 participants per condition will provide 80% power to detect an effect size of 0.60 for all pair-
1690 wise comparisons, with a two-sided type 1 error rate of 0.05. This is smaller than that found in
1691 our on-going study to date for CPD and smaller than the effect sizes reported by Hatsukami et
1692 al.⁸ for all measures except breath CO. In addition, this sample size provides greater than 95%
1693 power to detect a linear dose-response effect across the four experimental conditions. Because
1694 we have relied only on outcomes at Week 16, our proposed sample sizes are somewhat
1695 conservative, but we believe this is appropriate for this study given that the effects of VLNC
1696 cigarettes in this population, particularly in combination with e-cigarettes, are completely
1697 unknown. The sample size above assumes a 15% loss to follow-up, consistent with our
1698 experience in the current study. We will increase our overall sample size to 232 in order to
1699 allow pilot testing in a group of 20 participants.
1700

10. Potential Risks of Participation

10.1 Risks of Participation

- 1704 1) Survey Questionnaires. This interview will include questions about your medical and
1705 psychiatric histories, drug and alcohol use and history, breath tests for cigarette and
1706 alcohol use, urine or salivary tests of illicit drug use and pregnancy, and questionnaires
1707 about your mood. Answering these personal questions could make you uncomfortable. If
1708 you report thoughts of killing yourself or other indicators of suicidality, a study clinician
1709 will come to talk to you. You may also request to see a study clinician if you are in
1710 discomfort and would like help and/or referrals for mental health resources.
- 1711 2) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out
1712 the results.
- 1713 3) Undue Influence: Undue influence is a possible risk due to monetary compensation for
1714 participating in these studies. The likelihood of this risk is low because the compensation
1715 is commensurate with the amount of time and effort required for these studies.
- 1716 4) Drug Testing: A breach of confidentiality could occur and other people could learn of the
1717 participant's drug use.
- 1718 5) Obtaining Blood Pressure and Heart Rate. The blood pressure cuff may cause minimal
1719 discomfort. In obtaining blood pressure we may find a participant to have abnormal blood
1720 pressure and/or heart rate. If participant's blood pressure is abnormal, we will inform the
1721 participant of this, and participant may be advised to see a doctor, and may also be
1722 contacted by our study doctor. Also, smoking and nicotine can affect the cardiovascular
1723 system, which may result in changes in blood pressure and/or heart rate.
- 1724 6) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to
1725 significant medical problems including:
 - 1726 a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral
1727 vascular disease, reduced blood circulation, abdominal aortic aneurysm
 - 1728 b. Respiratory Diseases: Emphysema, bronchitis, and chronic airway obstruction
1729 Cancers: Cancer of the lung, bladder, cervix, esophagus, kidney, larynx, mouth,
1730 pancreas, throat, and stomach; leukemia
 - 1731 c. Metabolic Diseases: Type 2 Diabetes
 - 1732 d. Other Health Risks Associated with Smoking: Including but not limited to infertility,
1733 lower bone density in postmenopausal women, and hip fracture in women
 - 1734 e. Death
- 1735 7) Smoking Study Cigarettes. All cigarettes are harmful to a person's health and can lead to
1736 cardiovascular (heart) disease, respiratory (lung) disease, cancer and other health
1737 problems. In addition to the above medical problems, you may experience some minor
1738 negative health effects such as headaches. You may also experience smoking
1739 withdrawal symptoms, which are listed below. In addition, due to the altered nicotine

1740 levels, there could be a change in your use of cigarettes including the manner in which
1741 you inhale the smoke. Smoking the study cigarette does not necessarily provide any less
1742 risk than your usual brand of cigarette and could pose increased health risks.

- 1743 8) Using Study E-cigarettes. E-cigarettes are devices that heat nicotine to produce an
1744 aerosol. The health effects of e-cigarettes are still unclear, but appear to be less than
1745 that for tobacco cigarettes. Most e-cigarette users have lower nicotine levels than when
1746 they smoked regular cigarettes. Some e-cigarette users, especially those who use both
1747 e-cigarettes and regular tobacco cigarettes as well as youth and young adults, can have
1748 increased nicotine levels. In some rare cases, these use patterns have been associated
1749 with seizures. Whether this would occur with the concurrent use of very low nicotine
1750 cigarettes is unclear. E-cigarettes users very often maintain addiction to nicotine, but this
1751 addiction appears to be somewhat less than that from tobacco cigarettes. Abruptly
1752 quitting e-cigarettes could cause withdrawal symptoms similar to those from quitting
1753 tobacco cigarettes (see below) but slightly less severe. The most common side effects
1754 include dry mouth, irritation of the throat and mouth, and mild cough. The JUUL and
1755 Vuse e-cigarettes we will be providing have not been well-studied but appear to be of
1756 similar risk to other e-cigarettes. You may have heard that e-cigarettes, or "vapes," can
1757 explode and seriously injure people. Although they appear rare, these explosions are
1758 dangerous. The exact causes of these incidents are not yet clear, but some evidence
1759 suggests that battery-related issues may lead to vape explosions. In order to prevent e-
1760 cigarette related injuries, keep your e-cig away from other metal objects, never charge
1761 your e-cig with a phone or tablet charger, don't charge your e-cig overnight or leave it
1762 charging unattended, and stop using the e-cig if the batteries get damaged or wet.
1763 Always keep e-cig liquid out of kids' and pets' reach and sight after use. If we learn about
1764 additional risks of e-cigarettes during the study, we will inform you of these risks.

1765 Mood and Psychiatric Symptom Changes. You may experience smoking withdrawal
1766 symptoms during this study. These symptoms can include anger, anxiousness, craving
1767 for a cigarette, depressed mood, difficulty concentrating, frustration, increased appetite,
1768 impatience/impulsivity, irritability, restlessness, sleep problems, and weight gain. These
1769 feelings can be uncomfortable and can last a couple of weeks, but usually are of minimal
1770 risk. In addition, if you have a past history of anxiety, depression, or alcoholism, it is
1771 possible withdrawal could cause substantial increases in depression and anxiety
1772 symptoms, but this appears to be rare. At each visit, we will ask you how you feel. If you
1773 or we think that being in this study is putting your mental health at risk, we may have you
1774 meet with an on-site clinician and/or stop participating in the study. Further, if you report
1775 thoughts of killing yourself or other indicators of suicidality, a study clinician will come to
1776 talk to you. You may also request to see a study clinician if you are in discomfort and
1777 would like help and/or referrals for mental health resources.

- 1778 9) Returning to Regular Smoking: It is possible that if participants return to smoking their
1779 usual brand of cigarette at the end of the study they may experience mild and transient
1780 nausea, dizziness, and lightheadedness.
- 1781 10) Risk to Fetus. To avoid risks to a fetus, it is important that you are not pregnant during
1782 this study. Avoiding sexual activity is the only certain method to prevent pregnancy.
1783 However, if you choose to be sexually active, you should be using approved forms of
1784 birth control if applicable determined by the Project Medical Director, including but not
1785 limited to prescribed birth control pills, patch, ring, injections, implants or intrauterine
1786 device (IUD) or an appropriate "double barrier" method. If you choose to be sexually
1787 active during this study, pregnancy could still result even with the use of these birth
1788 control methods.

1789 **10.2 Avoiding Risks to Fetus:**

1791 If participants choose to be sexually active, they should use an appropriate "double barrier"
1792 method of birth control (such as female use of a diaphragm, or contraceptive sponge, in addition

1793 to male use of a condom) or the female should be using prescribed “birth control” pills, patch, ring,
1794 injections, implants or intrauterine device (IUD) if applicable determined by the Project Medical
1795 Director. If a participant endorses a “double barrier” method, our medical professional will speak
1796 to the participant to confirm which methods will be used during the duration of the study.
1797 Participants will be tested for pregnancy every two weeks beginning at screening through the last
1798 study visit. If a participant becomes pregnant during the study, she will be withdrawn from the
1799 study. Approximately 30 days after being withdrawn or having a positive pregnancy test at the last
1800 study visit, the research staff will call the participant to confirm her due date. The licensed
1801 medical professional will follow-up with the participant after delivery to ask questions about the
1802 baby’s health.
1803

1804 **10.3 Expected benefits of participation:**

1805 There are no benefits from participating in the study. The information obtained from this
1806 study may ultimately help the Food and Drug Administration decide how best to regulate nicotine
1807 and tobacco products with the goal of improving public health.
1808

1809 **11. Protection Against Risk**

1810 **11.1 Data Collection Protections**

1811 Research data without identifiers will be maintained in a locked file cabinet and on
1812 password-protected computers in the research staff workplace, with only code numbers
1813 identifying subjects. Study consent forms and the linkage between the participants’ names and
1814 codes will be stored in a locked file cabinet inside a locked office. Interviews with participants will
1815 be conducted in private rooms. Urine or saliva samples for drug and pregnancy tests and
1816 tobacco exposure biomarkers will be obtained in a private bathroom within the laboratory suite.
1817

1818 Subjective measures will be administered electronically. The biostatistics and data-
1819 management team will provide consistent data-management practices for all data in the Center.
1820 Using REDCap, which is housed on the University of Vermont Medical Center’s HIPAA-
1821 compliant computing system, will maximize validity and reliability of data. REDCap is a secure,
1822 web-based system that accommodates local and remote data collection by each project team,
1823 and allows for data entry work-flow monitoring and data quality control monitoring by biometry
1824 staff. The RedCap database for this project will be hosted on the UVMCOM servers. In addition,
1825 data will be collected from participants on a daily basis using an interactive voice recognition
1826 system (IVR) developed and hosted by TeleSage Inc (www.telesage.com, Chapel Hill, NC).
1827 TeleSage is a company with expertise on gathering patient-centered outcomes tracking data
1828 for mental health clinical and research institutions. TeleSage has developed and hosted
1829 behavioral health-related research software systems using IVR and Web-based
1830 technologies and is leader in behavioral health outcomes tracking technologies. For data
1831 integrity, data entry windows will follow the structure of paper forms as much as possible to allow
1832 for ease of entry, and will use predefined choices to minimize errors when possible. Data quality
1833 monitoring will be facilitated with periodic down loads and analysis using a variety of common
1834 statistical program format such as SAS, Stata, R, and SPSS. Quality control procedures will be
1835 conducted for all data collected, including analysis of missing data and logic checks for out of
1836 range and other anomalous values. This secure electronic data gathering and transmission plan,
1837 overseen by the experienced biostatistical team, will minimize opportunities for breaches of
1838 confidentiality. Biological samples for nicotine and carcinogen biomarker analysis will be marked
1839 with participant ID, stored in the locked laboratory suite, and sent to a laboratory for analysis on
1840 a quarterly basis.

1841 All information collected as part of this study will be accessible only to research staff. No
1842 information will be shared with participants’ clinicians unless the participant requests this in
1843 writing. All investigators and staff have undergone (and any new staff will undergo) human
1844 subjects’ ethics training as required by UVM and are fully conversant with relevant ethical
1845 principals around confidentiality. Assessments, consenting and study procedures will be closely
1846 supervised by the PI.

1847 The sponsors (NIDA/FDA) as well as the Institutional Review Board and regulatory
1848 authorities could be granted direct access to original medical and research records for
1849 verification of clinical trial procedures and/or data. If this is required, it will be done under
1850 conditions that will protect privacy to the fullest extent possible consistent with laws relating to
1851 public disclosure of information and the law-enforcement responsibilities of the agency.
1852

1853 **11.2 Data Storage:**

1854 Data will be stored locally at each site. Long-term storage of all study data, for at least 7 years
1855 after study completion, will be at the University of Vermont.
1856

1857 **12. Adverse Events**

1858
1859 The research assistant will ask about adverse events at each session, using a form that
1860 assesses the nature, severity, duration, action taken, and outcome of study-related adverse
1861 events. AEs will be captured from the time of first study cigarette. Participants will be given
1862 contact cards to inform us of events that occur between study contacts. Any AE that remains
1863 open will be reviewed and closed at an interview conducted 30 days after the study completion
1864 date (completers) or when the study should have ended had the participant completed the study
1865 (dropouts and those withdrawn by investigator).

1866 All procedures will be monitored to ensure that they conform to the approved protocol. In
1867 addition, monitoring will be done of all unforeseen circumstances that might arise and affect
1868 safety; of all reports of serious adverse events as defined in 38 CFR 46 (death, new or
1869 prolonged hospitalization, persistent or significant disability/incapacity); of other significant
1870 adverse events (adverse events that lead to drop out by the participant or termination by the
1871 investigator); of unexpected adverse events resulting from the study, and of expected adverse
1872 events.

1873 Any SAE will be brought to the attention of the site PIs as soon as possible and not longer
1874 than 24 hours. Any AE or SAE that is both unexpected and related to study participation will be
1875 reported to the IRB within 7 days of the event. The local IRB will make a determination as to
1876 whether additional reporting requirements are needed. IRB actions will be reported to the
1877 funding agency by the PIs no less than annually and more frequently as recommended by the
1878 local IRB. Any SAEs will be summarized in the yearly Progress Reports to the funding agency,
1879 including a review of frequency and severity. All SAEs will be followed through ongoing
1880 consultation with the physician caring for the patient until they resolve, result in death, or
1881 stabilize and are not expected to improve. The study staff will be in close contact with
1882 participants and health care providers throughout the study to monitor for potential unanticipated
1883 problems. Any unanticipated problems will be discussed at the weekly research staff meetings
1884 and reported as required to the local IRB.
1885

1886 **13. Withdrawal or Monitoring of Participants**

1887
1888 **For the participant's protection, participants will be withdrawn immediately from the**
1889 **study if any of the following occur:**

- 1890 1) Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA
1891 (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial
1892 blockages in arms or legs leading to procedure or surgery). Less common CVD problems
1893 would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease
1894 (e.g., mitral or aortic regurgitation).
- 1895 2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous
1896 system).
- 1897 3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time
1898 during participation in the study.
- 1899 4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for
1900 psychiatric reasons at any time during participation in the study.

- 1901 5) Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at any
 1902 time during the study, she will be withdrawn from the study, and this event will remain
 1903 open until delivery. At that time the licensed medical professional will contact the
 1904 participant to ask a few questions about the baby's health and will update the open
 1905 'Medical Event Form'. A positive pregnancy test at Week 16 will trigger a 'Medical Event
 1906 Form' to be completed but will not result in withdrawal since she is no longer receiving
 1907 study product.
- 1908 6) Expired breath carbon monoxide increase: A participant will be withdrawn from the study
 1909 if the average of two consecutive CO readings during the same visit is 100 ppm or greater.
- 1910 7) Marked increase in smoking: A participant will be withdrawn from the study if he/she meets
 1911 **BOTH** of the following criteria for two consecutive weeks
- 1912 a. Cigarette per day increase: The average CPD increases by more than 100% from
 1913 the average CPD during baseline.
- 1914 b. Expired breath carbon monoxide increase: If the average of two consecutive CO
 1915 measurements in the same visit is
- 1916 i. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
 1917 ii. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
 1918 iii. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
 1919 iv. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
 1920 v. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
- 1921 c. Note: If the second consecutive visit is the last study visit, then the participant
 1922 would not be withdrawn from the study.
- 1923 8) If a participant is discharged from or discontinues his or her methadone or buprenorphine
 1924 treatment, they will be discontinued from the study.

1926 **The following will be monitored and can lead to the participant being withdrawn by the PI**
 1927 **or Licensed Medical Professional:**

- 1928 1) Cigarettes per day increase: Continued participation will be evaluated by the site PI if the
 1929 average number of cigarettes per day (CPD) increases by more than 100% from the
 1930 average CPD during baseline as determined by CPD at Baseline 2.
- 1931 2) Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-
 1932 enrollment: 1) BP is at or above 160/100 or below 90/50, or 2) HR is at or above 115 bpm
 1933 or below 45 bpm a manual blood pressure and heart rate measurement will be taken after
 1934 10 minutes have passed. If the manual reading is still out of range, a 'Blood Pressure and
 1935 Heart Rate Symptom Checklist' and 'Medical Event Form' will be completed, and the
 1936 participant will be monitored by the medical professional.
- 1937 3) Expired breath Carbon Monoxide increase: If the average of two consecutive CO
 1938 measurements meets the criteria below then the 'Medical Event Form' will be completed
 1939 and the participant will be monitored by the medical professional.
- 1940 a. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
 1941 b. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
 1942 c. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
 1943 d. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
 1944 e. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
- 1945 4) Any hospitalization or debilitation in which participation in the study could be detrimental
 1946 to the recovery process. This will be self-reported by the participant and will be reviewed
 1947 by the site PI and medical professional to determine whether continued participation in the
 1948 study is appropriate.
- 1949 5) If a participant is behaving in an inappropriate or threatening manner, admits to lying about
 1950 eligibility criteria, is participating in other smoking research studies that could affect the
 1951 primary outcome measures, etc., then the PI can withdraw him/her from the study at the
 1952 PI's discretion.
- 1953 6) If a participant fails to attend regularly scheduled research assessment visits or comply
 1954 with the research procedures or schedule, then the PI can withdraw him/her from the study
 1955 at the PI's discretion.

- 1956 7) Increase in psychiatric symptoms: Exacerbation in symptoms noted during the study (i.e.,
1957 change in BDI category from mild to moderate or moderate to severe) will trigger review
1958 by the study's licensed medical professional. The PI will withdraw the participant upon the
1959 licensed medical professional's recommendation.
1960

14. Data Safety Monitoring Board

1961
1962
1963 A Data and Safety Monitoring Board (DSMB) has been established to monitor safety
1964 outcomes and will be comprised of four members. The DSMB will be chaired by Kevin Delucchi,
1965 PhD., Professor in Residence of Biostatistics in Psychiatry at the University of California San
1966 Francisco and Director of the Quantitative Core of the San Francisco Treatment Research Center;
1967 Eden Evins, MD, MPH., Cox Family Professor of Psychiatry at Harvard Medical School and
1968 Director of Center for Addiction Medicine at Massachusetts General Hospital; Ari Kirshenbaum,
1969 PhD, Professor of Psychology at Saint Michael's College who he teaches courses in
1970 psychopharmacology and neuroscience, and currently has grants from NIH and NSF for work in
1971 human behavioral pharmacology and his grant-funded work focuses on cognitive and behavioral
1972 responses to nicotine and cannabinoids; and Elisabeth Johnson, Ph.D., who has over twenty
1973 years of clinical experience in women's health and pediatrics, including caring for women with
1974 substance use disorders.

Conflict of Interest

1975
1976
1977 None of the board members will be otherwise affiliated with the center and each member will
1978 complete a conflict of interest disclosure form prior to each meeting. Ad hoc specialists may be
1979 invited to participate as non-voting members at any time if additional expertise is desired.
1980

Monitoring Activities and Frequency of Meetings

1981
1982 The DSMB will set their own agenda and decisions about monitoring; e.g. how frequently to
1983 monitor, what threshold requires changes to protocol or stopping the study, and whether to view
1984 raw or analyzed data. The DSMB will be given FDA and EMEA guidelines for DSMBs and recent
1985 reviews on DSMBs. A brief report will be generated from each meeting for the study record and
1986 forwarded to each of the study site's Institutional Review Boards (IRB) and NIDA's Program
1987 Officer with the progress report. The DSMB will be available to convene outside of the regular
1988 meetings, if necessary. If concerns should arise regarding a particular subject, or any troublesome
1989 trends in the experiences of participants, they will make appropriate recommendations for
1990 changes in protocol, as needed. The project investigators will continue to examine safety data,
1991 blind to study condition, in case they wish to make study modifications. Before modifications
1992 are made, they will inform the DSMB and request their comments.

Communication Plan to IRB, NIDA, and FDA (if applicable)

1993
1994
1995 All IRBs, the FDA and the NIDA's Program Officer will be informed of any significant action
1996 taken as a result of the Data and Monitoring Board's findings. Study Participants will be informed
1997 of any changes in risk.
1998

Protection of Confidentiality

1999
2000 For DSMB meetings only de-identified data, including blinded study site and condition type,
2001 will be provided to the board. All data and discussion during the meeting will be confidential.
2002

15. Investigational Tobacco Product

2003
2004
2005 The University of Vermont Center on Tobacco Regulatory Science will complete an
2006 Investigational Tobacco Product (ITP) application with the FDA to cover the experimental
2007 cigarettes being used in this study. This application encompasses both Project 3 sites.
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16. Certificate of Confidentiality

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To help protect the participant’s privacy, Dr. Stephen Higgins, PhD, will obtain a Certificate of Confidentiality from the national Institute on Drug Abuse. With this certificate, the researchers cannot be forced to disclose information that may identify the participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participants, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

The Certificate of Confidentiality does not prevent the participant or a member of their family from voluntarily releasing information about themselves and their involvement in the research. If an insurer, employer or other person obtains the participant’s written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without consent, information that would identify the individual as a participant of the research project in instances such as evidence of child abuse or a participant's threatened violence to self or others.

17. Outcome Variables

Primary Endpoints for Study 3:

- 1) Cigarette Smoked per Day (CPD)
- 2) Nicotine Dependence Severity

Secondary Endpoints for Study 3:

- 1) Measures of adherence: non-study cigarette use, drop-out rate
- 2) Measures of psychiatric symptoms: BDI, OASIS
- 3) Measures of discomfort/dysfunction: MNWS, QSU
- 4) Measures of other health-related behaviors: breath alcohol, urine or salivary drug screen, TLFB-drug use, Alcohol Use Questionnaire, Drug Use Questionnaire, weight
- 5) Measures of nicotine/tobacco dependence: FTND, WISDM
- 6) Measures of tobacco exposure: CO, total nicotine equivalents, NNN, NNAL, minor alkaloids
- 7) Measures of intention to quit: Stages of Change, Contemplation Ladder
- 8) Measures of compensatory smoking: puff topography, filter analysis
- 9) Measures of other tobacco use: TLFB-other tobacco
- 10) Measures of cigarette characteristics: CES, Cigarette Purchase Task
- 11) Measures of cardiovascular function: heart rate, blood pressure, urine 11-dehydroTXB2
- 12) Measures of perceived risk: Perceived Health Risk Questionnaire
- 13) Safety outcome variables: Adverse Events (AEs), Serious Adverse Events (SAEs)

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2363 **STUDY PROTOCOL: SMOKERS WITH OPIOID USE DISORDER**

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Abbreviations

2438

- 2439 • 3HC: 3-hydroxycotinine
- 2440 • BAL: Breath alcohol levels
- 2441 • BDI: Beck's Depression Inventory
- 2442 • BMI: Body Mass Index
- 2443 • BP: Blood pressure
- 2444 • BPM: Beats per minute
- 2445 • BRIEF-A: Behavioral Rating Inventory of Executive Function
- 2446 • CES: Cigarette Evaluation Scale
- 2447 • CO: Carbon monoxide
- 2448 • COT: Cotinine
- 2449 • CPD: Cigarettes per day
- 2450 • CPT: Cigarette Purchase Task
- 2451 • CPT: Continuous Performance Task
- 2452 • DAST: Drug Abuse Screening Test
- 2453 • DDT: Delay Discounting Task
- 2454 • D-KEFS: Delis-Kaplan Executive Function System
- 2455 • EDC: Electronic Data Capture
- 2456 • EQ-5D: Euro-Qol
- 2457 • FSPTCA: Family Smoking Prevention and Tobacco Control Act
- 2458 • FTND: Fagerström Test for Nicotine Dependence
- 2459 • GAD: Generalized Anxiety Disorder
- 2460 • HR: Heart rate
- 2461 • IVR: Interactive Voice Response
- 2462 • MDD: Major Depressive Disorder
- 2463 • MINI: Mini International Neuropsychiatric Interview
- 2464 • MNWS: Minnesota Nicotine Withdrawal Scale
- 2465 • NMR: Nicotine metabolite ratio
- 2466 • NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
- 2467 • NNC: Normal nicotine content
- 2468 • NNN: *N*-nitrosonornicotine
- 2469 • OASIS: Overall Anxiety Severity and Impairment Scale
- 2470 • OUD: Opioid Use Disorder
- 2471 • PANAS: Positive and Negative Affect Schedule
- 2472 • PHQ: Patient Health Questionnaire
- 2473 • PSS: Perceived Stress Scale
- 2474 • QSU: Questionnaire of Smoking Urges
- 2475 • RNC: Reduced nicotine content
- 2476 • SST: Stop Signal Task
- 2477 • TLFB: Timeline Follow Back
- 2478 • TPQ: Time Perspectives Questionnaire
- 2479 • VLNC: Very low nicotine content
- 2480 • WASI-II: Wechsler Abbreviated Scale of Intelligence-II
- 2481 • WISDM: Wisconsin Index of Smoking Dependence Motives

Protocol

1. OBJECTIVE

Prevalence of smoking among individuals with opioid use disorder (OUD) is six-fold that of the general US adult population. The mortality rate of opioid-dependent smokers is four times that of opioid-dependent nonsmokers, and their response to smoking cessation interventions is notoriously poor. A national policy of reducing the nicotine content of cigarettes has the potential to be an effective method of reducing tobacco use prevalence, dependence, and related adverse health outcomes. Controlled trials in the general smoker population have demonstrated that switching smokers to very low nicotine content cigarettes (VLNCCs) results in reductions in cigarettes per day (CPD), dependence and tobacco toxicant exposure, with few adverse consequences. Furthermore, our work during the current funding period indicates that smokers with OUD also respond to reductions in cigarette nicotine content with reductions in cigarette demand and other measures of addiction potential, although to a lesser extent than the other vulnerable smoker populations we have been examining (i.e., economically disadvantaged women, individuals with affective disorders). We believe that the impact of reduced nicotine standards on use of combusted cigarettes in this highly tobacco addicted population will be moderated considerably by other tobacco market conditions including (1) availability of alternative sources of non-combusted nicotine, and (2) whether these alternatives are available under conditions that optimize their appeal. We hypothesize the same for other vulnerable populations as well, but achieving significant reductions in use of combusted cigarettes in smokers with OUD seems especially unlikely in the absence of readily available and appealing alternative sources of non-combusted nicotine.

The goal of the proposed trial is to experimentally model whether increased availability and appeal of an alternative, non-combusted source of nicotine (e-cigarettes) will enhance the effectiveness of a reduced nicotine standard for cigarettes in smokers with OUD. Daily smokers receiving methadone or buprenorphine treatment will be recruited at University of Vermont and Johns Hopkins University and randomized to one of the following conditions: (1) normal nicotine content cigarettes (NNCC) alone, serving as the control condition, (2) VLNCCs alone, (3) VLNCCs + tobacco-flavored nicotinized e-cigarettes (TF e-cigs), or (4) VLNCCs + nicotinized e-cigarette with preferred flavoring (PF e-cigs). Participants will be asked to use only their assigned products for 16 weeks. Outcome measures include total CPD, product demand using behavioral-economic purchase tasks, craving, withdrawal, and biomarkers of tobacco toxicant exposure. In Week 17, participants will abstain from combusted cigarette use and we will assess effects on cigarette craving, withdrawal and demand.

This research will address the following specific aims:

Aim 1 (Primary): To compare the effects of: (1) NNCCs alone, (2) VLNCCs alone, (3) VLNCCs + TF e-cigs and (4) VLNCCs + PF e-cigs on total CPD in smokers with OUD. We hypothesize that at Week 16, total CPD will be reduced in a linear manner, with the largest reduction in the VLNCCs + PF e-cig condition.

Aim 2 (Secondary): To compare the effects of study conditions on measures of cigarette demand, smoke exposure (breath CO) and tobacco carcinogen biomarkers (NNAL, PAHs) in smokers with OUD. We hypothesize that at Week 16, these measures will have decreased in a linear manner, with the largest reduction in the VLNCCs + PF e-cig condition.

Aim 3 (Exploratory): To explore the effects of the four study conditions on cigarette demand,

2529 craving, and withdrawal in smokers with OUD during the abstinence assessment period.

2530 The integrative theme of this TCORS is vulnerable populations. The proposed research is relevant
2531 to FDA CTP's scientific domains of Addiction and Behavior by addressing whether reducing the
2532 nicotine content of cigarettes reduces cigarette use, dependence, and product appeal, and whether
2533 these effects are enhanced by availability of appealing alternative sources of non-combusted
2534 nicotine. It addresses the domain of Health Effects by assessing tobacco toxicant exposure and
2535 other biomarkers. The proposed study is significant and innovative by modeling the potential
2536 moderating effects of e-cigarette availability and appeal on a national reduced-nicotine policy for
2537 cigarettes in this understudied population. Finally, it is programmatic as it builds directly upon and
2538 extends the work our team accomplished during the Phase 1 funding period.

2539 2. SIGNIFICANCE

2540 2.1. Opioid Use Disorder (OUD) and smoking

2541 Cigarette smoking is the leading preventable cause of US morbidity and mortality.¹ While
2542 smoking has steadily declined in the general population, it remains entrenched among vulnerable
2543 populations. Individuals with substance use disorders, mental illness or socioeconomic
2544 disadvantage are disproportionately represented among current cigarette smokers and bear a
2545 disproportionate burden of smoking attributable disease and premature death.²⁻⁵ The focus of this
2546 proposal is on the vulnerable population of smokers with concurrent substance abuse. Recent data
2547 from Wave 1 of the Population Assessment of Tobacco and Health study show that among current
2548 adult cigarette smokers, 80.7% report past-year alcohol or drug use.⁶ Current smokers are more
2549 than twice as likely as non-smokers to report past-year misuse of painkillers/sedatives and more
2550 than four times as likely to be past-year users of other drugs, including heroin. Conversely,
2551 individuals with substance use disorders (SUDs) are substantially more likely to die of tobacco-
2552 related disorders (e.g., lung and larynx cancers, respiratory disease) than the general population.⁷⁻⁹
2553 They are also more likely to die of problems related to their tobacco use than other drug use.¹⁰

2554 As an exemplar of the larger population of smokers with SUDs, we have been focusing on
2555 those with concomitant opioid use disorder (OUD). The disproportionate burden of smoking and
2556 smoking-related consequences is especially evident in these individuals. **Prevalence of smoking
2557 among adults with OUD is six-fold that of the general US adult population (84-94% vs. 15%,
2558 respectively).**¹¹⁻¹⁷ Smokers with OUD also have greater severity of nicotine dependence. In recent
2559 analyses by our group of data from the National Survey on Drug Use and Health (2006- 2014),
2560 after accounting for sociodemographic and smoking characteristics, mean Nicotine Dependence
2561 Syndrome Scale scores were significantly higher for opioid-dependent smokers vs. smokers not
2562 dependent on opioids ($p < 0.05$).¹⁸ Finally, smoking is associated with significant morbidity and
2563 mortality in this population, with the **mortality rate of opioid-dependent smokers four times that
2564 of opioid-dependent nonsmokers.**^{7,9-10}

2565 The majority of OUD patients report knowledge of the adverse health consequences of
2566 smoking as well as a desire to quit smoking.^{12,16-17,19-23} Despite this, their responses to standard
2567 smoking cessation treatments, including standard pharmacotherapies, are notoriously poor, with
2568 quit rates one-fourth that of non-substance abusers.^{16, 24-29} Taken together, the high smoking
2569 prevalence, poor treatment response, and public health costs associated with smoking among
2570 opioid-dependent individuals are of significant concern given the scope of the current opioid
2571 epidemic, with 5% of Americans - over 16 million people - reporting recent opioid abuse.³⁰⁻³¹

2572 2.2. Reducing the addiction potential of tobacco products

2573 One potential way to reduce smoking prevalence is to implement public policy mandating a
2574 reduction in cigarette nicotine content below the threshold necessary to establish and sustain
2575 nicotine dependence.³² The 2009 Family Smoking Prevention and Tobacco Control Act gave the
2576 FDA the authority to regulate tobacco products to protect public health, including limiting the
2577 nicotine content of cigarettes. Nicotine is the constituent in tobacco that drives repeated use,
2578 dependence, and eventually the chronic diseases and premature death that result from chronic
2579 smoke exposure. Thus, reductions in nicotine content may reduce smoking prevalence and related
2580

disease by disrupting initiation of smoking by new users and increasing cessation rates among current smokers.³³⁻³⁴ This approach could be particularly beneficial to subpopulations of smokers who have less success with currently available cessation treatments, such as people with OUD.³⁵ Our work during the current funding period, reviewed below, indicates that smokers with OUD respond to reductions in the nicotine content of cigarettes with reductions in cigarette demand and other measures of addiction potential, although to a lesser extent than the other vulnerable smoker populations we have been examining (i.e., economically disadvantaged women, individuals with affective disorders (AD)). We anticipate that a *combination* of tobacco market conditions will be necessary to produce a maximal effect on combusted smoking in this population. In particular, we hypothesize that (1) making alternative sources of non-combusted nicotine (i.e., electronic cigarettes; e-cigs) available and (2) doing so under conditions that optimize their appeal (i.e., preferred flavoring) may enhance the ability of a national policy to reduce nicotine standards to decrease cigarette smoking, dependence, and related adverse health outcomes among smokers with OUD.

2.3. Relevance of the project to the integrative theme and goals of the TCORS

The integrative theme of our UVM TCORS is **vulnerable populations**, and our goals are to model the potential effects of tobacco product standards on product use in vulnerable populations, with the goal of reducing the risks of product use, dependence, and related adverse health outcomes. For the FDA to effectively execute its tobacco regulatory responsibilities, it must have sound scientific evidence on how product standards impact tobacco use in populations with high rates of tobacco dependence. Our goal is to provide the FDA with that evidence. This project is relevant to that goal because it will examine the effects of a reduced-nicotine standard for cigarettes, alone and combined with another FDA-regulated product (e-cigs) on measures of cigarette use, demand, dependence and tobacco toxicant exposure in this vulnerable population.

2.4. Relevance to the scientific domains and priorities of the FDA CTP

The proposed research is highly relevant to the CTP's scientific domains of **Addiction** and **Behavior** because it will address whether reducing the nicotine content of cigarettes reduces cigarette use, dependence, and product appeal, and whether these effects are enhanced by the availability of appealing alternative sources of non-combusted nicotine. It will address the **Health Effects** domain by assessing the effects of these conditions on tobacco toxicant exposure and a respiratory biomarker.

2.5. How study outcomes will improve scientific knowledge related to the manufacture, distribution and marketing of tobacco products

Outcomes will directly inform scientific knowledge concerning the manufacture of tobacco products by demonstrating whether a reduction in the maximum nicotine content of cigarettes to ≤ 0.4 mg nicotine/g tobacco would reduce smoking in this vulnerable population. The outcomes will also indicate whether continuing to allow the sale of e-cigs in characterizing flavors improves the efficacy of a reduced-nicotine standard for cigarettes on smoking reduction in this population.

3. RATIONALE

3.1 Effects of nicotine reduction in smokers with OUD

There is growing evidence to support the public health benefit of a nicotine reduction policy. Studies in the general smoker population have demonstrated that use of reduced nicotine content cigarettes decreases smoking rates, dependence and toxin exposure levels.^{33,36-46} However, these studies were conducted with psychiatrically and socioeconomically stable, healthy smokers. While a national nicotine reduction policy may hold significant potential to reduce smoking prevalence and related adverse health outcomes, it is important to first understand whether vulnerable populations of smokers may respond differently than the general population.^{43,47} This includes the possibility that these subgroups respond to reduced nicotine content cigarettes (RNCCs) with compensatory smoking, which could lead to increased carcinogen and other toxin exposure, failure to use RNCCs altogether, or transition to use of other products (e.g., cigars) which would undermine the merit of

2633 this regulatory strategy.^{48,49}

2634 Research conducted by our UVM TCORS provides encouraging evidence that the beneficial
2635 effects of very low nicotine content cigarettes (VLNCCs) may extend to populations that are highly
2636 vulnerable to tobacco addiction and its associated adverse health consequences. During the
2637 current funding period, we have been conducting two multi-site studies examining acute and
2638 extended exposure to RNCCs on the addiction potential of smoking. The initial acute exposure
2639 study consisted of three parallel, within-subject laboratory studies in economically disadvantaged
2640 women of reproductive age (n=56), individuals with
2641 OUD (n=60), and individuals with AD (n=53).⁵⁰
2642 Participants sampled NIDA-provided research
2643 cigarettes varying in nicotine content (15.8, 2.4, 1.3,
2644 0.4mg/g) under double-blind conditions, with the
2645 highest dose representing nicotine content typical of
2646 commercial cigarettes. Following brief abstinence,
2647 participants completed 14 sessions comparing the
2648 relative reinforcing effects of the 6 possible dose pairs
2649 in concurrent choice procedures. We also assessed
2650 demand for each cigarette dose using the Cigarette
2651 Purchase Task (CPT), a behavioral economic task
2652 that models hypothetical demand for cigarettes under
2653 varying prices. Lastly, we compared cigarettes on
2654 smoking topography and subjective effects.

2655 Results were collapsed across populations as
2656 similarities outnumbered differences. In concurrent
2657 choice testing, participants chose the higher over the
2658 lower nicotine content cigarettes across each of the
2659 six dose pairs when available at the same low price, providing strong evidence that reducing
2660 nicotine content decreases the relative reinforcing effects (i.e., addiction potential) of smoking in a
2661 graded dose-dependent manner (Figure 1, upper panel). Importantly in terms of
2662 regulatory implications, we also demonstrated that the robust preference for the high 15.8
2663 mg/g control dose over the 0.4 mg/g dose was reversed in all three populations by incrementing the
2664 response effort required to obtain the high dose while keeping the low dose available at the same
2665 low response requirement (lower panel). This suggests that product preference is conditional on
2666 environmental context. Demand for cigarettes on the CPT task also decreased as an orderly
2667 function of nicotine content consistent with the differences in relative reinforcing effects seen in the
2668 concurrent choice task. Importantly, there was no evidence of compensatory smoking. This study
2669 provided a compelling demonstration that RNCCs reduce the addiction potential of cigarettes in
2670 populations highly vulnerable to tobacco addiction. It is worth noting, however, that we observed
2671 greater overall cigarette demand across doses in smokers with OUD vs. the other vulnerable
2672 populations examined in this study.

2673 Our second multi-site study is ongoing and on schedule to be completed as planned. The study
2674 uses a three parallel-groups design to investigate the effects of 12-week exposure to RNCCs
2675 (15.8, 2.4, and 0.4 mg/g).

2676 Preliminary results on
2677 total cigarettes per day
2678 (CPD) are shown in
2679 Figure 2 for the
2680 individuals that have
2681 completed the study thus
2682 far. Presented are results
2683 for the 15.8 mg/g control
2684 (i.e., usual brand
2685 cigarette) dose and the
2686 VLNCC 0.4 mg/g dose,

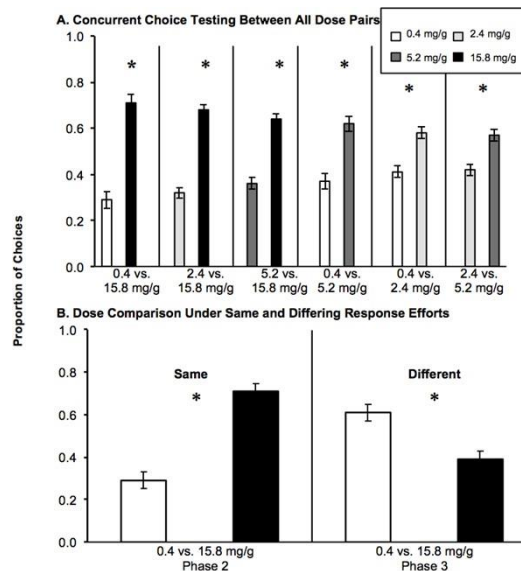


Figure 1. Concurrent Choice Testing

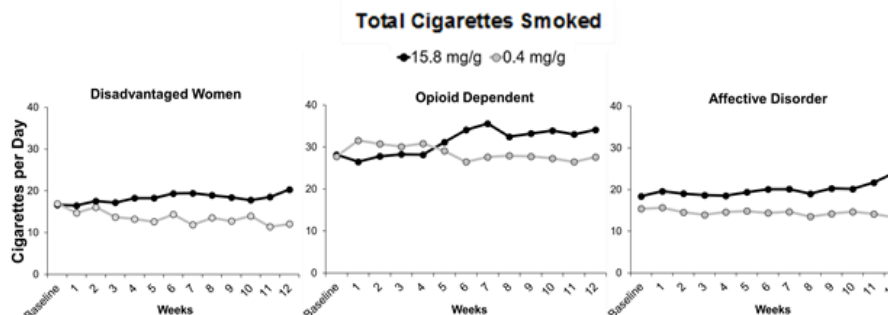


Figure 2. Total cigarettes smoked across 12-week period in three vulnerable populations.

2687 which has the lowest addiction potential. These also represent the two doses that we are proposing
2688 to study in this renewal. Thus far, there is no evidence of sustained compensatory smoking in any
2689 population receiving VLNCCs. CPD across the two doses separates over time in all three
2690 vulnerable smoker groups; however, it does so later and overall consumption is greater among
2691 smokers with OUD. Additionally, the current effect size for differences in CPD at 12 weeks among
2692 the dis-advantaged women and smokers with AD (Cohen's $d=0.70$ and 0.81 , respectively) are
2693 larger than those seen in the opioid dependent population ($d=0.38$) and consistent with those seen
2694 at 6 weeks in the general population of smokers (0.79^{51}). Fagerstrom dependence scores at 12
2695 weeks are also significantly decreased among those assigned to VLNCCs vs. the 15.8 mg/g dose
2696 in the disadvantaged women and those with AD but not in individuals with OUD. The overall greater
2697 cigarette demand and consumption exhibited by smokers with OUD serves as an important
2698 reminder of the especially persistent nature of smoking in this population.

2699 **3.2 Increasing appeal of alternative non-combusted nicotine sources**

2700 These data provide promising initial evidence that smokers with concomitant other
2701 socioeconomic, substance use and psychiatric vulnerabilities will respond to RNCCs with
2702 subsequent reductions in cigarette demand and other measures of addiction potential. However,
2703 there is growing recognition of the critical importance of having appealing alternative non-
2704 combusted nicotine sources readily available if the potential of a reduced nicotine standards policy
2705 for combusted products is going to be realized. In the words of Benowitz and colleagues, "*The
2706 RNCC and the emergence of non-combusted nicotine products like e-cigs should be viewed not as
2707 alternatives but as complementary components of regulatory interventions that could virtually end
2708 combusted tobacco use.*"⁵² Further, the primary conclusion of the 2014 Surgeon General's Report
2709 noted that "*the promotion of noncombustible tobacco products is much more likely to provide
2710 public health benefits only in an environment where the appeal, accessibility, promotion, and use of
2711 cigarettes and other combusted products are being rapidly reduced.*"⁵¹ Our data also lead us to
2712 anticipate that smokers with OUD and perhaps other SUDs may persist in smoking even if
2713 cigarette nicotine content is reduced to very low levels. This further highlights the critical
2714 importance of having non-combusted alternative sources of nicotine readily available at reinforcing
2715 doses and in forms that enhance appeal. We know of only one report empirically examining how
2716 the presence of non-combusted products influences use of VLNCCs and that was an exploratory
2717 study of participants selected from the general smoker population.⁴⁴ In that study, when individuals
2718 assigned to VLNCCs opted to also use a non-combusted product, they overwhelmingly chose e-
2719 cigs over other non-combusted options (i.e., snus, NRT). This is consistent with other research
2720 modeling the substitutability of non-combusted tobacco products for combusted cigarettes⁵³ and
2721 serves as the rationale for us focusing on e-cigs in this renewal application.
2722

2723 **3.3 E-cig use**

2724 E-cigs consist of a cartridge containing an e-liquid nicotine solution, propylene glycol (PG),
2725 vegetable glycerin (VG), flavoring, and other additives, which are heated with an atomizer that
2726 vaporizes the solution. First generation e-cigs resemble cigarettes and are disposable or
2727 rechargeable. Second generation products (and the product used in this study) often resemble
2728 pens and have refillable e-liquid reservoirs, while third generation devices have larger batteries,
2729 adjustable power delivery and replacement heating coils and wicks.⁵⁴ Nicotine delivery from e- cigs
2730 can be comparable to those from cigarettes, depending on e-cig characteristics, nicotine content
2731 and user topography.⁵⁵⁻⁵⁸ Toxin and carcinogen levels appear to be lower than those from cigarettes.
2732 Hecht et al.⁵⁹ reported that former smokers who had switched to e-cigs had 59-99% lower levels of
2733 6 tobacco toxicant and carcinogen metabolites than ongoing smokers, comparable to reductions
2734 seen in smokers who had switched to nicotine lozenges.⁴² Another study found that NNAL, a
2735 metabolite of the tobacco carcinogen NNK, was reduced by 64% in smokers who had switched to
2736 e-cigs for two weeks, as was chest tightness.⁶⁰ Initial data suggest that e-cigs may be a promising
2737 tool for supporting transition away from combusted cigarettes in smokers with OUD.^{61- 64} In a recent
2738 observational study with methadone- and buprenorphine-maintained smokers, 99% were familiar
2739 with e-cigs, 73% had ever tried them, and 34% were currently using e-cigs.⁶⁵ As in the general

2740 population, smokers with OUD reported that their reasons for e-cig use are primarily to quit or
2741 reduce smoking.⁶⁵
2742

2743 **3.4 E-cig effects on smoking**

2744 E-cig use is associated with smoking reduction⁶⁶⁻⁶⁸ and possibly quitting. In a trial using second
2745 generation e-cigs, cigarette abstinence rates were 34% after 8 weeks and 21% 6 months later, with
2746 an overall 60% reduction in CPD.⁶⁹ The only published study to our knowledge on the effects of e-
2747 cigs in smokers with OUD was an uncontrolled, 6-week pilot study with 12 methadone- maintained
2748 smokers. E-cig use was associated with significant reductions in self-reported combusted cigarette
2749 use, few adverse effects, and excellent e-cig adherence (89%⁷⁰). While e- cigs can reduce
2750 cigarette craving and nicotine withdrawal,^{55,69,71-72} these effects are generally determined by the
2751 extent to which e-cigs are used by smokers; in turn, determinants of e-cig use include product
2752 appeal and reinforcing effects.⁷³
2753

2754 **3.5 Importance of e-cig flavors**

2755 Over two-thirds of adult e-cig users use a flavored e-cig.^{5,74} Flavors have been shown to
2756 substantially enhance e-cig appeal and relative reinforcing effects⁷⁵⁻⁷⁶ and have been cited as a
2757 key feature affecting e-cig use among adults.^{5,77-78} Experimental studies show that flavors increase
2758 demand for e-cigs among cigarette smokers.⁷⁹⁻⁸⁰ Studies of e-cig users also highlight that flavors
2759 play an important role in their experience of the product as well as reducing cigarette consumption
2760 and craving.⁸¹⁻⁸⁴ Importantly, there is a higher prevalence of flavored tobacco use among smokers
2761 with SUDs relative to the general population.^{5,12,14} A growing literature also suggests that opioid-
2762 dependent individuals may be especially sensitive to flavors, as activation of the mu-opioid receptor
2763 by opioid administration is associated with increased preference for sweet flavors.⁸⁵⁻⁹⁰ These data
2764 suggest that combining a non-combusted nicotine source with a preferred, likely sweet, flavor may
2765 have substantial appeal and thus potential for reducing combusted cigarette use in OUD smokers.
2766

2767 **3.6 Products to be tested**

2768 Cigarettes to be assessed

2769 The cigarettes to be used in this study were made under an NIH contract with production being
2770 overseen by the Research Triangle Institute (referred to as "Spectrum cigarettes"). NIH currently
2771 has approximately 10 million of these cigarettes (of varying types) for research purposes. The
2772 cigarettes selected for the study span the range of yields likely to produce the hypothesized
2773 effects, as described above. Spectrum cigarettes are not currently commercially available,
2774 although they are similar in many ways to marketed cigarettes (e.g., similar manufacturing, filter,
2775 paper, etc.).
2776

2777 E-cigarettes to be assessed

2778 Both the JUUL and the Vuse Solo will be used and assessed in this study. . While JUUL will be
2779 offered to all participants, participants that are unwilling to use JUUL will be offered the Vuse Solo. JUUL
2780 is a commercially available closed system containing two components. One component contains a
2781 lithium-ion battery (200 mAh), nichrome coil heater, silica wick, and stainless steel vapor path. The
2782 other component is the prefilled e-liquid container that also serves as the mouthpiece. Each
2783 commercially available cartridge holds approximately 0.7 mL of e-liquid containing approximately
2784 40 mg of nicotine or 5% nicotine by weight (NBW). A lower dose containing approximately 23 mg
2785 of nicotine per cartridge or 3% NBW is also marketed but will not be used in this study. All
2786 containers contain glycerol, propylene glycol, natural oils, extracts and flavors, nicotine, benzoic
2787 acid. We will not alter the e-liquid in any way. The research staff will distribute the e-liquid
2788 containers as purchased from the manufacturer. The JUUL apparatus and 5% NBW e-liquids that
2789 will be used are legally purchasable and have been as of August 8, 2016. We will not alter them in
2790 any way.

2791 Vuse Solo is a commercially available closed system containing two components. The
2792 power/heating device includes a 270 mAh battery, silica wick, microchips, and sensor. The other

2793 component is the prefilled e-liquid container. Each commercially available cartridge holds
2794 approximately 1 mL of liquid containing 48 mg of nicotine or 4.8% NBW. All containers contain
2795 vegetable glycerin, propylene glycol, reverse-osmosis water, glycerin, flavorings, and nicotine.
2796 The research staff will distribute the e-liquid containers as purchased from the manufacturer. The
2797 Vuse apparatus and e-liquid cartridges that will be used are legally purchasable and have been as
2798 of August 8, 2016. We will not alter them in any way.

2799 3.7. Summary

2800 Although smoking rates have declined in the overall US population, there has been little to no
2801 decline among people with OUD. A nicotine reduction strategy for combustible tobacco combined
2802 with e-cig availability may have complementary effects on smoking reductions and consequent
2803 tobacco-related health effects in this vulnerable population. This research is highly significant
2804 because it will model how the availability of e-cigs impacts the effectiveness of a reduced-nicotine
2805 policy for cigarettes in vulnerable smokers. It is responsive to the goals of the FDA in that the study
2806 conditions are designed to model real-world scenarios of possible harm reduction policies in
2807 populations that are vulnerable to smoking persistence.

2808 4. Project Study Methods

2809 This study will use a four-condition, parallel-groups research design. After a baseline period in
2810 which daily smoking rate and other baseline assessments are completed, participants will be
2811 randomly assigned to one of the following four conditions for a 16-week experimental period: (1)
2812 normal nicotine content cigarettes (NNCCs, 15.8 mg/g) alone, which serves as the control
2813 condition; (2) very low nicotine content cigarettes (VLNCCs, 0.4 mg/g) alone; (3) VLNCCs +
2814 tobacco-flavored nicotine e-cigs (TF e-cig, 4.8 - 5.0% nicotine by weight, NBW, if they choose to
2815 use the Vuse or JULL device, respectively); or (4) VLNCCs + preferred-flavor nicotine e-
2816 cigarette (PF e-cig).
2817
2818

2819 5. Study Screening Procedures

2820 5.1 Participants

2821 Participants will be men and women, ages 21-70, who are currently receiving methadone or
2822 buprenorphine maintenance for OUD. They must report smoking ≥ 5 cigs/day for the past year and
2823 provide a breath CO ≥ 8 ppm or a positive urine cotinine value. They must be sufficiently literate to
2824 complete research tasks, be in good physical health without serious illness or change in health in
2825 the past 3 months, must not be daily e-cigarette users, and have the technological capabilities to
2826 complete weekly face-to-face video assessments and the compatibility to use ico Smartphone
2827 Smokerlyzers for assessing breath carbon monoxide (CO) levels.. As opioid and cocaine use can
2828 directly increase smoking rates,⁹¹⁻⁹⁶ participants must be maintained on a stable methadone or
2829 buprenorphine dose with no regular illicit-drug abuse (< 4 positive specimens) for the past month.
2830 Consent to confirm dose and drug abstinence with the participant's opioid clinic will be obtained at
2831 intake, and we will monitor any changes in dose throughout the study. These practices have been
2832 effective for confirming clinical stability in our prior smoking trials with opioid- maintained
2833 patients.^{50,96-100}
2834

2835 We will exclude those < 21 years old as users below that age have legal restrictions on ability to
2836 purchase these products that can alter use patterns for reasons that do not apply to adult
2837 populations. We will exclude pregnant and nursing women and women not reporting use of
2838 contraceptives, anyone currently using nicotine replacement, bupropion or other
2839 pharmacotherapies as cessation aids, those who report daily use of e-cigs in the past 30 days as
2840 they may not be compliant with the study e-cigs, and anyone intending to quit within 3 months, as
2841 participation in this study may not reduce smoking and could increase smoke and/or nicotine
2842 exposure. Those who exclusively use roll-your-own cigarettes or used other non-cigarette tobacco
2843 products (e.g., cigars, smokeless) ≥ 10 days in the last 30 are excluded as their use of these
2844 products may reduce the validity of our main outcome measure, total CPD (which includes study
2845 and non-study cigarettes). The following conditions are excluded as they could affect participants'

2846 abilities to complete the study: unstable medical or medication conditions (significant changes in a
2847 serious medical condition in the past 3 months, medication changes in the past 4 weeks; details
2848 provided in Protection of Human Subjects section), symptoms of psychosis or dementia, past-
2849 month suicidality, current (past-6 months) alcohol or SUDs other than nicotine and the OUD for
2850 which they are being treated, positive toxicology screen for illicit drugs (marijuana allowed; one re-
2851 screen opportunity), positive breath alcohol level (BAL) at screen (one re-screen opportunity).
2852 Participants who meet criteria and provide written informed consent will be enrolled into the trial.
2853

2854 **5.2 Recruitment**

2855 This study will be conducted at the University of Vermont (UVM) in Burlington, VT (primary site)
2856 and Johns Hopkins University (JHU) in Baltimore, MD. This collaboration will permit us to complete
2857 this study expeditiously, enhance sample diversity, and facilitate meaningful collaboration across
2858 multiple sites. Participants will be recruited through advertisements posted in local opioid treatment
2859 clinics, in local newspapers, on community bulletin boards, Craigslist, Facebook and word of
2860 mouth. Participants can choose to complete the pre-screening questionnaire online or by phone. At
2861 UVM, individuals recruited from online sources will be directed to a UVM-hosted recruitment
2862 website where they will have the opportunity to select which research studies interest them. They
2863 will then be redirected to a brief online screener to assess eligibility. Those who contact us by
2864 phone will be given a description of the study and asked questions to assess eligibility. The RA will
2865 read a script briefly explaining the study. Participants will be informed that this is not a smoking
2866 cessation program, and that smoking cessation services are available in the community
2867 independent of their decision to participate in this study. If interested and eligible, participants will
2868 be asked to present for a brief 10-minute in-person medical consent visit where research staff
2869 obtain informed consent to contact participant's opioid treatment provider to confirm stability in
2870 treatment. Participants will be asked to provide a urine sample for toxicology screening. If
2871 interested and eligible following the medical consent visit, they will be invited to participate in the
2872 first portion of the screening interview. Research assistants will inform eligible participants that the
2873 screening will occur over video chat, and will assist the participant with setting up an appropriately
2874 secure video platform.

2875 During this first portion of the screening, the participant will complete questionnaires through
2876 REDCap online while the research assistant is present over video chat or phone to deliver
2877 instructions and to answer any questions. The participant will then answer interviewer-
2878 administered questionnaires over video chat. Participants who did not yet set up their video
2879 platforms will do so with the research assistant before beginning any questionnaires. Participants
2880 will be instructed to have picture identification (e.g. driver's license) available to show the staff. If
2881 participants anticipate not having acceptable ID, staff should consult with the project coordinator or
2882 study PI. Initial study eligibility will be determined after data are collected from this visit.
2883 Participants who meet initial study eligibility will be scheduled for the second portion of the
2884 screening.

2885 Before the second portion of the screening occurs, eligible participants will receive the
2886 equipment necessary to use for collecting physiological measurements. Participants will be asked to
2887 pick up this equipment via curbside pickup at our clinic (UVM University Health Center, UHC),
2888 which will consist of participants calling staff once they arrive at UHC and staff coming out to give
2889 participants a bag/box containing the following equipment: a Smokerlyzer; an audio jack adapter
2890 for the Smokerlyzer if necessary; a blood pressure cuff; an oximeter; a thermometer; a urinary
2891 cotinine dipstick; urine cups with attached temperature test strips; a pregnancy test strip (if
2892 applicable) and urine toxicology test strips or a saliva toxicology test. Participants (and staff) will be
2893 asked to use cloth face coverings when exchanging product. Participants may be invited to come
2894 inside to pick up this equipment if the participant is asked to wait for this exchange. All participants
2895 must pass a COVID19 screening before entering the building. If there is any waiting that needs to
2896 occur inside the building, the participant will wait inside one of our five highly ventilated smoking
2897 chambers. If there happens to be no space in the smoking chambers, the participant will be told
2898 that they can not come up to the clinic until space is available. After each use, the all of the
2899 surfaces in the smoking chambers will be cleaned with 70% or greater of alcohol solution by staff

2900 wearing a mask and gloves, as well as all of the door handles. If the participant uses the bathroom
2901 while they are in the clinic, the bathroom surfaces and handles will be wiped down after use by staff
2902 while masks and gloves are worn. Participants who are using the smoking chambers at any point in
2903 the study to wait for product or equipment exchange will remain in the chambers until a staff
2904 member comes to knock on the door to let them out. In this way, we can avoid people coming into
2905 close contact with each other in the larger room that contains the smoking chambers. A minimum of
2906 6 feet of distance will be maintained for all staff and participants at all times. For participants who
2907 cannot come to the clinic, a commercial courier will deliver this equipment to them before the
2908 second portion of the screening.

2909 If at any point the Smokerlyzers are not available for distribution, we will conduct the CO test
2910 curbside before or after participants are invited inside and the courier service will not be available.
2911 Research Assistants will bring down the CO monitor to the participant. While maintaining 10 feet of
2912 distance and wearing gloves, staff will explain how the CO monitor works. Once the participant is
2913 ready, staff will press the button to obtain the measurement and will set the CO monitor down and
2914 will back away 10 feet. The participant will then come to pick up the device and will blow into the
2915 monitor. After the participant completes the test, they will set down the monitor and back up 10 feet
2916 and staff will retrieve the monitor. After every use, staff will wipe down the CO monitor with
2917 disinfectant wipes and hydrogen peroxide wipes. When using the monitor, a D-piece (a portable
2918 valve filter) must be placed into the monitor and then the single use plastic mouthpiece is placed into
2919 the D-piece. The monitor has built in SteriTouch technology to ensure optimum infection control,
2920 and the D-pieces filter out 99.9% of airborne bacteria and greater than 97% of viruses for excellent
2921 infection control. Each participant will be assigned their own D-piece to use throughout the study,
2922 and no D-piece will ever be shared among participants. Participants will gently exhale into the D-
2923 piece for the breath carbon monoxide reading. Participants will be instructed only to exhale through
2924 the device, not to inhale. D-piece technology also includes a one-way valve that prevents air from
2925 being drawn back from the monitor. D-pieces will also be wiped down after each use with
2926 disinfectant wipes and hydrogen peroxide wipes and stored in a container at the lab.

2927 Once participants have received the necessary equipment to complete the physiological portion
2928 of the screening, the research assistant will initiate a video call with the participant. During this call,
2929 the participant will be instructed on how to use the equipment and then will be asked to use the
2930 equipment to obtain the following physiological readings: blood pressure, heart rate, oxygen
2931 saturation, temperature, and breath CO levels. Participants will also be asked to collect a urine or
2932 saliva sample during the visit. If a saliva sample is collected, the participant you will provide the
2933 saliva sample over video chat while the staff observes. If a urine sample is collected, staff will ask
2934 participant to bring this urine sample to the video screen after collection to perform a urine
2935 toxicology test and a pregnancy test (if applicable). These urine cups will have temperature strips
2936 affixed to ensure that the sample is valid. Participants who have a carbon monoxide level of less
2937 than or equal to 8 will also be asked to use the urinary cotinine dipstick to determine whether they
2938 are positive for cotinine. The participant will obtain the physiological readings and perform the tests
2939 and then will hold the results of the test up to the camera so that the research assistant can
2940 interpret and record the readings on REDCap, UVM participants will be primarily recruited from our
2941 university opioid program, The Chittenden Center (CC). Dr. Sigmon is the Director of this clinic,
2942 which currently has 1,000 methadone- or buprenorphine-maintained patients. A survey of CC
2943 patients indicates that 88% currently smoke, which translates to approximately 880 smokers at our
2944 on-site clinic alone. Recruitment will also draw from patients receiving treatment at the office-based
2945 buprenorphine practices throughout the Burlington, VT community. JHU participants will be
2946 recruited primarily from two clinics located directly on the JHU Bayview Medical Center Campus:
2947 Addiction Treatment Services, a methadone clinic with 500 patients, and Comprehensive Care, a
2948 primary care clinic with 300 patients receiving buprenorphine. Should these resources be
2949 inadequate at any point in time, we will also recruit from two large community-based methadone
2950 programs in Baltimore with whom Dr. Stitzer has an on-going relationship as a PI of the NIDA
2951 Clinical Trials Network. Taken together, our access to opioid-maintained smokers is more than
2952 adequate to fulfill the recruitment needs of this project. Power estimations were based on the 15%
2953 dropout rate across populations in our current trials. Using an intent-to-treat approach, we require

2954 75 randomized in each condition (300 total) to test our primary aims.

2955 Participants will be also instructed to have handy a pack of their usual brand cigarettes, all
2956 prescription medications they are currently taking and identification (example, driver's license)
2957 during this second portion of the screening visit. If participants anticipate not having acceptable ID
2958 site staff should consult with the project coordinator or study PI.

2959 A participant must complete his/her two-part screening session within 90 days of completing
2960 the pre-screening questionnaire. If the participant is not able to complete the two-part screening
2961 visit in that timeframe, he/she will need to complete the pre-screening questionnaire again.
2962

2963 **5.3 Informed Consent Process:**

2964 Before beginning the informed consent process, potential participants will need to produce
2965 identification as described above. The interviewer will confirm the age and identity of the
2966 participant. If the participant is not between the ages of 21 and 70, he/she will be dismissed without
2967 payment. During the first portion of the screening session, study information will be presented and
2968 documentation of the participant's informed consent via electronic signature on REDCap will be
2969 required prior to participating in the screening session. In order to ensure adequate informed
2970 consent, participants will be asked to read the first several lines aloud (to determine literacy) and
2971 will then be given ample time to read the consent document. If the interviewer suspects the
2972 participant is not literate, he or she will have them continue reading further to confirm. Inability to
2973 read and comprehend written study materials will result in ineligibility and the interviewer will inform
2974 the participant that they are not eligible. Only after the participant and the researcher are fully
2975 satisfied that the participant understands the purpose of the study, the confidentiality of the data,
2976 the procedures, the risks/benefits and his/her rights as a research participant will the consent form
2977 be signed and the participant undergo screening procedures.
2978

2979 **5.4 Screening Measures**

2980 Those who consent will be screened for eligibility using the following measures:

2981 **The following physiological measures will be collected and entered directly into REDCap by**
2982 **the interviewer:**

- 2984 1) Expired breath carbon monoxide (CO) levels will be assessed using a Smartphone Monitor
2985 (Covita - for remote collection) or a Bedfont CO monitor (for curbside collection), a reliable
2986 and valid measure of recent smoking.
 - 2987 a. Urinary cotinine test strips will be used to assess urinary cotinine levels if a
2988 participant's CO reading is less than or equal to 8 ppm.
- 2989 2) A urine or saliva toxicological screen will be performed to assess the presence of illicit
2990 drugs including up to the following drugs: marijuana, cocaine, opiates, oxycodone,
2991 benzodiazepines, barbiturates, amphetamines, methadone, buprenorphine,
2992 methamphetamines, MDMA and PCP. Participants who fail the drug screen for drugs
2993 other than marijuana or their prescribed opioid medication may reschedule the interview
2994 but will need to be re-consented to ensure they have received adequate informed consent.
2995 They will be excluded if they are positive for drugs (other than marijuana or prescribed
2996 medications as determined by PI on a case-by-case basis) the second time.
- 2997 3) Urine Pregnancy Test (HCG detection) will be performed for all participants.
- 2998 4) Blood pressure and heart rate will be measured using an automated blood pressure
2999 monitor and a finger pulse oximeter to help the licensed medical professional determine
3000 final participant eligibility. Participants will be told if their blood pressure is in an abnormal
3001 range and advised to see a doctor by research staff. The research staff will also submit a
3002 medical event form for the LMP to review along with a Blood Pressure and Heart Rate
3003 Symptom Checklist form to ascertain details of the symptomatology for the LMP to review.
3004 In severe cases, the LMP may also choose to call the participant to follow-up and/or
3005 withdraw the participant from the study if necessary. All of these procedures are
3006 documented in our Blood Pressure/Heart Rate Collection: Standard Operating Procedure
3007 form which we can submit to the IRB if the Committee deems necessary.

- 3008 5) Body temperature, respiratory rate and oxygen saturation will be added as physiological
3009 measures based on the CDC recommendations and those of Dr. David Kaminsky.
3010 [https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)
3011 [disease/healthcare-providers/index.html](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)
3012

3013 **The following screening assessment will be administered as an interview:**

- 3014 1) The Mini International Neuropsychiatric Interview (MINI) 7.0⁷⁰
3015

3016 **The following screening assessments will be administered as an interview and entered**
3017 **directly into REDCap by the interviewer:**

- 3018 1) The MINI Plus Modules
3019 2) The MINI suicide subscale¹⁰⁴ to evaluate suicide risk.
3020 3) MINI Follow-up Questionnaire (if applicable)
3021 4) Tobacco Use History and Exposure Questionnaire, which measures variables such as
3022 smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts,
3023 duration of quit attempts and duration of smoking.
3024 5) Smoking Cessation Therapy Use Questionnaire
3025 6) Time Since Last Cigarette Questionnaire
3026 7) Maintenance Drug Dose Questionnaire – Screening Version
3027 8) Medical History Questionnaire to assess current diagnoses, symptoms and past health
3028 problems.
3029 a. Medications will be recorded directly onto the Concomitant Medications form in
3030 REDCap.
3031 9) Drug Abuse Screening Test (DAST-10), which assesses quantity and frequency of alcohol
3032 and drug use (12 month and 1 month version)
3033

3034 **The following screening assessments will be completed by the participant directly in**
3035 **REDCap, except where noted otherwise:**

- 3036 1) Demographic History Questionnaire, which will assess age, gender, ethnicity, race,
3037 education, income, marital status, and employment history.
3038 2) Alcohol Use Questionnaire---based on the Alcohol Use Disorders Identification Test¹⁰⁵ (12
3039 month and 1 month version)
3040 3) Drug Use Questionnaire---based on the Drug Abuse Screening Test¹⁰⁶ (12 month and 1
3041 month version)
3042 4) Fagerström Test for Nicotine Dependence (FTND)¹⁰⁷;
3043 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM)¹⁰⁸ will be
3044 administered to assess nicotine dependence severity.
3045 6) Penn State Electronic Cigarette Dependence Index¹⁰⁹;
3046 7) Smoking Stages of Change Algorithm¹¹⁰;
3047 8) Identifying Information Form will include the participant's REDCap Subject Identifier,
3048 name, address (including the county of residence), email address, phone number, age,
3049 date of birth, and social security number (if applicable).
3050 a. This form will be entered into the 'Identifying Information Access Database'.
3051 i. Each site will have a separate 'Identifying Information Access Database'.
3052 ii. Identifying information will not be shared with other sites. Each site is
3053 responsible for maintaining confidentiality of this information.
3054 iii. Identifying information will be kept in a locked file cabinet (source
3055 document) and in a password protected Access Database (electronic
3056 version) separate from all other study data.
3057 9) Beck Depression Inventory (BDI-II)⁶⁸, to assess depressive symptoms.
3058 (This form has been updated on 1.29.20 so as to use the BDI-II. The BDI-II will be used instead of the BDI so
3059 that the data collected will be directly comparable to other projects using the BDI-II).
3060 10) Overall Anxiety Severity and Impairment Scale⁶⁹(OASIS); to assess frequency and
3061 severity of anxiety symptoms.
3062 11) COVID19 Symptom Questionnaire

3063 12) Respiratory Symptom Questionnaire will be administered to assess respiratory health
3064

3065 In the event that the REDCap website is not functioning, the assessments will be administered
3066 aloud and participant answers will be recorded securely. The interviewer will enter the data into
3067 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
3068 Visit Evaluation Form'.
3069

3070 **5.5 Suicidality/Mental Health Monitoring**

3071 Participants who endorse suicidal intention in the past month or a suicide attempt in the
3072 past 6 months as indicated on the BDI (score > 1 on question 9) or MINI suicide subscale (endorse
3073 question 4 and/or 5 on the MINI suicide subscale or question 6 on the MINI suicide subscale with
3074 suicide attempt in the past 6 months) or answer "yes" to question A3g on the MINI
3075 Neuropsychiatric interview and symptoms have occurred in the past two weeks will be assessed
3076 by a clinician for eligibility and possible intervention. The research staff member will contact a
3077 licensed clinician for evaluation. In the event that no clinician is available, staff will put the
3078 participant in contact with the National Suicide Prevention Lifeline at 1-800-273-8255. They will
3079 also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible.
3080 Additionally, they will contact the Project Coordinator to inform her of the situation. The participant
3081 will be paid \$25 (+\$25 bonus if applicable) and provided with local mental health resources. Post
3082 enrollment, any report of suicidal ideation or attempt by a participant will be grounds for immediate
3083 withdrawal from the study.
3084

3085 **5.6 Inclusion/Exclusion Criteria**

3086 Inclusion Criteria:

- 3087 6) Men and women ages 21-70, who are currently receiving methadone or buprenorphine
3088 maintenance treatment for opioid dependence;
3089 7) Report smoking ≥ 5 cigarettes per day for the past year;
3090 8) Provide an intake breath CO sample >8 ppm, (if ≤ 8 ppm, then urinary-cotinine strip must be
3091 positive);
3092 9) Be without current (within the past year) serious mental disorder that would interfere with
3093 study results of completion as determined by the licensed medical professional or PI,
3094 10) Be sufficiently literate to complete the research-related tasks;
3095 11) Be in good physical health without serious illness or change in health or medication (not
3096 including methadone or buprenorphine dose) in the past three months as determined by the
3097 licensed medical professional at each site;
3098 12) Participants must be maintained on a stable methadone or buprenorphine dose for the past
3099 month, with no evidence of regular illicit-drug abuse ($<30\%$ positive specimens in the past
3100 30 days).
3101 a. Consent to confirm dose and drug abstinence with the participant's opioid clinic will
3102 be obtained prior to screening at a medical consent visit and we will monitor any
3103 changes in dose throughout the study.
3104 b. Participants must provide proof of at least three biochemical (e.g. urine, saliva)
3105 samples within the last 30 days of the date of the medical consent visit that have
3106 no evidence of illicit drug use. If they do not have three, they will be asked to
3107 provide additional samples as needed and coordinated by research staff to confirm
3108 clinical stability. They may provide up to two samples per week with at least one
3109 full day between samples.
3110 13) Have appropriate equipment to complete face-to-face video assessments and use ico
3111 Smartphone Smokerlyzer Monitors. For those who do not have a Smartphone, staff will
3112 explore potential alternate plans (e.g., project-provided inexpensive Android phone)
3113

3114 Exclusion Criteria:

- 3115 1) Exclusive use of roll-your-own cigarettes;

- 3116 2) Planning to quit smoking in the next 30 days;
- 3117 3) A quit attempt in the past 30 days resulting in greater than 3 days of abstinence;
- 3118 4) Significant use of other tobacco or nicotine products within the past month (more than 9
- 3119 days in the past 30).
- 3120 5) Currently taking anticonvulsant medications including:
- 3121 a. Phenytoin [Brand Name: Dilantin]
- 3122 b. Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Eptol]
- 3123 c. Oxcarbazepine [Brand Name: Trileptal]
- 3124 d. Primidone [Brand Name: Mysoline]
- 3125 e. Phenobarbital
- 3126 6) Positive toxicology screen for any of the following drugs: cocaine, opiates, methadone,
- 3127 oxycodone, buprenorphine, benzodiazepines, barbiturates, amphetamines,
- 3128 methamphetamines, MDMA and PCP will be grounds for exclusion.
- 3129 a. Marijuana will be tested for but will not be an exclusionary criterion. Participants will
- 3130 be discouraged from smoking marijuana during the study.
- 3131 b. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, or
- 3132 amphetamines will not necessarily be excluded.
- 3133 c. Participants failing the toxicology screen will be allowed to re-screen once. These
- 3134 participants will need to be re-consented before being rescreened to ensure they
- 3135 have received adequate informed consent.
- 3136 7) Not currently enrolled in a treatment program for opioid dependence and/or not currently
- 3137 stable on their methadone or buprenorphine dose,
- 3138 8) Self-report of binge drinking alcohol (more than 9 days in the past 30 days, 4/5 drinks in a 2
- 3139 hour period in females/males);
- 3140 9) Systolic blood pressure < 90 or ≥ 160 mmHg;
- 3141 a. Participants failing for blood pressure will be allowed to re-screen once.
- 3142 10) Diastolic blood pressure < 50 or ≥ 100 mmHg;
- 3143 a. Participants failing for blood pressure will be allowed to re-screen once.
- 3144 11) Breath CO > 80 ppm;
- 3145 12) Heart rate is greater than or equal to 115 bpm or less than 45 bpm;
- 3146 a. Participants failing for heart rate will be allowed to re-screen once.
- 3147 13) Currently seeking treatment for smoking cessation;
- 3148 14) Being pregnant or nursing, or not report using an approved form of birth control if
- 3149 applicable determined by the Project Medical Director.
- 3150 15) Have used nicotine replacement, bupropion or other pharmacotherapies as cessation aids in
- 3151 the past month (bupropion will be allowed for treatment of depression);
- 3152 16) Current symptoms of psychosis, dementia or mania;
- 3153 17) Suicidal ideation in the past month (score > 1 on the BDI question 9 or endorse question 4
- 3154 and/or 5 on the MINI suicide subscale);
- 3155 18) Reporting a plan or attempt to commit suicide, which is assessed on question A3g of the
- 3156 MINI Neuropsychiatric Interview Major Depressive Episode Module. Thoughts of suicide
- 3157 without an intent or plan is not an exclusion criteria;
- 3158 19) Suicide attempt in the past 6 months (endorse question 6 on the MINI suicide subscale with
- 3159 suicide attempt in the past 6 months);
- 3160 20) Participation in another research study in the past 30 days;
- 3161 21) Daily use of e-cigarettes in the past month (defined as 6 – 7 days per week); or
- 3162 22) Co-habitation with any research participant who has or is participating in the current study.
- 3163 23) Oxygen saturation of < 90%
- 3164 24) Reporting positive symptoms for COVID19
- 3165

3166 Individuals under age 21 are excluded because they cannot legally buy cigarettes. Those

3167 with unstable medical, psychiatric, or medication conditions (as determined by the licensed

3168 medical professional) are excluded as these symptoms could affect a participant's ability to

3169 complete the study. Examples include but are not limited to the following: angina, stroke, heart
3170 attack which occurred since phone screening, blood clots in the arms or legs for which the
3171 individual is undergoing active medical treatment, cancer requiring active chemotherapy or
3172 radiation therapy, severe shortness of breath caused by conditions such as uncontrolled
3173 asthma, COPD, or arrhythmia, active untreated infection such as pneumonia, active untreated
3174 endocrine disorder such as hyperthyroidism. We will exclude those currently seeking smoking
3175 treatment and those who plan to quit in the next 30 days, as participation in this study may not
3176 lead to reductions in smoking. We will exclude pregnant or nursing women and women of
3177 reproductive potential who are unwilling to use acceptable forms of birth control throughout the
3178 study if applicable determined by the Project Medical Director. We will also exclude anyone with
3179 current or recent alcohol or drug abuse problems as these factors could independently affect
3180 smoking behavior during the study. Individuals with baseline CO readings greater than 80 ppm,
3181 those with heart rate or blood pressure readings that are out of range (systolic: 90-159 mmHg;
3182 diastolic: 50-99 mmHg; HR: 45- 114 bpm) and anyone who has attempted suicide in the past six
3183 months will be excluded from the study for safety concerns. Individuals who smoke 'roll your
3184 own' cigarettes exclusively will be excluded from the study because we will be unable to
3185 standardize their baseline smoking behavior. Individuals who have reported daily use of e-
3186 cigarettes in the past 30 days will be excluded as they may not be compliant with experimenter-
3187 provided e-cigarettes. Individuals who have recently participated in a research study will be
3188 excluded as participation may have changed their smoking patterns, which may preclude a
3189 stable smoking baseline. Because participants are required to complete portions of the protocol
3190 independently, they will need to be able to independently read and comprehend the study
3191 materials.
3192

3193 **5.7 Eligibility Determination:**

3194 The research assistant will review the entire screening assessment battery for initial
3195 eligibility determination, confirming the participant meets the above described
3196 inclusion/exclusion criteria. All eligibility criteria that are not related to physiological
3197 measurements will be assessed during the first portion of the screening visit, and all criteria
3198 related to physiological measurements will be determined during the second portion of the
3199 screening. The final eligibility of the participant will be determined by a licensed medical
3200 professional (MD, DO, NP, PA, Master's prepared RN or CRN) at each site after reviewing the
3201 Medical History Questionnaire, BDI, Mini Neuropsychiatric Interview, and the MINI suicide
3202 subscale. The licensed medical professional may meet with a participant if available and think it
3203 necessary for eligibility determination. He/she will sign off on eligibility prior to the first baseline
3204 visit. If the licensed medical professional determines the participant is not medically eligible to
3205 participate in the study, has current symptomatology that would interfere with interpretation of
3206 the data, or is unlikely to complete the study he/she will inform the research assistants who will
3207 contact the participant prior to the first baseline visit. The licensed medical professional will not
3208 need to review the medical history forms of participants who are ineligible for other, non-medical
3209 reasons.

3210 If a participant fails the urine or saliva toxicology screen due to a prescription medication
3211 he/she is taking, then he/she will not be automatically excluded. The interviewer will make note
3212 of this when he/she submits the forms to the licensed medical professional for final eligibility
3213 determination.

3214 Once all the screening procedures have been completed, researchers will pay
3215 participants \$25 (+\$25 bonus if applicable) for their time as long as they pass the drug tests and
3216 meet the minimum requirements for carbon monoxide or urinary cotinine levels. Participants will
3217 be paid after the completion of the study visit. If participants are deemed ineligible at any point
3218 in the screening, the participant will be paid after determined ineligible. Marijuana will be tested
3219 for but will not be an exclusionary criterion. If a participant does not pass the drug test but has a
3220 current, valid prescription that would explain the failed test he/she will not be automatically
3221 excluded and will still receive the visit payment. Participants who meet all other eligibility criteria,
3222 sans the medical criteria, will be scheduled for the first baseline visit.

3223 At the end of the screening session, the researcher will complete the End of Visit
3224 Evaluation Form. This will allow the researcher to make note of any problems encountered
3225 during the visit and to assess the truthfulness of the participant in regards to self-report of
3226 tobacco use.
3227

3228 **6. Study Baseline Procedures**

3229
3230 This study will use a one-week, two-session baseline period to collect baseline individual
3231 difference measures and monitor daily usual-brand smoking behavior. At Baseline 1 or within 1
3232 business day of the Baseline 1 visit, participants will be provided their usual brand cigarettes to
3233 smoke, equivalent to 150% of their daily smoking rate. Participants will be encouraged to come to
3234 the lab to pick up their usual brand cigarettes after they complete the questionnaires and physio
3235 for the BL1 visit. Those who cannot come to the lab will receive product via a commercial courier.
3236 A time line follow back (TLFB) will be used during the period between Baseline 1 and Baseline 2
3237 to assess the daily cigarette use for the first 7 days the participant has product. The participant
3238 must have received their UB cigarettes from the lab before the 7-day assessment period starts,
3239 and Baseline 2 must occur at least 7 days after the participant receives their usual brand
3240 cigarettes from the lab. If the baseline period extends past seven days and if the participant has
3241 run out of product, participants will need to purchase their own usual brand cigarettes. Use of a
3242 two session baseline period will ensure stability of daily smoking reports, reduce reactivity to the
3243 daily cigarette monitoring, and reduce participant burden. During the two baseline sessions,
3244 participants will complete subjective questionnaires. Each visit will last approximately two to four
3245 hours. At the end of each baseline session, the researcher will complete the End of Visit
3246 Evaluation Form This will allow the researcher to make note of any problems encountered during
3247 the visit and to assess the truthfulness of the participant in regards to self-report of tobacco use.
3248 Participants will also be supplied with saliva test equipment and urine collection equipment during
3249 the Baseline 1 product exchange so that they can collect saliva and first void urine samples
3250 during the Baseline 2 visit.

3251 For the Baseline 1 visit and all subsequent visits, the participant will be sent a REDCap
3252 link within 15 minutes of the start of the scheduled visit to complete all of the non-interviewer
3253 administered questionnaires. The participant will complete these questionnaires on their own but
3254 can have the research assistant present on a video call if they desire. Before beginning the
3255 physiological assessment portion of the visit over video call, the research assistant must review
3256 the participant's questionnaire responses for that visit. Participants will be compensated after the
3257 completion of the study visit and when the participant has received their new product.

3258 At Baseline 2 and all subsequent visits, after the participant has answered the
3259 questionnaires and has completed the physiological portion of the visit over video call,
3260 participants will be asked to come to the lab for a curbside exchange of product and biological
3261 samples. Participants will bring in their used and unused product from the previous visit as well
3262 as a first-void urine sample for assessing tobacco-related toxin exposure and a salivary sample
3263 for assessing nicotine metabolism rate on applicable visits (BL2, Week 8 and Week 16) using
3264 equipment that was provided at the previous visit. Participants will be instructed to call the RA
3265 at the office when they get to the clinic to ensure that there is enough space in the smoking
3266 chambers to house all participants while abiding by safety guidelines as detailed on page 14 of
3267 the protocol. All participants must pass a COVID19 screening before entering the building. When
3268 invited into the lab, the participant will be shown to a smoking chamber and will instructed to
3269 place their bag of product outside of the chamber. The participant will wait here while the RA
3270 processes and returns product through the randomization database. Then the RA will dispense
3271 new product and bring the bag back to the participant. When the RA deems it safe for the
3272 participant to exit the chamber, the RA will instruct the participant that they can leave. The RA will
3273 instruct the participant to observe social distancing measures during this exchange, providing
3274 clarification if necessary. If a participant forgets their first-void urine sample at the Baseline 2
3275 visit, staff will ask participant to come back to the clinic with their first void urine sample before
3276 exchange of product occurs. If participant is unable to return to the clinic with their first void

3277 sample, staff can arrange to meet the participant off campus to pick up their urine sample and to
3278 give participant their study product. Distancing and safety measures as described above must be
3279 observed. For participants who cannot make it to UHC, special arrangements will be made to
3280 enable use of the randomization database and product return/distribution procedures to the
3281 extent possible. Each week, during - or scheduled as nearly as possible to – a virtual visit, a
3282 complete accounting of the participant's product inventory will be taken and processed remotely
3283 through the randomization database. The participant will separate product based on its type (e-
3284 cigarette or combustible inventory) and status (used/unused), and the RA will process return
3285 characteristics through the database accordingly. The RA will clarify barcode characteristics with
3286 the participant when legibility is compromised. The participant will be instructed to keep unused
3287 product in their possession, but to exchange any used product with the courier who will deliver
3288 newly dispensed replacement products within 48 hours.

3289 Product that will be given to participants for the Baseline 2 visit cannot be given/sent to
3290 participants until 7 days have passed following completion of the Baseline 1 visit. We will need to
3291 calculate baseline smoking rate during this 7-day period and so participants cannot have access
3292 to any blinded study product or e-cigarettes before this 7-day period has ended.

3294 **6.1 Visit scheduling requirements for baseline period:**

3295 Participants will be required to schedule the Baseline 1 visit within 30 days of the completion
3296 of their screening visit. If a participant still wants to be in the study after 30 days, he/she will need
3297 to be re-screened. The participant will need to be re-consented but will maintain the original
3298 REDCap Subject Identifier. The ideal target window separating Baseline 1 and Baseline 2 is
3299 between 7 and 12 days. The minimum is 7 days and the maximum is 21 days. If the participant
3300 does not complete the visit within 21 days, then he/she will not be rescheduled and will be
3301 discontinued from the study.

3302 **6.2 Measures/Assessments**

3303 **The following physiological measures will be collected and recorded directly into REDCap**
3304 **by the interviewer:**

- 3305 1) CO
- 3306 2) Blood Pressure
- 3307 3) Heart Rate
- 3308 4) Body temperature
- 3309 5) Oxygen saturation
- 3310 6) Respiratory rate
- 3311 7) Urine or Saliva Toxicology
- 3312 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

3313 **The following assessments will be administered as an interview at Baseline 1 and entered**
3314 **into REDCap by the interviewer at the end of the visit:**

- 3315 1) Concomitant Medications Form
- 3316 2) Health Changes Questionnaire, which will assess any weekly health changes,
- 3317 3) Time Since Last Cigarette Questionnaire
- 3318 4) Maintenance Drug Dose Questionnaire

3319

3320 **The following Baseline 1 assessments will be completed by the participant directly in**
3321 **REDCap:**

- 3322 1) BDI
- 3323 2) OASIS
- 3324 3) Respiratory Symptom Questionnaire
- 3325 4) COVID19 Symptom Questionnaire
- 3326 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM) will be

- 3327 administered to assess nicotine dependence severity.
- 3328 6) Perceived Health Risks Rating¹¹², a measure of the perceived addictive potential and
 3329 other health risks associated with cigarettes;
- 3330 7) Perceived Stress Scale (PSS)¹¹², assessing the degree to which life situations are
 3331 perceived as stressful;
- 3332 8) Positive and Negative Affect Scales (PANAS)¹¹³, a measure of changes in positive and
 3333 negative mood;
- 3334 9) Respiratory Health Questionnaire, a UVM measure of cough, shortness of breath and
 3335 other respiratory symptoms;
- 3336 10) Minnesota Nicotine Withdrawal Scale (MNWS)¹¹⁴, a measure of nicotine withdrawal;
- 3337 11) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU)¹¹⁵, which measures
 3338 the urge to smoke;
- 3339 12) Vaping Craving Questionnaire (VCQ)¹¹⁶ which measures the urge to vape;
- 3340 13) Cigarette Evaluation Scale – Usual Cigarette (CES)¹¹⁷, which measures responses to
 3341 cigarettes (e.g., reward, satisfaction);
- 3342 14) Vaping Evaluation Scale (VES), which measures responses to vaping (e.g. reward,
 3343 satisfaction)
- 3344 15) Cigarette Purchase Task – Usual Brand Version (CPT)¹¹⁸, a self-report analogue of a
 3345 progressive-ratio schedule that measures the relative reinforcing efficacy of cigarettes by
 3346 querying how many of that day's cigarette they would consume in a day at varying prices.
 3347 This task will indicate whether prolonged VLNC cigarette use reduces cigarette demand
 3348 and increases sensitivity to increases in cigarette costs;

3349

3350 All participants will also be asked to select their top three flavors of e-cigarette liquid from a list
 3351 read to them by the RA. This question will be asked in preparation for giving flavored pods to
 3352 participants who are randomized into the flavored e-cigarette condition. This information will be
 3353 recorded directly into REDCap. Participants will be asked to rate these top three flavors
 3354 based on either previous experience with these flavors or to indicate how much they believe that
 3355 they will like or dislike the flavors.

3356 **Physiological measures will be collected at Baseline 2 and entered directly into REDCap**
 3357 **by the interviewer:**

- 3358 1) CO
- 3359 2) Blood Pressure
- 3360 3) Heart Rate
- 3361 4) Body temperature
- 3362 5) Oxygen saturation
- 3363 6) Respiratory rate
- 3364 7) Urine or Saliva Toxicology
- 3365 8) Urine Pregnancy (if applicable, to be performed every 2 weeks)

3366 **The following assessments will be administered as an interview at Baseline 2 and entered**
 3367 **directly into REDCap by the interviewer:**

- 3368 1) Concomitant Medications Form
- 3369 2) Health Changes Questionnaire
- 3370 3) Time Since Last Cigarette Questionnaire
- 3371 4) Maintenance Drug Dose Questionnaire
- 3372

3373 **The following assessments will be administered at Baseline 2 and completed by the**
 3374 **participant directly in REDCap:**

- 3375 1) BDI
- 3376 2) OASIS

- 3377 3) COVID19 Symptom Questionnaire
3378 4) Respiratory Symptom Questionnaire
3379 5) MNWS
3380 6) WISDM
3381 7) PANAS
3382 8) QSU (usual brand)
3383 9) Vaping Craving Questionnaire
3384 10) CES (usual brand)
3385 11) Vaping Evaluation Scale
3386 12) CPT (usual brand)
3387 13) E-Cigarette Flavor Rating Questionnaire
3388 a. Participants will rate only the flavors that they received from staff for this visit
3389

3390 In the event that the REDCap website is not functioning, the assessments will be administered
3391 aloud and participant answers will be recorded securely. The interviewer will enter the data into
3392 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
3393 Visit Evaluation Form'.

3394 **6.3 E-cigarette Training Session (Baseline 2):**

3395 Participants assigned to an e-cig condition will be told that they will be provided with a JUUL.
3396 If a participant indicates an unwillingness to use the JUUL device, the research assistants will
3397 offer the participant the Vuse Solo as alternative device. If the participants does not wish to use
3398 either device, he or she would be ineligible for the study.

3399 Participants in the e-cigarette conditions will be given e-cigarette pods BEFORE the training
3400 session occurs. These pods will be either picked up at the lab (preferred) or delivered to the
3401 participant 1 to 2 days before their Baseline 2 visit occurs. Participants randomized to the e-
3402 cigarette conditions will be notified before their Baseline 2 visit (but after the 7-day period
3403 following Baseline 1) and informed of their e-cigarette condition. Participants randomized to the
3404 flavored condition will be given pods of up to three flavors of their choice. Staff will calculate how
3405 many total pods participants will be given at this time based on their smoking rate, and
3406 participants will be able to choose the proportion of each flavor that they would like to receive.

3407 The e-cigarette training session will occur over video chat after the physiological
3408 measurements have been collected. The first 30 minutes of the training session will consist the
3409 participant being taught how to use, charge, and replace pods. Participants will first try their
3410 JUUL using the tobacco flavor. At this point, participants who are in the tobacco-only flavor
3411 condition will conclude their training session.

3412 For all visits following Baseline 2, participants in the preferred flavor condition, participants
3413 are permitted to take up to three flavors home per week, but can choose to take less than three
3414 flavors if desired. Participants will take home their chosen pods or cartridges of up to three
3415 flavors. Participants will be able to change their flavors at only one point in the study if they
3416 desire. Participants will only be allowed to take home three flavors at one time. Participants will
3417 be given an E-cigarette instructional manual that reviews the e-cigarette training done at this
3418 visit. Participants will be encouraged to call with any device issues.
3419

3420 **6.4. Interactive Voice Response System:**

3421 At the end of the first baseline visit, participants will be trained to use the Interactive Voice
3422 Response (IVR) System, which will contact participants each day throughout the study and ask
3423 about their smoking behavior as well as withdrawal symptoms the week before and after Baseline
3424 2. We will also review the IVR adherence incentive program, which consists of \$1 per call plus a
3425 \$10 bonus for seven consecutive calls.

3426 The IVR system is operated by TeleSage (<https://telesage.com/about/>). To be enrolled in the
3427 IVR system, research staff will enter the participant's initials, telephone number, subject identifier,
3428 and visit dates into the IVR TCORS website. Identifying information (initials and telephone
3429 numbers) will not be extracted as part of the data by the bioinformatics group. Please refer to
3430 TeleSage's privacy statement and HIPAA compliance form for additional information.

3431

3432 **Baseline 2 biological specimens:**

3433 1) Urine sample for smoking biomarker assessment:

3434 Participants will be asked to provide a urine sample (first void of the day) at the second
3435 baseline session and to post-randomization weeks 8 and 16 for biomarker assessment.
3436 Biomarker analysis will provide nicotine and carcinogen exposure outcome measures and
3437 verify compliance with VLNC cigarettes. Samples will be stored at -80C. Urine samples
3438 will be analyzed for total nicotine (cotinine plus its glucuronide conjugate, a useful measure
3439 of daily nicotine exposure), the tobacco-specific nitrosamine 4-methylnitrosamineo-1-(3-
3440 pyridyl)-1-butanol (NNAL), and metabolites of 4 polycyclic aromatic hydrocarbons (PAHs),
3441 which are biomarkers of tobacco smoke carcinogens and decrease upon tobacco
3442 cessation or reduction. Anatabine is a minor alkaloid that is reduced in users of VLNC
3443 cigarettes and e-cigs. Therefore, anatabine levels in samples from those assigned to the
3444 VLNCC, VLNCC+TF e-cig and VLNCC+PF e-cig conditions should be lower than levels
3445 from those in the NNCC condition. These analyses will be preformed by the Murphy lab at
3446 the University of Minnesota.

3447 2) Saliva Samples for smoking biomarker assessment:

3448 We will collect a saliva sample at the second baseline session and post-randomization
3449 weeks 8 and 16 for analysis of nicotine metabolite ratio (NMR; ratio of 3-hydroxycotinine
3450 [3 HC] to cotinine [COT]), a phenotypic marker of nicotine metabolic rate. Analyses of
3451 these samples will be performed by the Tyndale lab.

3452 **Biomarker shipping and storage:**

3453 Biomarkers will be shipped quarterly to the University of Vermont Laboratory for Clinical
3454 Biochemistry Research (Tracy Lab). The Tracy Lab will serve as a central repository for all
3455 biomarker specimens and will be responsible for distributing specimens to the appropriate labs
3456 on a quarterly basis. Urine samples will be analyzed and stored at the University of Minnesota
3457 Murphy Lab. The saliva samples will be analyzed and stored at the University of Toronto Tyndale
3458 Lab.
3459

3460

7. Study Experimental Procedures

3461 **7.1. Experimental Period:**

3462 Participants will be seen weekly throughout the 16-week experimental period. Weeks 4, 8, 12,
3463 16 and the abstinence visit will take approximately 2-4 hours each. All other sessions will last
3464 approximately 2 hours. If a participant has a positive urine or saliva toxicology test or is visibly
3465 intoxicated as determined by slurred speech, swaying, or stumbling, the session will be
3466 rescheduled until a negative test result is obtained and intoxication is not present. As a part of
3467 each experimental visit, participants will be asked to come to UHC for a product exchange. All
3468 participants must pass a COVID19 screening before entering the building. Participants will be
3469 instructed to contact the RA at the office when they get to the clinic to ensure that there is enough
3470 space in the smoking chambers to house all participants while abiding by safety guidelines as
3471 detailed on page 14 of the protocol. All participants must pass a COVID19 screening before
3472 entering the building. When invited into the lab, the participant will be shown to a smoking
3473 chamber and will instructed to place their bag of product outside of the chamber. The participant
3474 will wait here while the RA processes and returns product through the randomization database.
3475 Then the RA will dispense new product and bring the bag back to the participant's smoking
3476 chamber and leave it on the ground in front of the chamber. When the RA deems it safe for the
3477 participant to exit the chamber, the RA will instruct the participant that they can leave. The RA will
3478 instruct the participant to observe social distancing measures during this exchange, providing
3479 clarification if necessary. At the end of each experimental session, the researcher will complete
3480 the End of Visit Evaluation Form, which will be filed in the participant's binder. This will allow the
3481 researcher to make note of any problems encountered during the visit and to assess the
3482 truthfulness of the participant in regards to self-report of tobacco use and compliance to study
3483 procedures.

3484

3485 **Visit scheduling requirements for experimental period:**

3486 The ideal scheduling window between each visit is 7 days based on the date of the Baseline
3487 2 Visit. For additional scheduling requirements, refer to the '*Scheduling Visits SOP*'. If a participant
3488 misses a visit and is unable to reschedule during the window (± 3 days), that visit will not be
3489 'made-up' in the future. All measures that were not completed will be considered missing data
3490 and will not be collected during future visits. If a visit mistakenly occurs outside of the designated
3491 window, this is a protocol deviation. A 'Non-Medical Event Form' will need to be completed.
3492 Additionally, each visit should occur at approximately the same time of day ± 1 hour. The interval
3493 between the time for the participant's methadone/buprenorphine dose should also be consistent
3494 for each visit (± 1 hour).

3495 If a participant is not able to attend his/her Week 16 visit, then it should be rescheduled even
3496 if it is outside of the scheduling window. This will be documented as a protocol deviation.

3497 **7.2. Experimental Visits Weeks 1, 3, 5, 7, 9, 11, 13, and 15 Procedures**

3498 **7.2.A. Measures/Assessments**

3499 **Physiological Measures Collected and entered directly into REDCap by the interviewer:**

- 3500 1) CO
- 3501 2) Blood Pressure
- 3502 3) Heart Rate
- 3503 4) Body temperature
- 3504 5) Oxygen saturation
- 3505 6) Respiratory rate
- 3506 7) Urine or Saliva Toxicology
- 3507 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

3508 **The following assessments will be administered as an interview and will be entered directly**
3509 **into REDCap by the interviewer:**

- 3510 1) Concomitant Medications
- 3511 2) Medical Event Form, if applicable
- 3512 3) Health Changes Questionnaire
- 3513 4) Time Since Last Cigarette Questionnaire
- 3514 5) Maintenance Drug Dose Questionnaire
- 3515

3516 ***The following assessments will be completed by the participant directly in REDCap:***

- 3517 1) BDI
- 3518 2) OASIS
- 3519 3) COVID19 Symptom Questionnaire
- 3520 4) Respiratory Symptom Questionnaire
- 3521 5) MNWS

3522 In the event that the REDCap website is not functioning, the assessments will be administered
3523 aloud and participant answers will be recorded securely. The interviewer will enter the data into
3524 REDCap when it resumes functioning properly. This information should be recorded in the 'End of
3525 Visit Evaluation Form'.

3526 **7.3. Experimental Visits Weeks 2, 4, 6, 8, 10, 12, 14, and 16 Procedures:**

3527 **7.3.A Measures/Assessments**

3528 **Physiological measures collected and entered directly into REDCap by interviewer:**

- 3529 1) CO

- 3530 2) Blood Pressure
- 3531 3) Heart Rate
- 3532 4) Body temperature
- 3533 5) Oxygen saturation
- 3534 6) Respiratory rate
- 3535 7) Urine or Saliva Toxicology
- 3536 8) Urine Pregnancy test (if applicable)

3537 **The following assessments will be administered as an interview and will be entered directly**
 3538 **into REDCap by the interviewer:**

- 3539 1) Concomitant Medications
- 3540 2) Medical Event Form, if applicable
- 3541 3) Health Changes Questionnaire
- 3542 4) Time Since Last Cigarette Questionnaire
- 3543 5) Maintenance Drug Dose Questionnaire
- 3544

3545 **The following assessments will be completed by the participant directly in REDCap:**

- 3546 1) BDI
- 3547 2) OASIS
- 3548 3) Respiratory Symptom Questionnaire
- 3549 4) COVID19 Symptom Questionnaire
- 3550 5) MNWS
- 3551 6) QSU (usual brand)
- 3552 7) QSU (study cigarette)
- 3553 8) Vaping Craving Questionnaire
- 3554 9) CES (usual brand)
- 3555 10) CES (study cigarette)
- 3556 11) Vaping Evaluation Questionnaire
- 3557 12) PANAS
- 3558 13) Cigarette Purchase Task - Usual Brand Cigarette Version (weeks 4, 8, 12 and 16 only)
- 3559 14) Cigarette Purchase Task – Study Cigarette Version (weeks 4, 8, 12 and 16 only)
- 3560 15) Cross-price Elasticity Task¹²⁰- e-cigarettes and combustible cigarettes (weeks 4, 8, 12 and
 3561 16 only) (for e-cigarette experimental conditions only)
- 3562 16) Penn State Electronic Cigarette Dependence Index (weeks 8 and 16 only)
- 3563 17) Respiratory Health Questionnaire (weeks 8 and 16 only)
- 3564 18) FTND (weeks 8 and 16 only)
- 3565 19) Perceived Health Risks Questionnaire (weeks 8 and 16 only)
- 3566 20) Smoking Stages of Change Algorithm and Contemplation Ladder (weeks 8 and 16 only)
- 3567 21) WISDM – Brief Scale
- 3568 22) Drug Use Questionnaire – 1 month version (weeks 8 and 16 only)
- 3569 23) Perceived Stress Scale (weeks 8 and 16 only)
- 3570 24) Alcohol Use Questionnaire – 1 month version (weeks 8 and 16 only)
- 3571 25) E-cigarette flavor rating questionnaire (weeks 4, 8, 12 and 16 only)
- 3572

3573 In the event that the REDCap website is not functioning, the assessments will be administered
 3574 aloud and participant answers will be recorded securely. interviewer will enter the data into
 3575 REDCap when it resumes functioning properly. This information should be recorded in the 'End
 3576 of Visit Evaluation Form'.

3577 ***Biological Samples to be collected:***

- 3578 1) First void urine sample (Weeks 8 and 16 only)
- 3579 2) Saliva sample (Weeks 8 and 16 only)
- 3580

3581 **7.4. Interactive Voice Response System:**

3582 Participants will continue to use the IVR system on a daily basis throughout the experimental
3583 period to record the number of study cigarettes smoked per day, measurement of e-cig use and
3584 use of non-study cigarettes or other tobacco products. Measurement of e-cig use will be
3585 collected by asking two questions: how many daily e-cigarette episodes occurred, where one
3586 episode consists **of around 10-15 puffs** or up to approximately 10 minutes, and what proportion
3587 of pods and/or cartridges were used per day. Participants will also be asked to log how many
3588 flavors of e-cigs they used per day. During the first week after Baseline 1, the IVR system will
3589 collect information about mood and withdrawal symptoms.
3590

3591 **7.5. Variable Incentive Program:**

3592 An incentive program has been developed with the goal of improving attendance at
3593 scheduled assessment sessions, compliance with using only study-provided tobacco products,
3594 and encouraging honest self-reports regarding all nicotine/tobacco use.

3595 Briefly, participants will receive a total of seven tickets for each weekly visit they attend after
3596 randomization (Visits 03-18, weeks 1-16). In total, participants could earn 112 valid tickets across
3597 the 16 visits. Participants will be instructed that these tickets correspond to attendance (one
3598 ticket), honest reporting (one ticket), compliance in bringing back used and unused
3599 pods/cartridges (two tickets) and adherence to using only the assigned study product (three
3600 tickets). Participants who do not bring back all of their unused study product and used packaging
3601 will be told that they may not be eligible to earn the two compliance tickets.

3602 Participants will be further instructed that all of the tickets that they receive “could” be eligible for
3603 entry into a monthly drawing for prizes, but that only tickets that are “validated” will be eligible for
3604 prizes.

3605 Since it is prohibitively expensive to test urine samples each week for each participant and
3606 because it is currently not feasible to detect with reasonable precision non-compliance based on
3607 biomarkers in the two higher nicotine group, we plan to only validate the attendance tickets.
3608 Hence, each participant who attends their regularly scheduled weekly session will have a total of
3609 seven validated tickets entered into the monthly drawing.

3610 To convey the message that we may be validating honest reporting and use of only study-
3611 provided products, in a bogus pipeline of sorts, we will tell the participants that a composite
3612 assessment of the measures that we collect MAY be used to validate the amount of nicotine and
3613 tobacco products that they are using. So there is some minor deception involved, but technically
3614 we could conduct urine toxicology testing for both purposes. Hence, if the urine toxicology testing
3615 is presented as something that MAY be done for validation purposes, we feel that any deception
3616 is relatively minor. For scientific/economic reasons we are just electing to restrict validation to
3617 attendance. Nevertheless, we will debrief all participants upon the completion of the trial. We will
3618 inform them that the incentive program was based exclusively on attendance due to the relatively
3619 high cost of urine toxicology testing and other practical problems with shipping the urines for
3620 prompt testing.

3621 Drawings will be conducted on the 1st of each month. Validation will be performed by staff
3622 who have no participant interaction and are not blind to condition. Any ticket drawn will be eligible
3623 for an incentive as the only true contingency is for attendance. There will be no mention of the
3624 basis for earning incentives (i.e., whether the ticket was for attendance, honesty, adherence).
3625 Participants will simply be informed that he or she earned an incentive from the drawing.

3626 Each drawing will be independent (without replacement); consequently, some participants will
3627 not win a prize and others may win more than one during the study if more than one of their
3628 tickets is drawn. After confirming winners, the remaining tickets from each month will be
3629 discarded (i.e., tickets will only be entered into one drawing). The monthly prize amounts are
3630 detailed below.

3631 We estimate based on the 2 ½ years we think it will take to complete this study, that
3632 participants will win an average of approximately \$65 in prizes or an additional \$5.50 per week
3633 per participant.
3634

3635 Grand Prize (1): \$500 cash
3636 Second Prize (1): \$200 cash
3637 Third Prize (5): \$10 cash

3638 **7.6. Product and Procedures Compliance Review Sessions:**

3639 At each visit, Baseline 2 through Week 16, participants will be counseled about their use of the
3640 study cigarettes and assigned e-cigarette (if applicable). Participants will be asked about any
3641 concerns or obstacles associated with use of the study cigarettes and assigned e-cigarette (if
3642 applicable). The importance of honest self-reporting will be stressed. Participants will be told that
3643 they will not be penalized for use of other nicotine or tobacco products and that it is crucial for
3644 them to report any use of these products. If difficulties are encountered, participants will be asked
3645 why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to
3646 problem-solve how to deal with these difficulties in order to meet the protocol requirements.
3647 Additionally, participants will be counseled about their IVR completion, visit attendance, task
3648 engagement and product accountability. Refer to the '*Product and Procedures Compliance
3649 Review Sessions SOP*' for more information.

3650 **7.7. Quit Attempts During the Study Protocol:**

3651 At each weekly session, we will ask each participant if s/he is currently abstaining from
3652 smoking with the intention of quitting and whether s/he is planning to quit smoking prior to his/her
3653 next scheduled visit. If a participant is currently abstaining from smoking with the intention to quit,
3654 we will encourage the participant to continue abstaining, schedule them for weekly visits, and
3655 provide them with NCI's Clearing the Air manual and local smoking cessation resources. We will
3656 give them the option of taking study product(s) home but not require that they take them, and if
3657 they do take the product(s) home we will suggest that they put the product(s) away at home so as
3658 to remove these cues from view. We will ask the participant to contact staff if they lapse and
3659 would like to receive study product(s) prior to his/her next visit. If a participant is planning to quit
3660 but has not initiated a quit attempt, we will ask if s/he has identified a quit date and if so what the
3661 date is, provide them with the Clearing the Air manual and local smoking cessation resources,
3662 provide them with the study product(s), and recommend that they put the product(s) away out of
3663 view on the quit date.

3664 For those in a condition including e-cigarettes, we will defer to the participant's interests in
3665 continuing to use e-cigarettes as part of their quit attempt. Those who indicate that they will
3666 continue to use them will be given their same weekly supplies base on their baseline smoking
3667 rate. Those who indicate that they are planning to abstain from both combusted and non-
3668 combusted tobacco, we will honor that request. As we state above about combusted cigarettes, if
3669 participant changes his or her mind about resuming e-cigarette use, they can contact us and
3670 obtain their weekly supply.

3671

3672 **7.7.A. If a participant is currently abstaining from smoking with the intention to quit:**

- 3673 • Encourage participant to continue abstaining from smoking
- 3674 • Schedule the participant for normal weekly visits
- 3675 • Provide the participant with the '*Clearing the Air*' manual and local smoking cessation
3676 resources
- 3677 • Give the participant the option to receive study product rather than require him/her to take
3678 the product
- 3679 • If the participant choses to receive the study product have him/her sign a form
3680 acknowledging that cigarette availability could be detrimental to the quit attempt.
3681 Recommend that he/she put the product "away" at home as to avoid unwanted cues to
3682 smoke.
- 3683 • If the participant chooses not to receive the study product, have him/her contact the lab if
3684 he/she lapses and would like to pick up or be mailed the study product prior to his/her next
3685 visit.
- 3686

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7.7.B. If a participant is planning to quit smoking, but has not initiated the quit attempt:

- Ask if he/she has identified a target quit date and, if so, what that target date is
- Provide the participant with the 'Clearing the Air' manual and local smoking cessation resources
- Provide the participant with the study product as usual. Recommend that on the target date he/she put the product "away" at home as to avoid unwanted cues to smoke.

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7.8. Abstinence Assessment Session:

After the week 16 visit, participants will be required to attend one additional visit the following day. During this visit, participants will have been encouraged to abstain from smoking until their next scheduled visit (approximately 24 hours later). The abstinence assessment session should be scheduled no less than 18 hours and no more than 30 hours after the Week 16 visit. Abstinence will be verified by an expired breath carbon monoxide level of less than or equal to 6ppm. This session will allow us to determine whether the experimental cigarettes and e-cigarette use (for the e-cigarette conditions) have reduced the effects of abstinence on these measures relative to the control conditions. If the participant does NOT meet abstinence criteria, he/she will only receive \$20 for the visit. Those who do meet abstinence criterion will do concurrent choice session detailed below.

3706

7.8.A Participants Who Meet Criteria for Abstinence

3707

7.8.A.1 Measures/Assessments

3708

Physiological measures collected and entered directly into REDCap by the interviewer:

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3714
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3716

- 1) CO
- 2) Blood Pressure
- 3) Heart Rate
- 4) Body temperature
- 5) Oxygen saturation
- 6) Respiratory rate
- 7) Urine or Saliva Toxicology

3717
3718

The following assessments will be administered as an interview and will be entered directly into REDCap by the interviewer:

3719
3720
3721
3722
3723
3724

- 1) Concomitant Medications
- 2) Medical Event Form, if applicable
- 3) Health Changes Questionnaire
- 4) Time Since Last Cigarette Questionnaire
- 5) Maintenance Drug Dose Questionnaire

3725

The following assessments will be completed by the participant directly in REDCap:

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- 1) BDI
- 2) OASIS
- 3) COVID19 Symptom Questionnaire
- 4) Respiratory Symptom Questionnaire
- 5) MNWS
- 6) PANAS
- 7) QSU-brief - Usual Cigarette
- 8) QSU-brief - Study Cigarette
- 9) Vaping Craving Questionnaire
- 10) Cigarette Purchase Task - Usual Brand Cigarette Version

- 3736 11) Cigarette Purchase Task - Study Cigarette Version
3737 12) E-cigarette Purchase Task- E-cigarette Version
3738

3739 In the event that the REDCap website is not functioning, the assessments will be administered
3740 aloud and participant answers will be recorded securely. The interviewer will enter the data into
3741 REDCap when it resumes functioning properly. This information should be recorded in the 'End
3742 of Visit Evaluation Form'.

3743 **7.8.B. Participants Who Do Not Meet Criteria for Abstinence**

3744 **7.8.B.1 Measures/Assessments**

3745 **Participants who do NOT meet abstinence criteria will be required to complete the**
3746 **following assessments:**

- 3747 1) CO
3748 2) Blood Pressure
3749 3) Heart Rate
3750 4) Body temperature
3751 5) Oxygen saturation
3752 6) Respiratory rate
3753 7) Urine or Saliva Toxicology
3754

3755 **The following assessments will be administered as an interview and entered directly into**
3756 **REDCap by the interviewer:**

- 3757 1) Concomitant Medications
3758 2) Health Changes Questionnaire
3759 3) Medical Event Form, if applicable
3760 4) TLFB
3761

3762 ***The following assessments will be completed by the participant directly in REDCap:***

- 3763 1) BDI
3764 2) OASIS
3765 3) COVID19 Symptom Questionnaire
3766 4) Respiratory Symptom Questionnaire
3767

3768 **7.9. Participant Compensation:**

3769 Participants will receive \$25 for the medical consent visit. Participants will receive \$25 plus
3770 a \$25 bonus for completing each screening visit, plus an additional \$25 bonus for completing the
3771 visit on time as scheduled. Payment for the first screening session will be made upon its
3772 completion. Payment for the second session will be made regardless of enrollment as long as the
3773 participant passes the drug test and meets the minimum requirements for carbon monoxide or
3774 urinary cotinine levels. Participants who do not pass the drug test or who are visibly intoxicated as
3775 determined by slurred speech, swaying, or stumbling will not be able to complete the visit and will
3776 be asked to take another test several days after the first positive. If they are negative for the
3777 second test, they will be eligible to participate, and if they are positive the for the second text they
3778 will be excluded. Participants will receive \$100 for each study visit from Baseline 1 to Week 16.
3779 Participants will also have a chance to earn an additional \$20 bonus for every study visit that is
3780 completed on time as scheduled starting at Week 1 and ending at Week 15. Participants can
3781 receive up to \$120.00 for the abstinence session (\$20 if participant does not achieve abstinence,
3782 \$120 if participant reaches abstinence), \$40 for biochemical verification of abstinence, and up to
3783 \$306 for completing daily IVR reports of study cigarette and other nicotine and tobacco use..
3784 There will also be a \$150 bonus distributed at Week 16 for completing the study. Participants who

do not complete the entire study will receive compensation for the sessions that they do complete. Total compensation for completing Study 3, including study visit payments, daily IVR calls and end of study bonus is \$2841. As mentioned above, participants will have a chance to earn additional incentives for compliance, honesty and attendance through urine testing. Participants will be given a debit card at the beginning of the study (during the second portion of the screening visit) and compensation for each visit will be automatically transferred to the card after they complete that visit. If debit cards are unavailable, participants will be paid via an alternate method (i.e. cash or check).

7.10. End of Study:

After a participant has completed all study procedures and has been paid for participation the research assistant will read the following script and give the participant the *Clearing the Air Manual*.

“If you’ve reduced your smoking during this study, we encourage you to continue these reductions or even consider quitting. We would like to provide you with some resources should you decide to try to abstain from smoking (give “Clearing the Air” and hotline information). Please also feel free to consult with your physician and use any medications he/she deems appropriate. We will call you in approximately 30 days to ask about your smoking since leaving the study. There is no right answer and we know how difficult quitting can be. Please just answer honestly. The call will take less than 5 minutes. Thanks again for your participation.”

The following assessments will be administered using REDCap:

- 1) End of Study Questionnaire

7.11. 30-Day Follow up Phone Call:

Participants will receive a follow-up phone call between 25 and 35 days after the abstinence assessment session to assess their smoking patterns. The phone questionnaire will last less than five minutes. The questionnaire will ask if the participant is still smoking, how much and whether he/she has attempted to quit smoking since the end of the study. Participants will receive 5 variable incentive program lottery tickets for completing the call as compensation.

Those who report abstinence will be invited to complete biochemical verification and be compensated \$40 for doing so. Abstinence will be achieved by a carbon monoxide reading of 6 parts per million (ppm) or under. A urine sample may also be collected to be sent to the lab for analysis. Additionally, any Medical Event Forms that remain open from the last session will be discussed. If the participant became pregnant during the study, this would have been recorded as a medical event. During this phone call, the research assistant will confirm her due date. This event will remain open until delivery. At that time the licensed medical professional will contact the participant to ask a few questions about the baby’s health and will update the Medical Event Form.

Once a participant has completed all study procedures and all open events have been closed, the PI or Project Manager will review the participant’s record and sign a form indicating study completion for that participant.

8.0 Study Randomization

8.1 Randomization Process

At the end of Baseline Session 2, participants will be randomized in equal probability to one of the four groups (NNCC, VLNCC, VLNCC + TF e-cig, VLNCC + PF e-cig) for a 16-week period, with stratification by site and menthol cigarette status. Participants will be randomized, using block randomization, in equal number to the dose conditions, with randomization stratified by study site and menthol status. Each site will randomize participants until the total goal of 310 participants across both sites is reached (205 at UVM and 105 at Johns Hopkins), and no effort will be made to recruit a specific number of menthol and non-menthol smokers at each site.

The lead statistician will create a randomization schedule for each of the two sites,

3836 amounting to 150% of expected enrollment at each site. The excess randomization codes will be
3837 used in the event that a site will have to enroll extra participants due to unexpectedly slow
3838 enrollment at another site. The nicotine doses will be identified by letter code and only
3839 Administrative Core personnel with no participant contact will have the link between the
3840 statistician's letter code and dose assignments. There will be no blinding of e-cigarette conditions.
3841 The Administrative Core will maintain the randomization schedule and the link between the
3842 alphabetic code and treatment assignment securely. A second sealed copy will be secured in a
3843 separate building to protect against loss related to fire or other unforeseen events.

3844 The University of Vermont will be responsible for removing all identifying information from
3845 cigarettes received from the Research Triangle Institute (RTI), labeling each carton with a blind
3846 code, assigning product using this blind code based on the randomization schedule being
3847 provided by the UVM Biostatistics Core, and shipping cigarettes and e-cigarettes to each site as
3848 needed based on recruitment. Each site will be responsible for tracking product received and
3849 distributed to participants, collecting unused product from participants, and returning unused
3850 cigarettes and e-cigarettes to UVM. The participants, investigators and study staff will not have
3851 knowledge of which product is given to a participant or whether different participants received the
3852 same or different product.

3853 **8.2 Study Product Administration**

3854 During the experimental period, participants will be provided with a 14-day supply of research
3855 cigarettes equivalent to 150% of their daily smoking rate. Those in the e-cigarette conditions will
3856 also be provided with a 14-day supply of e-cigarettes equivalent to their daily smoking rate. This
3857 rate will be calculated at Baseline 2 and will be an average daily smoking rate based on the IVR
3858 data that reports on the usage for the first seven days following the day of the first baseline visit.
3859 This will ensure adequate availability of cigarettes in the numerous locations participants may
3860 typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if
3861 they miss a scheduled visit. Participants will be instructed to use the research cigarettes for 16
3862 weeks, at which point they are to discontinue product use.

3863 If there is prior knowledge a participant will be missing a visit (i.e. planned vacation, laboratory
3864 closure, etc.), then the participant will be provided with an adequate supply of cigarettes to make
3865 up for the missed visit(s). The participant will be given a 21-day supply if one visit is going to be
3866 missed and a 28-day supply if two visits are going to be missed.

3867 **8.3 Guidelines for Reporting other Nicotine Product Use**

3868 Participants will be asked to refrain from use of other non-study cigarettes during the study
3869 period. If participants have to use another nicotine product, they will be told to use a non-
3870 combustible product (gum, patch, etc.). Additionally, they will be told there is not a penalty for use
3871 of non-study products, and that it is crucial for them to report any use of non-study tobacco
3872 products. Throughout the baseline and experimental periods, an Interactive Voice Response
3873 (IVR) system will be used on a daily basis to record the number of study cigarettes and non-study
3874 cigarettes used the previous day. During the baseline and first experimental week, participants will
3875 also answer daily IVR questions about their mood. Participants will be seen weekly for
3876 assessments. Brief standardized review sessions focusing on compliance with the study
3877 cigarettes and other study procedures will be provided at each visit.

3878 **8.4 Product Accountability:**

3879 Participants will be required to keep track of all the products provided to them. Therefore, they
3880 will be instructed to return all unused products and empty cigarette packs e-liquid pods/cartridges
3881 to the laboratory each week. Research staff will complete the 'Product Accountability Log' as they
3882 process participants' product. Any discrepancies in the product dispensed versus product
3883 returned will be discussed and recorded in the log. Research staff will weigh all opened e-cigarette
3884 pods /cartridges that the participant returns at all visits to determine how much e-liquid was used
3885 since the participant was last seen. Empty cigarette packs and e-liquid pods/cartridges will not be
3886 saved. Unused cigarette packs and e-liquid pods/cartridges will be re-distributed to the
3887 participants during Weeks 1-15. During Week 16, remaining unused cigarettes and e-cigarette
3888 pods/cartridges returned by the participants will be collected by the research staff.

3889 Participants who report running out of cigarettes or e-liquid pods/cartridges prior to a
3890 scheduled weekly visit will be allowed to come in for an unscheduled visit to obtain more research
3891 cigarettes. To determine whether a rate change for cigarettes is necessary, we will look at the
3892 past two CO levels as compared to the Baseline 2 CO. If the CO trend is consistent with the self-
3893 report of smoking all of the allotted cigarettes then a rate increase will be granted. The participant
3894 will then receive cigarettes at a rate of 175% of their daily smoking rate. The maximum increase is
3895 200% of their daily smoking rate. To determine whether a rate change for e-cigarettes is
3896 necessary, we will monitor the amount of e-cigarette use the participant is reporting and showing
3897 through product return along with any unscheduled visits. The investigator may grant an e-
3898 cigarette rate increase in increments of 25%. The maximum increase for e-cigarettes will be 200%
3899 of their baseline weekly e-cigarette dispensation rate.

3900 If participants lose more than two packs of cigarettes and/or pods/cartridges and require an
3901 unscheduled visit to the laboratory to supplement their supply, they will be told the next time they
3902 lose more than two packs they will have to wait until their next scheduled appointment to receive
3903 more cigarettes.
3904

3905 **9. Study 3 Statistical Methods and Sample Size**

3906 **9.1 Statistical Methods**

3907 Continuous outcomes will be summarized by mean, standard deviation, median and range.
3908 Categorical outcomes will be summarized by frequencies and percentages. Skewed continuous
3909 outcomes will be log- or square-root transformed as appropriate. Variables measured at each
3910 baseline visit will be averaged and the average will be used as the baseline measurement.. As we
3911 expect conditions to be balanced on important baseline characteristics due to randomization, our
3912 primary analysis for all endpoints will not be adjusted for potential confounders. However, a
3913 secondary analysis will be completed for all outcomes adjusting for demographic characteristics
3914 (e.g., age), that we have found to be important in prior studies. Potential moderators (e.g., SSRI
3915 vs. non-SSRI antidepressant, depression vs. anxiety disorders, BMI above or below 30) will be
3916 explored by adding that term and the moderator-by-condition term to the model. We will examine
3917 age group and gender as potential moderators in a similar fashion.

3918 Participants will be randomized in equal probability to one of the four conditions, with
3919 randomization stratified by site and menthol cigarette status. All analyses will follow the intent- to-
3920 treat principle (i.e. subjects will be analyzed according to condition assignment, regardless of
3921 compliance). The Primary Aim will examine the effects of condition on total CPD (study product
3922 and non-study product). CPD will be analyzed by week (mean over all days in a seven-day
3923 period) using a mixed model to account for repeated measures from the same individual.

3924 Models will include baseline CPD as a covariate. Using a mixed model also allows us to include
3925 the effect of study site as a random effect. Additional analyses conducted using data collected at
3926 the end of the study will use orthogonal comparisons to test for a linear trend in the decrease in
3927 CPD, such that $VLNCC + PF\ e-cig > VLNCC + TO\ e-cig > VLNCC > NNCC$, with the largest
3928 reduction in the $VLNCC + PF\ e-cig$ condition. As we expect that differences among conditions for
3929 some of the outcomes may not follow a linear pattern, we will use related planned comparisons to
3930 test for threshold effects, specifically contrasting the NNCC condition to all three VLNCC
3931 conditions, and NNCC to the two VLNC + e-cigarette conditions. Analysis of cigarette demand,
3932 smoke exposure and tobacco carcinogens (Aim 2) as well as additional outcomes, including
3933 subjective effects, will be analyzed in a similar manner. Because Exploratory Aim 3 is based on
3934 abstinence-induced effects and will be examined using data collected at a single visit at Week 17,
3935 analysis will be based on an analysis of co-variance model. In addition to the effect of condition,
3936 we will include important covariates noted above. Exploratory analyses will also be conducted
3937 combining data collected from three of the vulnerable populations (disadvantaged women of
3938 childbearing age, opioid dependent individuals, individuals with AD) to explore potential differences
3939 in effects of study condition across these populations. This will be done with the addition of the
3940 effects of population and population-by-condition terms to the models described above. Study staff
3941 will make every effort to minimize missing data, and results of our ongoing trial suggest that this

3942 will be minimal. We will examine the missing data pattern, and if it is missing at random, will use all
3943 data available, without imputation.

3944 9.2. Sample Size

3945 Sample size was determined using NQuery Advisor based on hypothesis tests related to
3946 Aim 1 to detect a significant difference between conditions on total CPD. The primary statistical
3947 approach will be repeated measures ANOVAs but
3948 required sample sizes were calculated focusing on
3949 expected outcomes at Week 16. This estimate is
3950 intentionally conservative and calculated based on one
3951 outcome at one time point; however, given the repeated
3952 measures nature of our data, we will have correlated
3953 observations within subjects and thus will achieve the
3954 stated power to detect differences of even lesser
3955 magnitude. Estimates are based on preliminary results
3956 from our current trial and from the Donny et al.⁴¹ study of
3957 VLNCCs and NNCCs. The between-group effect size is defined as the difference of study condition
3958 means divided by the common standard deviation. A sample size of 75 participants per condition
3959 will provide 80% power to detect an effect size of 0.50 for all pair-wise comparisons, with a two-
3960 sided type 1 error rate of 0.05. While this is larger than the effect size in our ongoing trial, we
3961 assume that the addition of e-cigs to the VLNCCs will decrease CPD from that seen with VLNCCs
3962 alone. Thus, while we recognize that we may have insufficient power to detect differences between
3963 the VLNCC and NNCC alone conditions, we expect a larger effect size when comparing the NNCC
3964 and either of the VLNCC + e-cig conditions. This sample size also provides greater than 95%
3965 power to detect a linear dose-response effect across conditions. Because we have relied only on
3966 outcomes at Week 16, our proposed sample sizes are somewhat conservative, but we believe this
3967 is appropriate given that the effects of VLNCCs in this population, particularly in combination with
3968 e-cigs, are unknown. The sample size assumes a 15% loss to follow-up, consistent with our
3969 experience in the current study. We will increase our overall sample size to 310 in order to allow
3970 pilot testing with 10 participants.
3971

Outcome	Observed between-group ES (15.8 vs. 0.4 mg/g)
CPD	0.38
Craving	0.74
FTND	0.14
Breath CO	0.06

3972 10. Potential Risks of Participation

3974 10.1 Risks of Participation

- 3975 1) Survey Questionnaires. Surveys include questions about participants' medical and
3976 psychiatric histories, drug and alcohol use and history, breath tests for cigarette and alcohol
3977 use, urine or salivary tests of illicit drug use and pregnancy, and questionnaires about your
3978 mood. Answering these personal questions can make participants uncomfortable. If a
3979 participant reports thoughts of killing themselves or other indicators of suicidality, a study
3980 clinician will come to talk to the participant. The participant may also request to see a study
3981 clinician if he or she is in discomfort and would like help and/or referrals for mental health
3982 resources.
- 3983 2) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out
3984 the results.
- 3985 3) Undue Influence: Undue influence is a possible risk due to monetary compensation for
3986 participating in these studies. The likelihood of this risk is low because the compensation is
3987 commensurate with the amount of time and effort required for these studies.
- 3988 4) Drug Testing: A breach of confidentiality could occur and other people could learn of the
3989 participant's drug use.
- 3990 5) Obtaining Blood Pressure and Heart Rate. The blood pressure cuff may cause minimal
3991 discomfort. In obtaining blood pressure we may find a participant to have abnormal blood
3992 pressure and/or heart rate. If participant's blood pressure is abnormal, we will inform the
3993 participant of this, and participant may be advised to see a doctor, and may also be

3994 contacted by our study doctor. Also, smoking and nicotine can affect the cardiovascular
3995 system, which may result in changes in blood pressure and/or heart rate.

3996 6) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to
3997 significant medical problems including:

- 3998 a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral
3999 vascular disease, reduced blood circulation, abdominal aortic aneurysm
- 4000 b. Respiratory Diseases: Emphysema, bronchitis, and chronic airway obstruction
- 4001 c. Cancers: Cancer of the lung, bladder, cervix, esophagus, kidney, larynx, mouth,
4002 pancreas, throat, and stomach; leukemia
- 4003 d. Metabolic Diseases: Type 2 Diabetes
- 4004 e. Other Health Risks Associated with Smoking: Including but not limited to infertility,
4005 lower bone density in postmenopausal women, and hip fracture in women
- 4006 f. Death

4007 7) Smoking Study Cigarettes. All cigarettes are harmful to a person's health and can lead to
4008 cardiovascular (heart) disease, respiratory (lung) disease, cancer and other health
4009 problems. In addition to the above medical problems, participants may experience some
4010 minor negative health effects such as headaches. Participants may also experience
4011 smoking withdrawal symptoms, which are listed below. In addition, due to the altered
4012 nicotine levels, there could be a change in a participant's use of cigarettes including the
4013 manner in which he or she inhales the smoke. Smoking the study cigarette does not
4014 necessarily provide any less risk than the participant's usual brand of cigarette and could
4015 pose increased health risks.

4016 8) Using Study E-cigarettes. E-cigarettes are devices that heat nicotine to produce an aerosol.
4017 The health effects of e-cigarettes are still unclear, but appear to be less than that for
4018 tobacco cigarettes. Most e-cigarette users have lower nicotine levels than when they
4019 smoked regular cigarettes. Some e-cigarette users, especially those who use both e-
4020 cigarettes and regular tobacco cigarettes as well as youth and young adults, can have
4021 increased nicotine levels. In some rare cases, these use patterns have been associated
4022 with seizures. Whether this would occur with the concurrent use of very low nicotine
4023 cigarettes is unclear. E-cigarettes users very often maintain addiction to nicotine, but this
4024 addiction appears to be somewhat less than that from tobacco cigarettes. Abruptly quitting
4025 e-cigarettes could cause withdrawal symptoms similar to those from quitting tobacco
4026 cigarettes (see below) but slightly less severe. The most common side effects include dry
4027 mouth, irritation of the throat and mouth, and mild cough. The JUUL and Vuse e-cigarettes
4028 we will be providing have not been well-studied but appear to be of similar risk to other e-
4029 cigarettes. Participants may have heard that e-cigarettes, or "vapes," can explode and
4030 seriously injure people. Study staff should instruct participants that although they appear
4031 rare, these explosions are dangerous. The exact causes of these incidents are not yet
4032 clear, but some evidence suggests that battery-related issues may lead to vape explosions.
4033 In order to prevent e-cigarette related injuries, instruct participants to keep their e-cig away
4034 from other metal objects, never charge the e-cig with a phone or tablet charger, don't
4035 charge the e-cig overnight or leave it charging unattended, and to stop using the e-cig if the
4036 batteries get damaged or wet. The participant will be instructed to always keep e-cig liquid
4037 out of kids' and pets' reach and sight after use. If the study staff learns about additional
4038 risks of e-cigarettes during the study, participants will be informed of these risks.

4039 9) Mood and Psychiatric Symptom Changes. Participants may experience smoking withdrawal
4040 symptoms during this study. These symptoms can include anger, anxiousness, craving for
4041 a cigarette, depressed mood, difficulty concentrating, frustration, increased appetite,
4042 impatience/impulsivity, irritability, restlessness, sleep problems, and weight gain. These
4043 feelings can be uncomfortable and can last a couple of weeks, but usually are of minimal
4044 risk. In addition, if participants have a past history of anxiety, depression, or alcoholism, it
4045 is possible withdrawal could cause substantial increases in depression and anxiety

4046 symptoms, but this appears to be rare. At each visit, study staff will ask participants how
4047 they feel. If either study staff or the participant thinks that being in this study is putting the
4048 participant's mental health at risk, staff may have the participant meet with an on-site
4049 clinician and/or stop participating in the study.

4050 Further, if a participant report thoughts of killing oneself or other indicators of suicidality, a
4051 study clinician will come to talk to the participant. Participants may also request to see a
4052 study clinician if he or she is in discomfort and would like help and/or referrals for mental
4053 health resources.

4054 10) Returning to Regular Smoking: It is possible that if participants return to smoking their usual
4055 brand of cigarette at the end of the study they may experience mild and transient nausea,
4056 dizziness, and lightheadedness.

4057 11) Risk to Fetus. To avoid risks to a fetus, it is important that participants are not pregnant
4058 during this study. Avoiding sexual activity is the only certain method to prevent pregnancy.
4059 However, if participants choose to be sexually active, participants should be using
4060 approved forms of birth control if applicable determined by the Project Medical
4061 Director, including but not limited to prescribed birth control pills, patch, ring,
4062 injections, implants or intrauterine device (IUD) or an appropriate "double barrier"
4063 method. If you choose to be sexually active during this study, pregnancy could still
4064 result even with the use of these birth control methods.

4065 **10.2 Avoiding Risks to Fetus:**

4066 If participants choose to be sexually active, they should use an appropriate "double barrier"
4067 method of birth control (such as female use of a diaphragm, or contraceptive sponge, in addition to
4068 male use of a condom) or the female should be using prescribed "birth control" pills, patch, ring,
4069 injections, implants or intrauterine device (IUD) if applicable determined by the Project Medical
4070 Director. If a participant endorses a "double barrier" method, our medical professional will speak to
4071 the participant to confirm which methods will be used during the duration of the study. Participants
4072 will be tested for pregnancy every two weeks beginning at screening through the last study visit. If a
4073 participant becomes pregnant during the study, she will be withdrawn from the study.
4074 Approximately 30 days after being withdrawn or having a positive pregnancy test at the last study
4075 visit, the research staff will call the participant to confirm her due date. The licensed medical
4076 professional will follow-up with the participant after delivery to ask questions about the baby's
4077 health.

4078 **10.3 Expected benefits of participation:**

4079 There are no benefits from participating in the study. The information obtained from this
4080 study may ultimately help the Food and Drug Administration decide how best to regulate nicotine
4081 and tobacco products with the goal of improving public health.

4082 **11. Protection Against Risk**

4083 **11.1 Data Collection Protections**

4084 Research data without identifiers will be maintained in a locked file cabinet and on password-
4085 protected computers in the research staff workplace, with only code numbers identifying subjects.
4086 Study consent forms and the linkage between the participants' names and codes will be stored in a
4087 locked file cabinet inside a locked office. Interviews with participants will be conducted in private
4088 rooms. Urine or saliva samples for drug and pregnancy tests and tobacco exposure biomarkers
4089 will be obtained in a private bathroom within the laboratory suite. Subjective measures will be
4090 administered electronically. The biostatistics and data-management team will provide consistent
4091 data-management practices for all data in the Center. Using REDCap, which is housed on the
4092 University of Vermont Medical Center's HIPAA-compliant computing system, will maximize validity
4093 and reliability of data. REDCap is a secure, web-based system that accommodates local and
4094 remote data collection by each project team, and allows for data entry work-flow monitoring and
4095 data quality control monitoring by biometry staff. The RedCap database for this project will be
4096
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4098

4099 hosted on the UVMCOM servers. In addition, data will be collected from participants on a daily
4100 basis using an interactive voice recognition system (IVR) developed and hosted by TeleSage Inc
4101 (www.telesage.com, Chapel Hill, NC). TeleSage is a company with expertise on gathering patient-
4102 centered outcomes tracking data for mental health clinical and research institutions. TeleSage has
4103 developed and hosted behavioral health-related research software systems using IVR and Web-
4104 based technologies and is leader in behavioral health outcomes tracking technologies. For data
4105 integrity, data entry windows will follow the structure of paper forms as much as possible to allow
4106 for ease of entry, and will use predefined choices to minimize errors when possible. Data quality
4107 monitoring will be facilitated with periodic down loads and analysis using a variety of common
4108 statistical program format such as SAS, Stata, R, and SPSS. Quality control procedures will be
4109 conducted for all data collected, including analysis of missing data and logic checks for out of
4110 range and other anomalous values. This secure electronic data gathering and transmission plan,
4111 overseen by the experienced biostatistical team, will minimize opportunities for breaches of
4112 confidentiality. Biological samples for nicotine and carcinogen biomarker analysis will be marked
4113 with participant ID, stored in the locked laboratory suite, and sent to a laboratory for analysis on a
4114 quarterly basis.

4115 All information collected as part of this study will be accessible only to research staff. No
4116 information will be shared with participants' clinicians unless the participant requests this in writing.
4117 All investigators and staff have undergone (and any new staff will undergo) human subjects' ethics
4118 training as required by UVM and are fully conversant with relevant ethical principals around
4119 confidentiality. Assessments, consenting and study procedures will be closely supervised by the PI.

4120 The sponsors (NIDA/FDA) as well as the Institutional Review Board and regulatory authorities
4121 could be granted direct access to original medical and research records for verification of clinical
4122 trial procedures and/or data. If this is required, it will be done under conditions that will protect
4123 privacy to the fullest extent possible consistent with laws relating to public disclosure of information
4124 and the law-enforcement responsibilities of the agency.

4125 **11.2 Data Storage:**

4126 Data will be stored locally at each site. Long-term storage of all study data, for at least 7 years
4127 after study completion, will be at the University of Vermont.
4128

4129 **12. Adverse Events**

4130 The research assistant will ask about adverse events at each session, using a form that
4131 assesses the nature, severity, duration, action taken, and outcome of study-related adverse
4132 events. AEs will be captured from the time of first study cigarette. Participants will be given contact
4133 cards to inform us of events that occur between study contacts. Any AE that remains open will be
4134 reviewed and closed at an interview conducted 30 days after the study completion date
4135 (completers) or when the study should have ended had the participant completed the study
4136 (dropouts and those withdrawn by investigator).
4137

4138 All procedures will be monitored to ensure that they conform to the approved protocol. In
4139 addition, monitoring will be done of all unforeseen circumstances that might arise and affect safety;
4140 of all reports of serious adverse events as defined in 38 CFR 46 (death, new or prolonged
4141 hospitalization, persistent or significant disability/incapacity); of other significant adverse events
4142 (adverse events that lead to drop out by the participant or termination by the investigator); of
4143 unexpected adverse events resulting from the study, and of expected adverse events.

4144 Any SAE will be brought to the attention of the site PIs as soon as possible and not longer than
4145 24 hours. Any AE or SAE that is both unexpected and related to study participation will be reported
4146 to the IRB within 7 days of the event. The local IRB will make a determination as to whether
4147 additional reporting requirements are needed. IRB actions will be reported to the funding agency
4148 by the PIs no less than annually and more frequently as recommended by the local IRB. Any SAEs
4149 will be summarized in the yearly Progress Reports to the funding agency, including a review of
4150 frequency and severity. All SAEs will be followed through ongoing consultation with the physician
4151 caring for the patient until they resolve, result in death, or stabilize and are not expected to

4152 improve. The study staff will be in close contact with participants and health care providers
4153 throughout the study to monitor for potential unanticipated problems. Any unanticipated problems
4154 will be discussed at the weekly research staff meetings and reported as required to the local IRB.
4155

4156 13. Withdrawal or Monitoring of Participants

4157 **For the participant's protection, participants will be withdrawn immediately from the study if**
4158 **any of the following occur:**

- 4159 1) Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA
4160 (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial
4161 blockages in arms or legs leading to procedure or surgery). Less common CVD problems
4162 would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g.,
4163 mitral or aortic regurgitation).
- 4164 2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous
4165 system).
- 4166 3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time
4167 during participation in the study.
- 4168 4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for
4169 psychiatric reasons at any time during participation in the study.
- 4170 5) Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at any
4171 time during the study, she will be withdrawn from the study, and this event will remain open
4172 until delivery. At that time the licensed medical professional will contact the participant to
4173 ask a few questions about the baby's health and will update the open 'Medical Event Form'.
4174 A positive pregnancy test at Week 16 will trigger a 'Medical Event Form' to be completed
4175 but will not result in withdrawal since she is no longer receiving study product.
- 4176 6) Expired breath carbon monoxide increase: A participant will be withdrawn from the study if
4177 the average of two consecutive CO readings during the same visit is 100 ppm or greater.
- 4178 7) Marked increase in smoking: A participant will be withdrawn from the study if he/she meets
4179 **BOTH** of the following criteria for two consecutive weeks
 - 4180 a. Cigarette per day increase: The average CPD increases by more than 100% from
4181 the average CPD during baseline.
 - 4182 b. Expired breath carbon monoxide increase: If the average of two consecutive CO
4183 measurements in the same visit is
 - 4184 i. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
 - 4185 ii. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
 - 4186 iii. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
 - 4187 iv. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
 - 4188 v. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
 - 4189 c. Note: If the second consecutive visit is the last study visit, then the participant
4190 would not be withdrawn from the study.
- 4191 8) If a participant is discharged from or discontinues his or her methadone or buprenorphine
4192 treatment, they will be discontinued from the study.
4193

4194 **The following will be monitored and can lead to the participant being withdrawn by the PI or**
4195 **Licensed Medical Professional:**

- 4196 1) Cigarettes per day increase: Continued participation will be evaluated by the site PI if the
4197 average number of cigarettes per day (CPD) increases by more than 100% from the
4198 average CPD during baseline as determined by CPD at Baseline 2.
- 4199 2) Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-
4200 enrollment: 1) BP is at or above 160/100 or below 90/50, or 2) HR is at or above 115 bpm or
4201 below 45 bpm a manual blood pressure and heart rate measurement will be taken after 10

4202 minutes have passed. If the manual reading is still out of range, a 'Blood Pressure and Heart
4203 Rate Symptom Checklist' and 'Medical Event Form' will be completed, and the participant
4204 will be monitored by the medical professional.

- 4205 3) Expired breath Carbon Monoxide increase: If the average of two consecutive CO
4206 measurements meets the criteria below then the 'Medical Event Form' will be completed
4207 and the participant will be monitored by the medical professional.
- 4208 a. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
 - 4209 b. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
 - 4210 c. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
 - 4211 d. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
 - 4212 e. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
- 4213 4) Any hospitalization or debilitation in which participation in the study could be detrimental to
4214 the recovery process. This will be self-reported by the participant and will be reviewed by
4215 the site PI and medical professional to determine whether continued participation in the study
4216 is appropriate.
- 4217 5) If a participant is behaving in an inappropriate or threatening manner, admits to lying about
4218 eligibility criteria, is participating in other smoking research studies that could affect the
4219 primary outcome measures, etc., then the PI can withdraw him/her from the study at the
4220 PI's discretion.
- 4221 6) If a participant fails to attend regularly scheduled research assessment visits or comply with
4222 the research procedures or schedule, then the PI can withdraw him/her from the study at the
4223 PI's discretion.
- 4224 7) Increase in psychiatric symptoms: Exacerbation in symptoms noted during the study (i.e.,
4225 change in BDI category from mild to moderate or moderate to severe) will trigger review by
4226 the study's licensed medical professional. The PI will withdraw the participant upon the
4227 licensed medical professional's recommendation.
4228

4229 **14. Data Safety Monitoring Board**

4230 A Data and Safety Monitoring Board (DSMB) has been established to monitor safety outcomes
4231 and will be comprised of four members. The DSMB will be chaired by Kevin Delucchi, PhD.,
4232 Professor in Residence of Biostatistics in Psychiatry at the University of California San Francisco
4233 and Director of the Quantitative Core of the San Francisco Treatment Research Center; Eden
4234 Evins, MD, MPH., Cox Family Professor of Psychiatry at Harvard Medical School and Director of
4235 Center for Addiction Medicine at Massachusetts General Hospital; Ari Kirshenbaum, PhD,
4236 Professor of Psychology at Saint Michael's College who he teaches courses in
4237 psychopharmacology and neuroscience, and currently has grants from NIH and NSF for work in
4238 human behavioral pharmacology and his grant-funded work focuses on cognitive and behavioral
4239 responses to nicotine and cannabinoids; and Elisabeth Johnson, Ph.D., who has over twenty years
4240 of clinical experience in women's health and pediatrics, including caring for women with substance
4241 use disorders.

4242 **Conflict of Interest**

4243 None of the board members will be otherwise affiliated with the center and each member will
4244 complete a conflict of interest disclosure form prior to each meeting. Ad hoc specialists may be
4245 invited to participate as non-voting members at any time if additional expertise is desired.

4246 **Monitoring Activities and Frequency of Meetings**

4247 The DSMB will set their own agenda and decisions about monitoring; e.g. how frequently to
4248 monitor, what threshold requires changes to protocol or stopping the study, and whether to view
4249 raw or analyzed data. The DSMB will be given FDA and EMEA guidelines for DSMBs and recent
4250 reviews on DSMBs. A brief report will be generated from each meeting for the study record and
4251 forwarded to each of the study site's Institutional Review Boards (IRB) and NIDA's Program Officer
4252 with the progress report. The DSMB will be available to convene outside of the regular meetings, if
4253 necessary. If concerns should arise regarding a particular subject, or any troublesome trends in the

4254 experiences of participants, they will make appropriate recommendations for changes in protocol,
4255 as needed. The project investigators will continue to examine safety data, blind to study condition,
4256 in case they wish to make study modifications. Before modifications are made, they will inform the
4257 DSMB and request their comments.
4258

4259 **Communication Plan to IRB, NIDA, and FDA (if applicable)**

4260 All IRBs, the FDA and the NIDA's Program Officer will be informed of any significant action
4261 taken as a result of the Data and Monitoring Board's findings. Study Participants will be informed of
4262 any changes in risk.
4263

4264 **Protection of Confidentiality**

4265 For DSMB meetings only de-identified data, including blinded study site and condition type, will
4266 be provided to the board. All data and discussion during the meeting will be confidential.
4267

4268 **15. Investigational Tobacco Product**

4269
4270 The University of Vermont Center on Tobacco Regulatory Science will complete an
4271 Investigational Tobacco Product (ITP) application with the FDA to cover the experimental
4272 cigarettes being used in this study. This application encompasses both Project 2 sites.
4273

4274 **16. Certificate of Confidentiality**

4275 To help protect the participant's privacy, Dr. Stephen Higgins, PhD, will obtain a Certificate of
4276 Confidentiality from the national Institute on Drug Abuse. With this certificate, the researchers
4277 cannot be forced to disclose information that may identify the participants, even by a court
4278 subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other
4279 proceedings. The researchers will use the Certificate to resist any demands for information that
4280 would identify the participants, except as explained below. The Certificate cannot be used to resist a
4281 demand for information from personnel of the United States Government that is used for auditing or
4282 evaluation of federally funded projects or for information that must be disclosed in order to meet the
4283 requirements of the Federal Food and Drug Administration (FDA).

4284 The Certificate of Confidentiality does not prevent the participant or a member of their family
4285 from voluntarily releasing information about themselves and their involvement in the research. If an
4286 insurer, employer or other person obtains the participant's written consent to receive research
4287 information, then the researcher may not use the Certificate to withhold that information.

4288 The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily,
4289 without consent, information that would identify the individual as a participant of the research
4290 project in instances such as evidence of child abuse or a participant's threatened violence to self or
4291 others.
4292

4293 **17. Outcome Variables**

4294 **Primary Endpoints for Study 3:**

- 4295 1) Cigarette Smoked per Day (CPD)
- 4296 2) Nicotine Dependence Severity

4297 **Secondary Endpoints for Study 3:**

- 4298 1) Measures of adherence: non-study cigarette use, drop-out rate
- 4299 2) Measures of psychiatric symptoms: BDI, OASIS
- 4300 3) Measures of discomfort/dysfunction: MNWS, QSU
- 4301 4) Measures of other health-related behaviors: breath alcohol, urine or salivary drug screen,
4302 TLFB-drug use, Alcohol Use Questionnaire, Drug Use Questionnaire, weight
- 4303 5) Measures of nicotine/tobacco dependence: FTND, WISDM
- 4304 6) Measures of tobacco exposure: CO, total nicotine equivalents, NNN, NNAL, minor

- 4305 alkaloids
 - 4306 7) Measures of intention to quit: Stages of Change, Contemplation Ladder
 - 4307 8) Measures of compensatory smoking: puff topography, filter analysis
 - 4308 9) Measures of other tobacco use: TLFB-other tobacco
 - 4309 10) Measures of cigarette characteristics: CES, Cigarette Purchase Task
 - 4310 11) Measures of cardiovascular function: heart rate, blood pressure, urine 11-dehydroTXB2
 - 4311 12) Measures of perceived risk: Perceived Health Risk Questionnaire
 - 4312 13) Safety outcome variables: Adverse Events (AEs), Serious Adverse Events (SAEs)
 - 4313
 - 4314
 - 4315
-

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STUDY PROTOCOL: SMOKERS WITH SOCIOECONOMIC DISADVANTAGE (WOMEN OF REPRODUCTIVE AGE)

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- 3HC: 3-hydroxycotinine
- BAL: Breath alcohol levels
- BDI: Beck's Depression Inventory
- BMI: Body Mass Index
- BP: Blood pressure
- BPM: Beats per minute
- BRIEF-A: Behavioral Rating Inventory of Executive Function
- CES: Cigarette Evaluation Scale
- CO: Carbon monoxide
- COT: Cotinine
- CPD: Cigarettes per day
- CPT: Cigarette Purchase Task
- CPT: Continuous Performance Task
- DAST: Drug Abuse Screening Test
- DDT: Delay Discounting Task
- D-KEFS: Delis-Kaplan Executive Function System
- EDC: Electronic Data Capture
- EQ-5D: Euro-Qol
- FSPTCA: Family Smoking Prevention and Tobacco Control Act
- FTND: Fagerström Test for Nicotine Dependence
- GAD: Generalized Anxiety Disorder
- HR: Heart rate
- IVR: Interactive Voice Response
- MDD: Major Depressive Disorder
- MINI: Mini International Neuropsychiatric Interview
- MNWS: Minnesota Nicotine Withdrawal Scale
- NMR: Nicotine metabolite ratio
- NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
- NNC: Normal nicotine content
- NNN: *N*-nitrosonornicotine
- OASIS: Overall Anxiety Severity and Impairment Scale
- OUD: Opioid Use Disorder
- PANAS: Positive and Negative Affect Schedule
- PHQ: Patient Health Questionnaire
- PSS: Perceived Stress Scale
- QSU: Questionnaire of Smoking Urges
- RNC: Reduced nicotine content
- SST: Stop Signal Task
- TLFB: Timeline Follow Back
- TPQ: Time Perspectives Questionnaire
- VLNC: Very low nicotine content
- WASI-II: Wechsler Abbreviated Scale of Intelligence-II
- WISDM: Wisconsin Index of Smoking Dependence Motives

Protocol

1. OBJECTIVE

Despite marked reductions in cigarette smoking prevalence in the general U.S. adult population over the past approximately 50 years, smoking rates among women have decreased at a slower rate and have even increased among socioeconomically disadvantaged women where smoking prevalence can be as high as 40%. Smoking among women of reproductive age is a particular concern related to the potential for serious complications should they become pregnant, although smoking also increases risk for other serious adverse impacts on women's reproductive health including cervical cancer. Each of these potential smoking-related adverse health impacts are exacerbated by socioeconomic disadvantage, which is associated with heavier smoking, greater prevalence and severity of nicotine dependence, and a lower likelihood of quitting.

A national policy of reducing the nicotine content of cigarettes has the potential to be an effective method of reducing prevalence of cigarette smoking and associated adverse health outcomes. Controlled trials in the general population of smokers demonstrate that reduced nicotine content cigarettes decrease smoking rates, dependence, and toxin exposure.

Furthermore, our research during the current funding period indicates that reducing the nicotine content of cigarettes decreases the addiction potential of smoking in socioeconomically disadvantaged women, and other groups vulnerable to tobacco addiction. However, tobacco market conditions are likely to exert considerable influence over the extent to which the potential of this promising policy is realized. We hypothesize that the following two conditions will have significant moderating effects on disadvantaged women and other vulnerable populations due to their higher rates of heavy smoking, dependence, and difficulty quitting: (1) having reinforcing alternative sources of non-combusted nicotine readily available and (2) having those alternatives available under conditions that optimize appeal.

The overall goal of the proposed research is to experimentally model whether the availability and appeal of an alternative, non-combusted source of nicotine (i.e., e-cigarettes) will enhance the effectiveness of a reduced nicotine policy for cigarettes in socioeconomically disadvantaged women of reproductive age. Daily female smokers (ages 21-44) will undergo a baseline assessment period and then be randomized to one of the following four conditions: (1) normal nicotine content cigarettes (NNCCs) alone, which will serve as the control condition, (2) very low nicotine content cigarettes (VLNCCs) alone, (3) VLNCC's + nicotinized tobacco-flavored e-cigarettes (TF e-cigs), or (4) VLNCC's + nicotinized preferred flavor e-cigarettes (PF e-cigs). Participants will be asked to use only their assigned products for 16 weeks, and will visit the laboratory weekly to complete measures of smoking topography, cigarette demand using behavioral-economic purchase tasks, withdrawal and craving, and biomarkers of toxicant exposure. In Week 17, participants will be given monetary incentives to abstain from combusted cigarette use for a week and we will assess effects on cigarettes per day (CPD), cigarette demand, and craving and withdrawal.

This research will address the following specific aims:

Aim 1 (Primary): Compare the effects of (1) NNCCs alone, (2) VLNCCs alone, (3) VLNCC's + TF e-cigs, or (4) VLNCC's + PF e-cigs flavoring on total number of CPD. We hypothesize that at Week 16, cigarette smoking rates will have decreased in a linear, graded manner (condition 4 > 3 > 2 > 1) with the largest reduction in smoking rate from control levels observed in the VLNCC's + PF e-cigs condition.

Aim 2 (Secondary): To compare the effects of the four study conditions on cigarette demand, smoke exposure (breath carbon monoxide) and tobacco carcinogen biomarkers (NNAL, PAH metabolites). We hypothesize that at Week 16, cigarette demand and these biomarkers will have decreased in a linear, graded manner with the largest reduction observed in the VLNC's + PF e-

4820 cig condition.

4821 Aim 3 (Exploratory): To explore the effects of the four study conditions on abstinence- induced
4822 cigarette demand, craving, and withdrawal in socioeconomically disadvantaged women of
4823 reproductive age.

4824 The integrative theme of this TCORS is vulnerable populations. The proposed research is
4825 relevant to FDA CTP's scientific domains of Addiction and Behavior by addressing whether
4826 reducing the nicotine content of cigarettes reduces cigarette use, dependence, and product
4827 appeal, and whether these effects are enhanced by availability of appealing alternative sources of
4828 non-combusted nicotine. It addresses Health Effects by assessing tobacco toxicant exposure and
4829 other biomarkers. The proposed study is significant and innovative by modeling the impact of a
4830 national reduced nicotine standards policy for cigarettes in this understudied population. Finally, it
4831 is programmatic as it builds upon and extends the work our team accomplished during the current
4832 funding period.

4833 2. SIGNIFICANCE

4834
4835 The 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA) gives the Food and
4836 Drug Administration (FDA) regulatory authority over tobacco products, including nicotine levels in
4837 cigarettes. That is an exciting development as it creates the opportunity to examine the Benowitz
4838 and Henningfield hypothesis¹ that smoking prevalence, nicotine dependence, and smoking-
4839 related morbidity and mortality can be lowered substantially by reducing the nicotine content of
4840 cigarettes to non-addictive levels. Computer modeling predicts that reducing nicotine levels in
4841 cigarettes would produce substantial improvements in population health.² An essential initial step
4842 towards the implementation of such a policy is to thoroughly investigate its potential effectiveness,
4843 safety, and potential unintended adverse consequences. Indeed, the FDA's Center for Tobacco
4844 Products (FDA CTP) seeks to continue programs of multidisciplinary research to assist with the
4845 mission of investigating such regulatory matters related to the FSPTCA (see RFA-OD-17-006).
4846 The FDA explicitly notes that researching tobacco regulatory questions, including the Scientific
4847 Domains of addiction and behavior, in vulnerable populations is a crosscutting agency priority,
4848 listing women of reproductive age (21-44) among the vulnerable populations of interest.

4849 Despite marked reductions in cigarette smoking prevalence in the general U.S. adult
4850 population over the past approximately 50 years, smoking rates have decreased at a slower rate
4851 among women than men, and even increased among economically disadvantaged women.^{3,4} We
4852 recently examined tobacco and other nicotine delivery product use among women of reproductive
4853 age using the first wave of data from the Population Assessment of Tobacco and Health (PATH)
4854 dataset.^{5,6} Approximately 21% were current smokers, but smoking was strikingly overrepresented
4855 among socioeconomically disadvantaged women with nearly twice as many women of
4856 reproductive age with a high school degree or less being current smokers compared to
4857 women with more education (35% vs. 19%, respectively). These data underscore a robust
4858 and pervasive inverse association between educational attainment and smoking among women of
4859 childbearing age.⁷⁻¹⁰

4860 2.1 Special Health Risks of Smoking Among Women

4861 In addition to the adverse health consequences of smoking that cross genders, smoking also has
4862 adverse consequences specific to women's reproductive health. Women who smoke have an
4863 increased risk of cardiovascular disease, with women who smoke and use oral contraceptives – a
4864 common combination among women of reproductive age - having a dose-dependent higher risk of
4865 heart attacks and strokes.^{11,12} Women who smoke also have increased risk of cervical cancer,
4866 infertility, and early menopause.¹³⁻¹⁶ Rates of unintended pregnancy are also high in this
4867 population (61%),¹⁷ while smoking cessation during pregnancy is relatively low (25-35%),^{6, 18, 19}
4868 introducing additional risk for serious adverse maternal and fetal/neonatal consequences. For
4869 example, smoking during pregnancy increases risk for placenta previa, placental abruption,
4870 premature rupture of membranes, and preterm delivery. Meta-analyses report increased risks of

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20-90% for these complications among smokers, with the highest risks among heavier smokers.²⁰⁻²² A robust relationship between smoking and intrauterine growth retardation (IUGR) has also been demonstrated in many studies,¹⁵ with increased risks of more than 50% among smokers.^{23,24}

2.2 Empirical Evidence on Reduced Nicotine Content Cigarettes

While results of extended exposure to very low nicotine content cigarettes (VLNCCs) among more socioeconomically stable smokers are quite promising, little is known about specific effects that VLNCCs may have in disadvantaged women and other more vulnerable populations. With these more medically and socially unstable populations, it was agreed that an acute, laboratory model was an appropriate and safe setting to begin examining reduced nicotine content cigarettes. As described in more detail in the Overall Plan (Section 5.C.3), during the current funding period we completed multisite, double-blind, within- subject assessments of acute response to research cigarettes with varying nicotine content; the first was a small pilot study²⁵ followed by three larger multisite trials.²⁶ Participants in these studies were socioeconomically disadvantaged women of reproductive age (21-44), women and men with affective disorders, and women and men with opioid dependence, as smoking prevalence in each of these populations is significantly above prevalence for the U.S. adult population (30%, 32% and 92% vs. 21%, respectively) (National Survey on Drug Use and Health, 2016).²⁷

Following brief smoking abstinence, participants were exposed to the varying nicotine dose cigarettes (0.4, 2.3, 5.2, 15.8 mg nicotine/g tobacco) across fourteen 2-4 hour outpatient test sessions. Addiction potential of the cigarettes was assessed using concurrent choice testing and behavioral economic simulation modeling (i.e., Cigarette Purchase Task). Subjective effects were assessed using validated questionnaires, and smoking topography and smoke exposure by a Clinical Research Support System (CRess) device and expired breath carbon monoxide testing, respectively. In both reports and in all three populations, reducing nicotine content decreased the reinforcing value of smoking. The 0.4 mg/g dose differed significantly from the 15.8 mg/g dose (representative of the nicotine content of commercial cigarettes) across all measures of addiction potential, including preference in concurrent choice testing (Figure 1, Panel A). The only difference between populations in that regard was seen in the 0.4 versus 2.4 mg/g dose comparison, where smokers with affective disorders chose the higher dose more often, while disadvantaged women and those with opioid dependence did not exhibit a significant preference between those two doses. Importantly in terms of regulatory implications, preference for higher over lower nicotine- content cigarettes could be reversed by increasing cost of obtaining the higher dose (Figure 1, Panel B). All doses reduced withdrawal symptoms; compensatory smoking was not observed. The consistency of effects noted across the three vulnerable populations underscores the generality of these results, especially regarding the control that nicotine content exerts over smoker preferences despite considerable individual differences.

These initial studies assessed acute response in a laboratory setting, leaving unanswered whether results can be generalized to vulnerable populations chronically using reduced nicotine content cigarettes in naturalistic settings. That question is being answered in our multisite, double-blind field trials in the same three vulnerable populations which are currently underway. Preliminary results for total CPD (study and non-study cigarettes) from initial study completers in each population (41 economically disadvantaged women of reproductive age (non-pregnant), 35 individuals with opioid dependence, and 49 individuals with affective disorders) are shown in

Figure 1

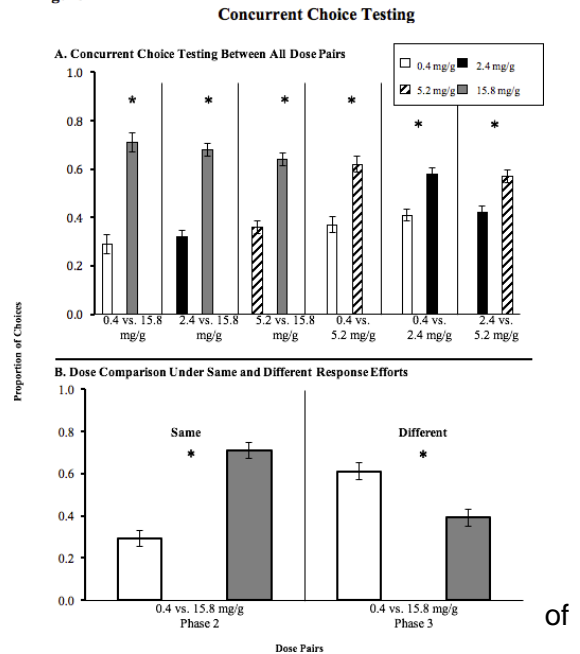


Figure 2. We show results for the 15.8 mg/g control dose representative of commercial cigarettes and the VLNC 0.4 mg/g dose. Mean CPD was significantly lower among those assigned to the VLNC than control cigarette at the 12-week assessment among disadvantaged women ($p=.03$, $d=0.70$) and smokers with affective disorders ($p<.006$, $d=0.81$), but not those with opioid dependence ($p = .25$, $d=.38$). These preliminary results provide encouraging initial evidence that these vulnerable populations are sensitive to the effects of VLNCs on smoking rate. Fagerstrom dependence total scores at 12 weeks are also decreased significantly among those assigned to VLNCs compared to the 15.8 mg/g dose in the disadvantaged women and those with affective disorders but not the opioid dependent population, although we are not yet seeing any evidence of VLNCs increasing measures of quitting in any of the three populations, which, while still preliminary, could represent an important difference in response to VLNCs between healthier and more vulnerable populations of smokers in whom rates of quitting are well known to be lower.

Our work during the Phase 1 funding period indicates that economically disadvantaged women, like more socioeconomically stable smokers, respond to reductions in the nicotine content of cigarettes with reductions in cigarette demand and other measures of addiction potential. However, tobacco market conditions are likely to exert considerable influence over the extent to which the promising effects of reduced-nicotine cigarettes are realized in the natural environment. This may be particularly true of female smokers, who are more motivated to smoke for nonpharmacological reasons as compared to men (e.g.,²⁸). Use of electronic cigarettes (e-cigarettes) is increasing sharply in the US and it is important to consider the potential effects of e-cigarette use on a nicotine reduction policy for cigarettes. We believe that encouraging the use of e-cigarettes, by making them more appealing to smokers, may enhance the efficacy of a reduced-nicotine policy for cigarettes.

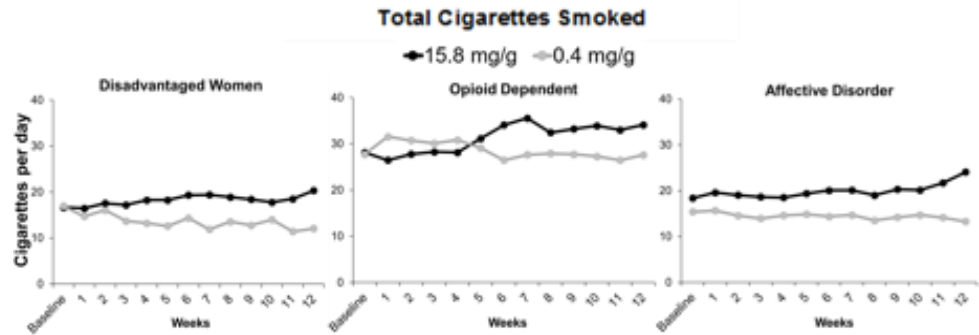


Figure 2. Total cigarettes smoked across 12-week period in three vulnerable populations.

reduced-nicotine cigarettes are realized in the natural environment. This may be particularly true of female smokers, who are more motivated to smoke for nonpharmacological reasons as compared to men (e.g.,²⁸). Use of electronic cigarettes (e-cigarettes) is increasing sharply in the US and it is important to consider the potential effects of e-cigarette use on a nicotine reduction policy for cigarettes. We believe that encouraging the use of e-cigarettes, by making them more appealing to smokers, may enhance the efficacy of a reduced-nicotine policy for cigarettes.

2.3 Relevance of the Project to the Integrative Theme and Goals of the TCORS

The integrative theme of this TCORS is **vulnerable populations**, and its goals are to model the potential effects of tobacco product standards on product use in vulnerable populations, with the goal of reducing the risks of product use, dependence, and product-related adverse health outcomes. For the FDA to effectively execute its tobacco regulatory responsibilities, it must have sound scientific evidence on how product standards impact tobacco use in populations with high rates of tobacco dependence. Our goal is to provide the FDA with that evidence. This project is relevant to that goal because it will examine the effects of a reduced-nicotine standard for cigarettes, alone and combined with another FDA-regulated product, e-cigarettes, on measures of cigarette use, demand, dependence and tobacco toxicant exposure in this vulnerable population.

2.4 Relevance to the Scientific Domains and Priorities of the FDA CTP

This project is highly relevant to CTP's domain of **Addiction** ("understanding the effect of tobacco characteristics on addiction and abuse liability"). By comparing the effects of VLNCs and NNCCs on smoking rates and cigarette dependence this project addresses the first priority in this domain, which is understanding the impact of changes in tobacco product characteristics on dependence. By examining whether e-cig availability and flavors that increase e-cig appeal increase the effects of VLNCs on smoking, this project addresses the second priority in this domain, which is understanding differences in dependence and tobacco use patterns with use of low-nicotine content cigarettes in context with other tobacco products. Several other domains and priorities of the FDA CTP will also be addressed. The **Health Effects** domain refers to

4978 understanding the short- and long-term health effects of tobacco products. This project will
4979 address this domain by assessing effect of VLNCCs alone and with e-cigs on biomarkers of
4980 tobacco-related carcinogen exposure and respiratory disease. The **Behavior** domain refers to the
4981 goal of understanding knowledge, attitudes, and behaviors related to tobacco product use and
4982 changes in tobacco product characteristics. This project will assess this domain by examining how
4983 reducing the nicotine content of cigarettes and e-cig flavors affect measures such as product
4984 appeal, health risk perceptions, and cigarette use.

4985 **2.5 How Study Outcomes Will Improve Scientific Knowledge Related to the Manufacture,** 4986 **Distribution and Marketing of Tobacco Products.**

4987 Study outcomes will directly inform scientific knowledge concerning tobacco product
4988 manufacturing by testing whether a reduction in nicotine content of cigarettes to ≤ 0.4 mg
4989 nicotine/g tobacco would reduce smoking in this vulnerable population. The outcomes will also
4990 indicate whether continuing to allow the sale of flavored e-cigs improves the efficacy of a reduced-
4991 nicotine standard for cigarettes on smoking reduction in this population.

4992 **3. RATIONALE**

4993 **3.1 Use and Effects of E-Cigarettes**

4994 E-cigarettes consist of a cartridge containing an e-liquid solution of nicotine, propylene glycol
4995 (PG), vegetable glycerin (VG), flavorings, and other additives, which is heated with a battery-
4996 operated atomizer that vaporizes the solution. The vapor is inhaled and absorbed through the
4997 mouth, throat and lungs. E-cigarette subtypes include first generation products that resemble
4998 cigarettes (“cigalikes”) and are disposable or rechargeable, second generation products that
4999 often resemble pens and have reservoirs that are refilled using e- liquid purchased separately,
5000 and third generation devices that have use larger batteries, adjustable power delivery and
5001 replacement heating coils and wicks.²⁹ Nicotine levels from e-cigarettes can be comparable to
5002 those observed with cigarettes, depending on e-cigarette characteristics, e-liquid nicotine content
5003 and user topography.³⁰⁻³³ Potential risks of e- cigarette use include exposure to low levels of
5004 carcinogens, toxicants and metals in the vapor, and cytotoxic effects of flavors.^{34,35} However, toxin
5005 and carcinogen levels from e- cigarettes appear to be far lower than those from cigarettes.^{36,37}
5006 Former smokers who had switched to e-cigarettes had 59-99% lower levels of 6 tobacco toxicant
5007 and carcinogen metabolites than ongoing smokers,³⁶ which were comparable to reductions seen
5008 in smokers who had switched from cigarettes to nicotine lozenges.³⁸ Another study found that
5009 NNAL, a metabolite of the tobacco-specific carcinogen NNK, was reduced by 57% in 20 smokers
5010 who had switched to e-cigarettes for one week and by 64% in those who had switched for 2
5011 weeks.³⁹

5012 **3.2 E-cigarette Prevalence**

5013 E-cigarette use is increasing sharply in the US and may be particularly so among women, with
5014 uptake of e-cigarettes in recent years faster in females than males⁴⁰ and initial satisfaction with e-
5015 cigarettes higher among women than men.⁴¹ We recently examined tobacco and other nicotine
5016 delivery product use among non-pregnant and pregnant women of reproductive age using the first
5017 wave of data from PATH and found that 6.2% and 4.9% were current e-cigarette users,
5018 respectively, but current cigarette smokers were orders of magnitude more likely (~ 86 times in
5019 non-pregnant women) to currently use e-cigarettes compared to never smokers.^{5,6} Another recent
5020 study we conducted surveyed 800 women of reproductive age using Amazon Mechanical Turk
5021 and also found that e-cigarette use was significantly higher among current cigarette smokers and
5022 associated with use of nicotine replacement products and other activities consistent with trying to
5023 reduce or quit smoking.⁴²

5024 **3.3 E-cigarette Effects on Smoking**

5025 To date, randomized clinical trials of e-cigarette effects on smoking show significant
5026 reductions in CPD, although little effect on quitting.⁴³⁻⁴⁵ Modest effects on quitting in these trials
5027 may have been due to use of first generation e-cigarettes that provided variable nicotine delivery
5028 and are subject to battery failure.⁴⁶ A trial using second generation e- cigarette devices found a

5029 cigarette abstinence rates of 34% after 8 weeks of use and 21% 6 months later, with an overall
5030 reduction in CPD of 60%.⁴⁷ E-cigarettes may reduce cigarette smoking by reducing cigarette
5031 craving and nicotine withdrawal symptoms.⁴⁸ Although early studies found that e-cigarettes were
5032 less effective than cigarettes at reducing cigarette craving and withdrawal,⁴⁹⁻⁵¹ second-generation
5033 e-cigarettes (those with characteristics most similar to the product proposed for this study) reduce
5034 craving and withdrawal under natural *ad lib* puff topography conditions.^{30,47,52}

5035 E-cigarette effects on cigarette craving and withdrawal symptoms are determined by the
5036 extent to which e-cigarettes are used by smokers. One factor that impacts e-cigarette use is
5037 flavors. More than two-thirds of current adult e-cigarette users in 2013-2014 used a flavored e-
5038 cigarette.^{53,54} Flavors in e-cigarettes have been shown to substantially enhance the subjective
5039 appeal and relative reinforcing effects of e-cigarettes^{55,56} and have been cited as a reason for e-
5040 cigarette use among adults^{54,57} and key feature of e-cigarette products.⁵⁸ Experimental studies
5041 show that flavors increase demand for e-cigarettes among cigarette smokers.^{59,60} particularly
5042 smokers who are not current e-cigarette users.⁶⁰ Studies of e- cigarette users also highlight that
5043 flavors play an important role in their experience of the product⁶¹⁻⁶³ and in reducing cigarette
5044 consumption and craving.^{62,64}

5045 Few studies have examined the effects of e-cigarettes expressly in women. One recent study
5046 reported on gender effects in a study comparing smokers of combusted cigarettes to experienced
5047 dual users of combusted cigarettes and e-cigarettes and examined gender effects.⁶⁵ All
5048 participants engaged in week-long periods of *ad lib* use interspersed with periods of
5049 combusted cigarette reduction. Compared to smokers of combusted cigarettes, dual users
5050 smoked the same number of cigarettes during *ad lib* periods, but quadrupled their use of e-
5051 cigarettes during smoking reduction periods and were more successful at achieving smoking
5052 reduction. Among women, dual use was associated with higher nicotine levels and greater
5053 withdrawal suppression compared to women smoking combusted cigarettes. These results
5054 suggest that e-cigarettes may be a meaningful alternative to combusted cigarettes among
5055 women. Also encouraging in terms of the aims of the proposed study are data showing that
5056 women are more likely than men to use flavored (e.g., menthol, fruit, candy/sweet flavors) tobacco
5057 products compared to men.^{54,66} Another recent survey of women of reproductive age who have
5058 used e-cigarettes reported that 71% of them have used flavored e-cigarettes.⁶⁷

5059 **3.4 Products to be Tested**

5060 Cigarettes to be assessed

5061 The cigarettes to be used in this study were made under an NIH contract with production being
5062 overseen by the Research Triangle Institute (referred to as "Spectrum cigarettes"). NIH currently
5063 has approximately 10 million of these cigarettes (of varying types) for research purposes. The
5064 cigarettes selected for the study span the range of yields likely to produce the hypothesized
5065 effects, as described above. Spectrum cigarettes are not currently commercially available,
5066 although they are similar in many ways to marketed cigarettes (e.g., similar manufacturing, filter,
5067 paper, etc.).

5069 E-cigarettes to be assessed

5070 Both the JUUL and the Vuse Solo will be used and assessed in this study. While JUUL will be
5071 offered to all participants, participants that are unwilling to use JUUL will be offered the Vuse Solo.

5072 JUUL is a commercially available closed system containing two components. One component
5073 contains a lithium-ion battery (200 mAh), nichrome coil heater, silica wick, and stainless steel
5074 vapor path. The other component is the prefilled e-liquid container that also serves as the
5075 mouthpiece. Each commercially available cartridge holds approximately 0.7 mL of e-liquid
5076 containing approximately 40 mg of nicotine or 5% nicotine by weight (NBW). A lower dose
5077 containing approximately 23 mg of nicotine per cartridge or 3% NBW is also marketed but will not
5078 be used in this study. All containers contain glycerol, propylene glycol, natural oils, extracts and
5079 flavors, nicotine, benzoic acid. We will not alter the e-liquid in any way. The research staff will
5080 distribute the e-liquid containers as purchased from the manufacturer. The JUUL apparatus and

5081 5% NBW e-liquids that will be used are legally purchasable and have been as of August 8, 2016.
5082 We will not alter them in any way.

5083 Vuse Solo is a commercially available closed system containing two components. The
5084 power/heating device includes a 270 mAh battery, silica wick, microchips, and sensor. The other
5085 component is the prefilled e-liquid container. Each commercially available cartridge holds
5086 approximately 1 mL of liquid containing 48 mg of nicotine or 4.8% NBW. All containers contain
5087 vegetable glycerin, propylene glycol, reverse-osmosis water, glycerin, flavorings, and nicotine.
5088 The research staff will distribute the e-liquid containers as purchased from the manufacturer. The
5089 Vuse apparatus and e-liquid cartridges that will be used are legally purchasable and have been as
5090 of August 8, 2016. We will not alter them in any way.
5091

5092 **3.5. Summary**

5093 Although cigarette smoking is declining in the overall US population, smoking rates have
5094 decreased at a slower rate among women than men, and even increased among
5095 economically disadvantaged women. Data from the current funding period indicate that VLNCCs
5096 significantly reduce addiction potential of smoking during acute exposure and reduce overall
5097 smoking rates during extended exposure in disadvantaged women and it is highly encouraging
5098 that a policy of reduced nicotine standards in cigarettes can benefit this vulnerable population.
5099 However, considering the modest effects of VLNCCs on quitting thus far in studies in the general
5100 population of smokers, and the difficulties that disadvantaged women and other vulnerable
5101 populations have with quitting smoking, we believe that other market conditions may need to be in
5102 place for the considerable potential of reduced nicotine standards to be realized. One such policy
5103 that we deem critical is the ready availability of alternative, non-combusted sources of nicotine.
5104 The elevated rates of e-cig uptake among women noted above indicate that they find e-cigs highly
5105 reinforcing, which is encouraging. We also believe that the appeal of e-cigs will have to be
5106 enhanced. The method for enhancing appeal that we are proposing to investigate is availability of
5107 flavors. That market condition also appears to have considerable potential to benefit
5108 disadvantaged women in light of the greater preference that women have for flavored tobacco
5109 products.

5110 So, while there is considerable reason for optimism, there is also tremendous need for
5111 empirical evidence as there has only been a single controlled study reported examining how the
5112 effects of VLNCCs are moderated by the availability of non-combusted sources of nicotine, and
5113 that was a preliminary study in the general populations of smokers. As such, the proposed study
5114 has the potential to contribute significant new knowledge of relevant to the FDA CTP regarding
5115 the potential impact of a reduced nicotine standards policy in this vulnerable population of
5116 smokers. The research is also programmatic, as it will build on and complement the work that the
5117 UVM TCORS team of investigators has accomplished during the current funding period on the
5118 effects of reduced nicotine content cigarettes in disadvantaged women and other vulnerable
5119 populations.
5120

5121 **4. Project Study Methods**

5122 This study will use a four-condition, parallel-groups research design. After a baseline period in
5123 which daily smoking rate and other baseline assessments are completed, participants will be
5124 randomly assigned to one of the following four conditions for a 16-week experimental period: (1)
5125 normal nicotine content cigarettes (NNCCs, 15.8 mg/g) alone, which serves as the control
5126 condition; (2) very low nicotine content cigarettes (VLNCCs, 0.4 mg/g) alone; (3) VLNCCs +
5127 tobacco-flavored nicotine e-cigs (TF e-cig, 4.8 - 5.0% nicotine by weight, NBW, if they choose
5128 to use the Vuse or JULL device, respectively); or (4) VLNCCs + preferred-flavor nicotine e-
5129 cigarette (PF e-cig).
5130

5131 **5. Study Screening Procedures**

5132 **5.1 Participants** 5133

5134 Participants will be women ages 21–44 years who have a high school education or less. For
5135 inclusion, participants must smoke ≥ 5 cigarettes per day, have smoked daily for ≥ 1 year and
5136 have breath CO levels ≥ 8 ppm or have positive urine cotinine results. Additionally, they must be
5137 sufficiently literate to complete the research tasks, be in good physical health without serious
5138 illness or change in health in past three months, and have the technological capabilities to
5139 complete weekly face-to-face video assessments and the compatibility to use ico Smartphone
5140 Smokerlyzers for assessing breath carbon monoxide (CO) levels. Exclusionary criteria: We will
5141 exclude those under the age of 21 for scientific and legal reasons. We will exclude pregnant and
5142 nursing women and women not reporting use of contraceptives, anyone currently using nicotine
5143 replacement, bupropion or other pharmacotherapies as cessation aids, those who report daily use
5144 of e-cigarettes in the past 30 days as they may not be compliant with the study e-cigarettes, and
5145 anyone intending to quit within 3 months, as participation in this study may not reduce smoking
5146 and could increase smoke and/or nicotine exposure. Those who exclusively use roll-your-own
5147 cigarettes or who use other non-cigarette tobacco products (e.g., cigars, smokeless) ≥ 10 days in
5148 the past 30 days are excluded because their use of these products may reduce the validity of our
5149 main outcome measure, total cigarettes per day (which includes study and non-study cigarettes).
5150 The following conditions are excluded as they could affect participants' abilities to complete the
5151 study: unstable medical or medication conditions (significant changes in a serious medical
5152 condition in the past 3 months, medication changes in the past 4 weeks; details provided in
5153 Protection of Human Subjects section), symptoms of psychosis or dementia, past-month
5154 suicidality, suicide attempt in the past 6 months, current (past-6 months) alcohol or substance use
5155 disorders other than nicotine, positive toxicology screen for illicit drugs (marijuana allowed; one re-
5156 screen opportunity), positive breath alcohol level (BAL) at screen (one re-screen opportunity).
5157

5158 **5.2 Recruitment**

5159 This study will be conducted at two sites, University of Vermont in Burlington, VT (primary site)
5160 and Johns Hopkins University in Baltimore, MD. This collaboration will permit us to complete
5161 studies in a timely manner, enroll a more ethnically diverse sample, and facilitate meaningful
5162 collaboration across multiple sites, which is one goal of this funding announcement. Power
5163 estimations were based on preliminary evidence from trials conducted during Phase 1 UVM
5164 TCORS funding which included an approximately 15% dropout rate across populations. For the
5165 analyses of primary aims using an intent-to-treat approach, we require 53 randomized in each
5166 condition (212 total) to test our primary aims. We estimate 10% attrition prior to randomization and
5167 will therefore enroll up to 59 per condition (236 total) to randomize 212. In addition, we will pilot
5168 study procedures with 5 participants per e-cigarette condition (10 total).

5169 Participants at both sites will be recruited through Facebook, craigslist, ads in local
5170 newspapers and on community bulletin boards, and through word of mouth. At UVM, individuals
5171 recruited from online sources will be directed to a UVM-hosted recruitment website where they will
5172 have the opportunity to select which research studies interest them. They will then be redirected to
5173 a brief online screener to assess eligibility. Those who contact us by phone will be given a
5174 description of the study and asked questions to assess eligibility. If a participant appears to be
5175 eligible, they will be invited to participate in the first portion of the screening. Research assistants
5176 will inform eligible participants that the screening will occur over video chat, and will assist the
5177 participant with setting up an appropriately secure video platform.

5178 During this first portion of the screening, the participant will complete questionnaires through
5179 REDCap online while the research assistant is present over video chat or phone to deliver
5180 instructions and to answer any questions. The participant will then answer interviewer-
5181 administered questionnaires over video chat. Participants who did not yet set up their video
5182 platforms will do so with the research assistant before beginning any questionnaires. Participants
5183 will be instructed to have picture identification (e.g. driver's license) available to show the staff. If
5184 participants anticipate not having acceptable ID, staff should consult with the project coordinator
5185 or study PI. Initial study eligibility will be determined after data are collected from this visit.
5186 Participants who meet initial study eligibility will be scheduled for the second portion of the
5187 screening.

5188 Before the second portion of the screening occurs, eligible participants will receive the
5189 equipment necessary to use for collecting physiological measurements. Participants will be asked
5190 to pick up this equipment via curbside pickup at our clinic (UVM University Health Center, UHC),
5191 which will consist of participants calling staff once they arrive at UHC and staff coming out to give
5192 participants a bag/box containing the following equipment: a Smokerlyzer; an audio jack adapter
5193 for the Smokerlyzer if necessary; a blood pressure cuff; an oximeter; a thermometer; a urinary
5194 cotinine dipstick; urine cups with attached temperature test strips; a pregnancy test strip (if
5195 applicable) and urine toxicology test strips or a saliva toxicology test. Participants (and staff) will
5196 be asked to use cloth face coverings when exchanging product. Participants may be invited to
5197 come inside to pick up this equipment if the participant is asked to wait for this exchange. All
5198 participants must pass a COVID19 screening before entering the building. If there is any waiting
5199 that needs to occur inside the building, the participant will wait inside one of our five highly
5200 ventilated smoking chambers. If there happens to be no space in the smoking chambers, the
5201 participant will be told that they can not come up to the clinic until space is available. After each
5202 use, the all of the surfaces in the smoking chambers will be cleaned with 70% or greater of
5203 alcohol solution by staff wearing a mask and gloves, as well as all of the door handles. If the
5204 participant uses the bathroom while they are in the clinic, the bathroom surfaces and handles will
5205 be wiped down after use by staff while masks and gloves are worn. Participants who are using the
5206 smoking chambers at any point in the study to wait for product or equipment exchange will remain
5207 in the chambers until a staff member comes to knock on the door to let them out. In this way, we
5208 can avoid people coming into close contact with each other in the larger room that contains the
5209 smoking chambers. A minimum of 6 feet of distance will be maintained for all staff and
5210 participants at all times. For participants who cannot come to the clinic, a commercial courier will
5211 deliver this equipment to them before the second portion of the screening.

5212 If at any point the Smokerlyzers are not available for distribution, we will conduct the CO test
5213 curbside before or after participants are invited inside and the courier service will not be available.
5214 Research Assistants will bring down the CO monitor to the participant. While maintaining 10 feet
5215 of distance and wearing gloves, staff will explain how the CO monitor works. Once the participant
5216 is ready, staff will press the button to obtain the measurement and will set the CO monitor down
5217 and will back away 10 feet. The participant will then come to pick up the device and will blow into
5218 the monitor. After the participant completes the test, they will set down the monitor and back up
5219 10 feet and staff will retrieve the monitor. After every use, staff will wipe down the CO monitor with
5220 disinfectant wipes and hydrogen peroxide wipes. When using the monitor, a D-piece (a portable
5221 valve filter) must be placed into the monitor and then the single use plastic mouthpiece is placed
5222 into the D-piece. The monitor has built in SteriTouch technology to ensure optimum infection
5223 control, and the D- pieces filter out and remove 99.9% of airborne bacteria and greater than 97%
5224 of viruses for excellent infection control. Each participant will be assigned their own D-piece to use
5225 throughout the study, and no D-piece will ever be shared among participants. Participants will
5226 gently exhale into the D-piece for the breath carbon monoxide reading. Participants will be
5227 instructed only to exhale through the device, not to inhale. D-piece technology also includes a
5228 one-way valve that prevents air from being drawn back from the monitor. D- pieces will also be
5229 wiped down after each use with disinfectant wipes and hydrogen peroxide wipes and stored in a
5230 container at the lab.

5231 Once participants have received the necessary equipment to complete the physiological
5232 portion of the screening, the research assistant will initiate a video call with the participant. During
5233 this call, the participant will be instructed on how to use the equipment and then will be asked to
5234 use the equipment to obtain the following physiological readings: blood pressure, heart rate,
5235 oxygen saturation, temperature, and breath CO levels. Participants will also be asked to collect a
5236 urine or saliva sample during the visit. If a saliva sample is collected, the participant you will
5237 provide the saliva sample over video chat while the staff observes. If a urine sample is collected,
5238 staff will ask participant to bring this urine sample to the video screen after collection to perform a
5239 urine toxicology test and a pregnancy test (if applicable). These urine cups will have temperature
5240 strips affixed to ensure that the sample is valid. Participants who have a carbon monoxide level of
5241 less than or equal to 8 will also be asked to use the urinary cotinine dipstick to determine whether

5242 they are positive for cotinine. The participant will obtain the physiological readings and perform
5243 the tests and then will hold the results of the test up to the camera so that the research assistant
5244 can interpret and record the readings on REDCap, Participants will also be instructed to have
5245 handy a pack of their usual brand cigarettes, all prescription medications they are currently taking
5246 and identification (example, driver's license) during this second portion of the screening visit. If
5247 participants anticipate not having acceptable ID site staff should consult with the project
5248 coordinator or study PI.

5249 A participant must complete his/her two-part screening session within 90 days of completing
5250 the pre-screening questionnaire. If the participant is not able to complete the two-part screening
5251 visit in that timeframe, he/she will need to complete the pre-screening questionnaire again.

5252 **5.3 Informed Consent Process:**

5253 Before beginning the informed consent process, potential participants will need to produce
5254 identification as described above. The interviewer will confirm the age and identity of the
5255 participant. If the participant is not between the ages of 21 and 44 or has a degree greater than
5256 high school, she will be dismissed without payment. During the first portion of the screening
5257 session, study information will be presented and documentation of the participant's informed
5258 consent via electronic signature on REDCap will be required prior to participating in the screening
5259 session. In order to ensure adequate informed consent, participants will be asked to read the first
5260 several lines aloud (to determine literacy) and will then be given ample time to read the consent
5261 document. If the interviewer suspects the participant is not literate, he or she will have them
5262 continue reading further to confirm. Inability to read and comprehend written study materials will
5263 result in ineligibility and the interviewer will inform the participant that they are not eligible. Only
5264 after the participant and the researcher are fully satisfied that the participant understands the
5265 purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and his/her
5266 rights as a research participant will the consent form be signed and the participant undergo
5267 screening procedures.

5268 **5.4 Screening Measures**

5269 Those who consent will be screened for eligibility using the following measures:

5270 **The following physiological measures will be collected and recorded directly into REDCap**
5271 **by the interviewer:**

- 5272 1. Expired breath carbon monoxide (CO) levels will be assessed using an ico Smokerlyzer
5273 Smartphone Monitor (Covita – for remote collection) or a Bedfont CO monitor (for curbside
5274 collection), a reliable and valid measure of recent smoking.
 - 5275 a. Urinary cotinine test strips will be used to assess cotinine levels if a participant's CO
5276 reading is less than or equal to 8 ppm.
- 5277 2. A urine or saliva toxicology screen will be performed to assess the presence of illicit drugs
5278 including up to the following drugs: marijuana, cocaine, opiates, oxycodone,
5279 benzodiazepines, barbiturates, amphetamines, methadone, buprenorphine,
5280 methamphetamines, MDMA and PCP. Participants who fail the drug screen for drugs other
5281 than marijuana or their prescribed opioid medication may reschedule the interview but
5282 will need to be re-consented to ensure they have received adequate informed consent. They
5283 will be excluded if they are positive for drugs (other than marijuana or prescribed
5284 medications as determined by PI on a case-by-case basis) the second time.
- 5285 3. Urine Pregnancy Test (HCG detection) will be performed for all participants.
- 5286 4. Blood pressure and heart rate will be measured using an automated blood pressure monitor
5287 and a finger pulse oximeter to help the licensed medical professional determine final
5288 participant eligibility. Participants will be told if their blood pressure is in an abnormal range
5289 and advised to see a doctor by research staff. The research staff will also submit a medical
5290 event form for the LMP to review along with a Blood Pressure and Heart Rate Symptom
5291 Checklist form to ascertain details of the symptomatology for the LMP to review. In severe
5292 cases, the LMP may also choose to call the participant to follow-up and/or withdraw the
5293 participant from the study if necessary. All of these procedures are documented in our Blood

- 5294 Pressure/Heart Rate Collection: Standard Operating Procedure form which we can submit to
5295 the IRB if the Committee deems necessary.
- 5296 5. Body temperature, respiratory rate and oxygen saturation will be added as physiological
5297 measures based on the CDC recommendations and those of Dr. David Kaminsky.
5298 [https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)
5299 [disease/healthcare-providers/index.html](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html)

5300 **The following screening assessment will be administered as an interview:**

- 5302 1) The Mini International Neuropsychiatric Interview (MINI) 7.0⁷⁰

5303 **The following screening assessments will be administered as an interview and entered**
5304 **directly into REDCap by the interviewer:**

- 5305 1) The MINI Plus Modules
- 5306 2) The MINI suicide subscale⁷¹ to evaluate suicide risk.
- 5307 3) MINI Follow-up Questionnaire (if applicable)
- 5308 4) Tobacco Use History and Exposure Questionnaire, which measures variables such as
5309 smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts,
5310 duration of quit attempts and duration of smoking.
- 5311 5) Smoking Cessation Therapy Use Questionnaire
- 5312 6) Time Since Last Cigarette Questionnaire
- 5313 7) Medical History Questionnaire to assess current diagnoses, symptoms and past health
5314 problems.
- 5315 a. Medications will be recorded directly onto the Concomitant Medications form in
5316 REDCap.
- 5317 8) Drug Abuse Screening Test (DAST-10), which assesses quantity and frequency of
5318 alcohol and drug use (12 month and 1 month version)

5319 **The following screening assessments will be completed by the participant directly in**
5320 **REDCap, except where noted otherwise:**

- 5322 1) Demographic History Questionnaire, which will assess age, gender, ethnicity, race,
5323 education, income, marital status, and employment history.
- 5324 2) Alcohol Use Questionnaire---based on the Alcohol Use Disorders Identification Test⁷² (12
5325 month and 1 month version)
- 5326 3) Drug Use Questionnaire---based on the Drug Abuse Screening Test⁷³ (12 month and 1
5327 month version)
- 5328 4) Fagerström Test for Nicotine Dependence (FTND)⁷⁴;
- 5329 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM)⁷⁵ will be
5330 administered to assess nicotine dependence severity.
- 5331 6) Penn State Electronic Cigarette Dependence Index⁷⁶;
- 5332 7) Smoking Stages of Change Algorithm⁷⁷;
- 5333 8) Identifying Information Form will include the participant's REDCap Subject Identifier,
5334 name, address (including the county of residence), email address, phone number, age,
5335 date of birth, and social security number (if applicable).
- 5336 a. This form will be entered into the 'Identifying Information Access Database'.
- 5337 i. Each site will have a separate 'Identifying Information Access Database'.
- 5338 ii. Identifying information will not be shared with other sites. Each site is
5339 responsible for maintaining confidentiality of this information.
- 5340 iii. Identifying information will be kept in a locked file cabinet (source
5341 document) and in a password protected Access Database (electronic
5342 version) separate from all other study data.

- 5343 9) Beck Depression Inventory (BDI-II)⁶⁸, to assess depressive symptoms.
 5344 (This form has been updated on 1.29.20 so as to use the BDI-II. The BDI-II will be used instead of the BDI so
 5345 that the data collected will be directly comparable to other projects using the BDI-II).
- 5346 10) Overall Anxiety Severity and Impairment Scale⁶⁹(OASIS); to assess frequency and
 5347 severity of anxiety symptoms.
- 5348 11) COVID19 Symptom Questionnaire
- 5349 12) Respiratory Symptom Questionnaire will be administered to assess respiratory health

5350
 5351 In the event that the REDCap website is not functioning, the assessments will be
 5352 administered aloud and participant answers will be recorded securely. The interviewer will enter
 5353 the data into REDCap when it resumes functioning properly. This information should be recorded
 5354 in the 'End of Visit Evaluation Form'.
 5355

5.5 Suicidality/Mental Health Monitoring

5357 Participants who endorse suicidal intention in the past month or a suicide attempt in the past
 5358 6 months as indicated on the BDI (score > 1 on question 9) or MINI suicide subscale (endorse
 5359 question 4 and/or 5 on the MINI suicide subscale or question 6 on the MINI suicide subscale with
 5360 suicide attempt in the past 6 months) or answer "yes" to question A3g on the MINI
 5361 Neuropsychiatric interview and symptoms have occurred in the past two weeks will be assessed
 5362 by a clinician for eligibility and possible intervention.. The research staff member will contact a
 5363 licensed clinician for evaluation. In the event that no clinician is available, staff will put the
 5364 participant in contact with the National Suicide Prevention Lifeline at 1-800-273-8255. They will
 5365 also contact the Study Coordinator and Site PI to inform them of the situation as soon as
 5366 possible. Additionally, they will contact the Project Coordinator to inform her of the situation. The
 5367 participant will be paid \$25 (+\$25 bonus if applicable) and provided with local mental health
 5368 resources. Post enrollment, any report of suicidal ideation or attempt by a participant will be
 5369 grounds for immediate withdrawal from the study.

5.6 Inclusion/Exclusion Criteria

Inclusion Criteria:

- 5370
 5371
 5372 1) Women ages 21-44 years who have < an Associates Degree,
 5373 2) Report smoking ≥ 5 cigarettes per day for the past year,
 5374 3) Provide an intake breath CO sample >8 ppm, (if ≤ 8 ppm, then urinary-cotinine strip must
 5375 be positive)
 5376 4) Be without current (within the past year) serious mental disorder that would interfere with
 5377 study results or completion as determined by the licensed medical professional or PI,
 5378 5) Be without current substance abuse/dependence other than nicotine,
 5379 6) Be sufficiently literate to complete the research-related tasks,
 5380 7) Be in good physical health without serious illness or change in health or medication in
 5381 the past three months as determined by the licensed medical professional at each site
 5382 8) Have appropriate equipment to complete face-to-face video assessments and use ico
 5383 Smartphone Smokerlyzer Monitors. For those who do not have a Smartphone, staff will
 5384 explore potential alternate plans (e.g., project-provided inexpensive Android phone)
 5385

Exclusion Criteria:

- 5387 1) Exclusive use of roll-your-own cigarettes;
 5388 2) Planning to quit smoking in the next 30 days;
 5389 3) A quit attempt in the past 30 days resulting in greater than 3 days of abstinence;
 5390 4) Significant use of other tobacco or nicotine products within the past month (more
 5391 than 9 days in the past 30).
 5392 5) Currently taking anticonvulsant medications including:
 5393 a. Phenytoin [Brand Name: Dilantin]
 5394 b. Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]
 5395 c. Oxcarbazepine [Brand Name: Trileptal]

- 5396 d. Primidone [Brand Name: Mysoline]
5397 e. Phenobarbital
5398 6) Positive toxicology screen for any of the following drugs: cocaine, opiates, methadone,
5399 oxycodone, buprenorphine, benzodiazepines, barbiturates, amphetamines,
5400 methamphetamines, MDMA and PCP will be grounds for exclusion.
5401 a. Marijuana will be tested for but will not be an exclusionary criterion. Participants
5402 will be discouraged from smoking marijuana during the study.
5403 b. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, or
5404 amphetamines will not necessarily be excluded.
5405 c. Participants failing the toxicology screen will be allowed to re-screen once. These
5406 participants will need to be re-consented before being rescreened to ensure they
5407 have received adequate informed consent.
5408 7) Self-report of binge drinking alcohol (more than 9 days in the past 30 days, 4/5 drinks in
5409 a 2 hour period in females/males);
5410 8) Systolic blood pressure < 90 or ≥ 160 mmHg;
5411 a. Participants failing for blood pressure will be allowed to re-screen once.
5412 9) Diastolic blood pressure < 50 or ≥ 100 mmHg;
5413 a. Participants failing for blood pressure will be allowed to re-screen once.
5414 10) Breath CO > 80 ppm;
5415 11) Heart rate is greater than or equal to 115 bpm or less than 45 bpm;
5416 a. Participants failing for heart rate will be allowed to re-screen once.
5417 12) Currently seeking treatment for smoking cessation;
5418 13) Being pregnant or nursing, or not report using an approved form of birth control if
5419 applicable determined by the Project Medical Director.
5420 14) Have used nicotine replacement, bupropion or other pharmacotherapies as cessation
5421 aids in the past month (bupropion will be allowed for treatment of depression);
5422 15) Current symptoms of psychosis, dementia or mania;
5423 16) Suicidal ideation in the past month (score > 1 on the BDI question 9 or endorse question
5424 4 and/or 5 on the MINI suicide subscale);
5425 17) Reporting a plan or attempt to commit suicide, which is assessed on question A3g of the
5426 MINI Neuropsychiatric Interview Major Depressive Episode Module. Thoughts of suicide
5427 without an intent or plan is not an exclusion criteria;
5428 18) Suicide attempt in the past 6 months (endorse question 6 on the MINI suicide subscale
5429 with suicide attempt in the past 6 months);
5430 19) Participation in another research study in the past 30 days;
5431 20) Daily use of e-cigarettes in the past month (defined as 6 – 7 days per week); or
5432 21) Co-habitation with any research participant who has or is participating in the current
5433 study.
5434 22) Oxygen saturation of < 90%
5435 23) Reporting positive symptoms for COVID19
5436

5437 Women with academic degrees greater than high school are excluded because they have a
5438 lower risk of smoking and thus are not of interest in this experiment on smoking among
5439 socioeconomically disadvantaged women. Individuals under age 21 are excluded because they
5440 cannot legally buy cigarettes. Those with unstable medical, psychiatric, or medication conditions
5441 (as determined by the licensed medical professional) are excluded as these symptoms could
5442 affect a participant's ability to complete the study. Examples include but are not limited to the
5443 following: angina, stroke, heart attack which occurred since phone screening, blood clots in the
5444 arms or legs for which the individual is undergoing active medical treatment, cancer requiring
5445 active chemotherapy or radiation therapy, severe shortness of breath caused by conditions such
5446 as uncontrolled asthma, COPD, or arrhythmia, active untreated infection such as pneumonia,
5447 active untreated endocrine disorder such as hyperthyroidism. We will exclude those currently
5448 seeking smoking treatment and those who plan to quit in the next 30 days, as participation in this
5449 study may not lead to reductions in smoking. We will exclude pregnant or nursing women and

women of reproductive potential who are unwilling to use acceptable forms of birth control throughout the study if applicable determined by the if applicable determined by the Project Medical Director. We will also exclude anyone with current or recent alcohol or drug abuse problems as these factors could independently affect smoking behavior during the study. Individuals with baseline CO readings greater than 80 ppm, those with heart rate or blood pressure readings that are out of range (systolic: 90-159 mmHg; diastolic: 50-99 mmHg; HR: 45-114 bpm) and anyone who has attempted suicide in the past six months will be excluded from the study for safety concerns. Individuals who smoke 'roll your own' cigarettes exclusively will be excluded from the study because we will be unable to standardize their baseline smoking behavior. Individuals who have reported daily use of e-cigarettes in the past 30 days will be excluded as they may not be compliant with experimenter-provided e-cigarettes. Individuals who have recently participated in a research study will be excluded as participation may have changed their smoking patterns, which may preclude a stable smoking baseline. Because participants are required to complete portions of the protocol independently, they will need to be able to independently read and comprehend the study materials.

5.7 Eligibility Determination:

The research assistant will review the entire screening assessment battery for initial eligibility determination, confirming the participant meets the above described inclusion/exclusion criteria. All eligibility criteria that are not related to physiological measurements will be assessed during the first portion of the screening visit, and all criteria related to physiological measurements will be determined during the second portion of the screening. The final eligibility of the participant will be determined by a licensed medical professional (MD, DO, NP, PA, Master's prepared RN or CRN) at each site after reviewing the Medical History Questionnaire, BDI, Mini Neuropsychiatric Interview, and the MINI suicide subscale. The licensed medical professional may meet with a participant if available and think it necessary for eligibility determination. He/she will sign off on eligibility prior to the first baseline visit. If the licensed medical professional determines the participant is not medically eligible to participate in the study, has current symptomatology that would interfere with interpretation of the data, or is unlikely to complete the study he/she will inform the research assistants who will contact the participant prior to the first baseline visit. The licensed medical professional will not need to review the medical history forms of participants who are ineligible for other, non-medical reasons.

If a participant fails the urine or saliva toxicology screen due to a prescription medication he/she is taking, then he/she will not be automatically excluded. The interviewer will make note of this when he/she submits the forms to the licensed medical professional for final eligibility determination.

Once all the screening procedures have been completed, researchers will pay participants \$25 (+\$25 bonus if applicable) for their time as long as they pass the drug tests and meet the minimum requirements for carbon monoxide or urinary cotinine levels. Participants will be paid after the completion of the study visit. If participants are deemed ineligible at any point in the screening, the participant will be paid after determined ineligible. Marijuana will be tested for but will not be an exclusionary criterion. If a participant does not pass the drug test but has a current, valid prescription that would explain the failed test he/she will not be automatically excluded and will still receive the visit payment. Participants who meet all other eligibility criteria, sans the medical criteria, will be scheduled for the first baseline visit.

At the end of the screening session, the researcher will complete the End of Visit Evaluation Form. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regards to self-report of tobacco use.

6. Study Baseline Procedures

This study will use a one-week, two-session baseline period to collect baseline individual difference measures and monitor daily usual-brand smoking behavior. At Baseline 1 or within 1 business day of the Baseline 1 visit, participants will be provided their usual brand cigarettes to

5504 smoke, equivalent to 150% of their daily smoking rate. Participants will be encouraged to
5505 come to the lab to pick up their usual brand cigarettes after they complete the
5506 questionnaires and physio for the BL1 visit. Those who cannot come to the lab will
5507 receive product via a commercial courier. A timeline follow back (TLFB) will be used during
5508 the period between Baseline 1 and Baseline 2 to assess the daily cigarette use for the first 7
5509 days the participant has product. The participant must have received their UB cigarettes from the
5510 lab before the 7-day assessment period starts, and Baseline 2 must occur at least 7 days after
5511 the participant receives their usual brand cigarettes from the lab. If the baseline period extends
5512 past seven days and if the participant has run out of product, participants will need to purchase
5513 their own usual brand cigarettes. Use of a two-session baseline period will ensure stability of
5514 daily smoking reports, reduce reactivity to the daily cigarette monitoring, and reduce participant
5515 burden. During the two baseline sessions, participants will complete subjective questionnaires.
5516 Each visit will last approximately two to four hours. At the end of each baseline session, the
5517 researcher will complete the End of Visit Evaluation Form. This will allow the researcher to make
5518 note of any problems encountered during the visit and to assess the truthfulness of the
5519 participant in regards to self-report of tobacco use. Participants will also be supplied with urine
5520 collection equipment during the Baseline 1 product exchange so that they can collect first
5521 void urine samples during the Baseline 2 visit.

5522 For the Baseline 1 visit and all subsequent visits, the participant will be sent a REDCap
5523 link within 15 minutes of the start of the scheduled visit to complete all of the non-
5524 interviewer administered questionnaires. The participant will complete these
5525 questionnaires on their own but can have the research assistant present on a video call if
5526 they desire. Before beginning the physiological assessment portion of the visit over video
5527 call, the research assistant must review the participant's questionnaire responses for that
5528 visit. Participants will be compensated after the completion of the study visit and when
5529 the participant has received their new product.

5530 At Baseline 2 and all subsequent visits, after the participant has answered the
5531 questionnaires and has completed the physiological portion of the visit over video call,
5532 participants will be asked to come to the lab for exchange of product and biological
5533 samples. Participants will bring in their used and unused product from the previous visit
5534 as well as a first-void urine sample for assessing tobacco-related toxin exposure for
5535 assessing nicotine metabolism rate on applicable visits (BL2, Week 8 and Week 16)
5536 using equipment that was provided at the previous visit. Participants will be instructed to
5537 call the RA at the office when they get to the clinic to ensure that there is enough space
5538 in the smoking chambers to house all participants while abiding by safety guidelines as
5539 detailed on page 14 of the protocol. All participants must pass a COVID19 screening before
5540 entering the building. When invited into the lab, the participant will be shown to a smoking
5541 chamber and will instructed to place their bag of product outside of the chamber. The
5542 participant will wait here while the RA processes and returns product through the
5543 randomization database. Then the RA will dispense new product and bring the bag back
5544 to the participant. When the RA deems it safe for the participant to exit the chamber, the
5545 RA will instruct the participant that they can leave. The RA will instruct the participant to
5546 observe social distancing measures during this exchange, providing clarification if
5547 necessary. If a participant forgets their first-void urine sample at the Baseline 2 visit, staff
5548 will ask participant to come back to the clinic with their first void urine sample before
5549 exchange of product occurs. If participant is unable to return to the clinic with their first
5550 void sample, staff can arrange to meet the participant off campus to pick up their urine
5551 sample and to give participant their study product. Distancing and safety measures as
5552 described above must be observed. For participants who cannot make it to UHC, special
5553 arrangements will be made to enable use of the randomization database and product
5554 return/distribution procedures to the extent possible. Each week, during - or scheduled

5555 as nearly as possible to – a virtual visit, a complete accounting of the participant's
5556 product inventory will be taken and processed remotely through the randomization
5557 database. The participant will separate product based on its type (e-cigarette or
5558 combustible inventory) and status (used/unused), and the RA will process return
5559 characteristics through the database accordingly. The RA will clarify barcode
5560 characteristics with the participant when legibility is compromised. The participant will
5561 be instructed to keep unused product in their possession, but to exchange any used
5562 product with the courier who will deliver newly dispensed replacement products within 48
5563 hours.

5564 Product that will be given to participants for the Baseline 2 visit cannot be given/sent
5565 to participants until 7 days have passed following completion of the Baseline 1 visit. We
5566 will need to calculate baseline smoking rate during this 7-day period and so participants
5567 cannot have access to any blinded study product or e-cigarettes before this 7-day period
5568 has ended.

5569 5570 **6.1 Visit scheduling requirements for baseline period:**

5571 Participants will be required to schedule the Baseline 1 visit within 30 days of the completion
5572 of their screening visit. If a participant still wants to be in the study after 30 days, he/she will need
5573 to be re-screened. The participant will need to be re-consented but will maintain the original
5574 REDCap Subject Identifier. The ideal target window separating Baseline 1 and Baseline 2 is
5575 between 7 and 12 days. The minimum is 7 days and the maximum is 21 days. If the participant
5576 does not complete the visit within 21 days, then he/she will not be rescheduled and will be
5577 discontinued from the study.

5578 5579 **6.2 Measures/Assessments**

5580
5581 **The following physiological measures will be collected and recorded directly into REDCap**
5582 **by the interviewer:**

- 5583 1) CO
- 5584 2) Blood Pressure
- 5585 3) Heart Rate
- 5586 4) Body temperature
- 5587 5) Oxygen saturation
- 5588 6) Respiratory rate
- 5589 7) Urine or Saliva Toxicology
- 5590 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

5591
5592 **The following assessments will be administered as an interview at Baseline 1 and entered**
5593 **directly into REDCap by the interviewer:**

- 5594 1) Concomitant Medications Form
- 5595 2) Health Changes Questionnaire, which will assess any weekly health changes,
- 5596 3) Time Since Last Cigarette Questionnaire

5597
5598
5599 **The following Baseline 1 assessments will be completed by the participant directly in**
5600 **REDCap:**

- 5601 1) BDI
- 5602 2) OASIS
- 5603 3) COVID19 Symptom Questionnaire
- 5604 4) Respiratory Symptom Questionnaire
- 5605 5) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM) will be
5606

- administered to assess nicotine dependence severity.
- 6) Perceived Health Risks Rating⁷⁸, a measure of the perceived addictive potential and other health risks associated with cigarettes;
 - 7) Perceived Stress Scale (PSS)⁷⁸, assessing the degree to which life situations are perceived as stressful;
 - 8) Positive and Negative Affect Scales (PANAS)⁷⁹, a measure of changes in positive and negative mood;
 - 9) Respiratory Health Questionnaire, a UVM measure of cough, shortness of breath and other respiratory symptoms;
 - 10) Minnesota Nicotine Withdrawal Scale (MNWS)⁸⁰, a measure of nicotine withdrawal;
 - 11) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU)⁸¹, which measures the urge to smoke;
 - 12) Vaping Craving Questionnaire (VCQ)⁸², which measures the urge to vape;
 - 13) Cigarette Evaluation Scale – Usual Cigarette (CES)⁸³, which measures responses to cigarettes (e.g., reward, satisfaction);
 - 14) Vaping Evaluation Scale (VES), which measures responses to vaping (e.g. reward, satisfaction)
 - 15) Cigarette Purchase Task – Usual Brand Version (CPT)⁸⁴, a self-report analogue of a progressive-ratio schedule that measures the relative reinforcing efficacy of cigarettes by querying how many of that day's cigarette they would consume in a day at varying prices. This task will indicate whether prolonged VLNC cigarette use reduces cigarette demand and increases sensitivity to increases in cigarette costs;

All participants will also be asked to select their top three flavors of e-cigarette liquid from a list read to them by the RA. This question will be asked in preparation for giving flavored pods to participants who are randomized into the flavored e-cigarette condition. This information will be recorded directly into REDCap. Participants will be asked to rate these top three flavors based on either previous experience with these flavors or to indicate how much they believe that they will like or dislike the flavors.

The following Baseline 2 physiological measures will be collected and recorded directly into REDCap by the interviewer:

- 1) CO
- 2) Blood Pressure
- 3) Heart Rate
- 4) Body temperature
- 5) Oxygen saturation
- 6) Respiratory rate
- 7) Urine or Saliva Toxicology
- 8) Urine Pregnancy (if applicable; to be performed every 2 weeks)

The following assessments will be administered as an interview at Baseline 2 and then entered directly into REDCap by the interviewer:

- 1) Concomitant Medications Form
- 2) Health Changes Questionnaire
- 3) Time Since Last Cigarette Questionnaire

The following assessments will be administered at Baseline 2 and completed by the participant directly in REDCap:

- 1) BDI
- 2) OASIS
- 3) COVID19 Symptom Questionnaire
- 4) Respiratory Symptom Questionnaire
- 5) MNWS
- 6) WISDM

- 5661 7) PANAS
5662 8) QSU (usual brand)
5663 9) Vaping Craving Questionnaire
5664 10) CES (usual brand)
5665 11) Vaping Evaluation Scale
5666 12) CPT (usual brand)
5667 13) E-cigarette flavor rating questionnaire
5668 a. Participants will rate only the flavors that they received from staff for this visit
5669

5670 In the event that the REDCap website is not functioning, the assessments will be
5671 administered aloud and participant answers will be recorded securely. The interviewer will enter
5672 the data into REDCap when it resumes functioning properly. This information should be recorded
5673 in the 'End of Visit Evaluation Form'.
5674

5675 **6.3 E-cigarette Training Session (Baseline 2):**

5676 Participants assigned to an e-cig condition will be told that they will be provided with a JUUL.
5677 If a participant indicates an unwillingness to use the JUUL device, the research assistants will
5678 offer the participant the Vuse Solo as alternative device. If the participant does not wish to use
5679 either device, he or she would be ineligible for the study.

5680 Participants in the e-cigarette conditions will be given e-cigarette pods BEFORE the training
5681 session occurs. These pods will be either picked up at the lab (preferred) or delivered to the
5682 participant 1 to 2 days before their Baseline 2 visit occurs. Participants randomized to the e-
5683 cigarette conditions will be notified before their Baseline 2 visit (but after the 7-day period
5684 following Baseline 1) and informed of their e-cigarette condition. Participants randomized to the
5685 flavored condition will be given pods of up to three flavors of their choice. Staff will calculate how
5686 many total pods participants will be given at this time based on their smoking rate, and
5687 participants will be able to choose the proportion of each flavor that they would like to receive.

5688 The e-cigarette training session will occur over video chat after the physiological
5689 measurements have been collected. The first 30 minutes of the training session will consist of the
5690 participant being taught how to use, charge, and replace pods. Participants will first try their JUUL
5691 using the tobacco flavor. At this point, participants who are in the tobacco-only flavor condition
5692 will conclude their training session.

5693 For all visits following Baseline 2, participants in the preferred flavor condition are permitted
5694 to take up to three flavors home per week but can choose to take less than three flavors if
5695 desired. Participants will take home their chosen pods (or cartridges) of up to three flavors.
5696 Participants will be able to change their flavors at only one point in the study if they desire.
5697 Participants will only be allowed to take home three flavors at one time. Participants will be given
5698 an E-cigarette instructional manual that reviews the e-cigarette training done at this visit.
5699 Participants will be encouraged to call with any device issues.

5700 **6.4 Interactive Voice Response System:**

5701 At the end of the first baseline visit, participants will be trained to use the Interactive Voice
5702 Response (IVR) System, which will contact participants each day throughout the study and ask
5703 about their smoking behavior as well as withdrawal symptoms the week before and after
5704 Baseline 2. We will also review the IVR adherence incentive program, which consists of \$1 per call
5705 plus a \$10 bonus for seven consecutive calls.

5706 The IVR system is operated by TeleSage (<https://telesage.com/about/>). To be enrolled in the
5707 IVR system, research staff will enter the participant's initials, telephone number, subject
5708 identifier, and visit dates into the IVR TCORS website. Identifying information (initials and
5709 telephone numbers) will not be extracted as part of the data by the bioinformatics group. Please
5710 refer to TeleSage's privacy statement and HIPAA compliance form for additional information.
5711

5712 **Baseline 2 biological specimens:**

5713 Urine sample for smoking biomarker assessment:

5714 Participants will be asked to provide a urine sample (first void of the day) at the second
5715 baseline session and to post-randomization weeks 8 and 16 for biomarker assessment.
5716 Biomarker analysis will provide nicotine and carcinogen exposure outcome measures and verify
5717 compliance with VLNC cigarettes. Samples will be stored at -80C. Urine samples will be
5718 analyzed for total nicotine (cotinine plus its glucuronide conjugate, a useful measure of daily
5719 nicotine exposure), the tobacco-specific nitrosamine 4-methylnitrosamine-1-(3-pyridyl)-1-
5720 butanol (NNAL), and metabolites of 4 polycyclic aromatic hydrocarbons (PAHs), which are
5721 biomarkers of tobacco smoke carcinogens and decrease upon tobacco cessation or reduction.
5722 Anatabine is a minor alkaloid that is reduced in users of VLNC cigarettes and e-cigs. Therefore,
5723 anatabine levels in samples from those assigned to the VLNCC, VLNCC+TF e-cig and
5724 VLNCC+PF e-cig conditions should be lower than levels from those in the NNCC condition.
5725 These analyses will be performed by the Murphy lab at the University of Minnesota.

5726 **Biomarker shipping and storage:**

5727 Biomarkers will be shipped quarterly to the University of Vermont Laboratory for Clinical
5728 Biochemistry Research (Tracy Lab). The Tracy Lab will serve as a central repository for all
5729 biomarker specimens and will be responsible for distributing specimens to the appropriate labs
5730 on a quarterly basis. Urine samples will be analyzed and stored at the University of Minnesota
5731 Murphy Lab.
5732

5733 **7. Study Experimental Procedures**

5734 **7.1. Experimental Period:**

5735 Participants will be seen weekly throughout the 16-week experimental period. Weeks 4, 8,
5736 12, 16 and the abstinence visit will take approximately 2-4 hours each. All other sessions will last
5737 approximately 2 hours. If a participant has a positive urine or saliva toxicology test or is visibly
5738 intoxicated as determined by slurred speech, swaying, or stumbling, the session will be
5739 rescheduled until a negative test result is obtained and intoxication is not present. As a part of
5740 each experimental visit, participants will be asked to come to UHC for a product exchange. All
5741 participants must pass a COVID19 screening before entering the building. Participants will be
5742 instructed to contact the RA at the office when they get to the clinic to ensure that there is
5743 enough space in the smoking chambers to house all participants while abiding by safety
5744 guidelines as detailed on page 14 of the protocol. All participants must pass a COVID19
5745 screening before entering the building. When invited into the lab, the participant will be shown to
5746 a smoking chamber and will be instructed to place their bag of product outside of the chamber. The
5747 participant will wait here while the RA processes and returns product through the randomization
5748 database. Then the RA will dispense new product and bring the bag back to the participant's
5749 smoking chamber and leave it on the ground in front of the chamber. When the RA deems it
5750 safe for the participant to exit the chamber, the RA will instruct the participant that they can
5751 leave. The RA will instruct the participant to observe social distancing measures during this
5752 exchange, providing clarification if necessary. At the end of each experimental session, the
5753 researcher will complete the End of Visit Evaluation Form, which will be filed in the participant's
5754 binder. This will allow the researcher to make note of any problems encountered during the visit
5755 and to assess the truthfulness of the participant in regards to self-report of tobacco use and
5756 compliance to study procedures.

5757 **Visit scheduling requirements for experimental period:**

5758 The ideal scheduling window between each visit is 7 days based on the date of the Baseline
5759 2 Visit. For additional scheduling requirements, refer to the '*Scheduling Visits SOP*'. If a
5760 participant misses a visit and is unable to reschedule during the window (± 3 days), that visit will
5761 not be 'made-up' in the future. All measures that were not completed will be considered missing
5762 data and will not be collected during future visits. If a visit mistakenly occurs outside of the
5763 designated window, this is a protocol deviation. A 'Non-Medical Event Form' will need to be
5764 completed. Additionally, each visit should occur at approximately the same time of day ± 2 hours.

5765 If a participant is not able to attend his/her Week 16 visit, then it should be rescheduled even if it
5766 is outside of the scheduling window. This will be documented as a protocol deviation.

5767 **7.2. Experimental Visits Weeks 1, 3, 5, 7, 9, 11, 13, and 15 Procedures**

5768 **7.2.A. Measures/Assessments**

5769 **Physiological Measures Collected and entered directly into REDCap by the interviewer:**

- 5770 1) CO
- 5771 2) Blood Pressure
- 5772 3) Heart Rate
- 5773 4) Body temperature
- 5774 5) Oxygen saturation
- 5775 6) Respiratory rate
- 5776 7) Urine or Saliva Toxicology
- 5777 8) Urine Pregnancy test (if applicable, to be performed every 2 weeks)

5778 **The following assessments will be administered as an interview and entered directly into**
5779 **REDCap by the interviewer:**

- 5780 1) Concomitant Medications
- 5781 2) Medical Event Form, if applicable
- 5782 3) Health Changes Questionnaire
- 5783 4) Time Since Last Cigarette Questionnaire

5784 **The following assessments will be completed by the participant directly in REDCap:**

- 5785 1) BDI
- 5786 2) OASIS
- 5787 3) COVID19 Symptom Questionnaire
- 5788 4) Respiratory Symptom Questionnaire
- 5789 5) MNWS

5791 In the event that the REDCap website is not functioning, the assessments will be
5792 administered aloud and participant answers will be recorded securely. The interviewer will enter
5793 the data into REDCap when it resumes functioning properly. This information should be
5794 recorded in the 'End of Visit Evaluation Form'.

5795 **7.3. Experimental Visits Weeks 2, 4, 6, 8, 10, 12, 14, and 16 Procedures:**

5796 **7.3.A Measures/Assessments**

5797 **Physiological measures collected and entered directly into REDCap by interviewer:**

- 5798 1) CO
- 5799 2) Blood Pressure
- 5800 3) Heart Rate
- 5801 4) Body Temperature
- 5802 5) Oxygen Saturation
- 5803 6) Respiratory rate
- 5804 7) Urine or Saliva Toxicology
- 5805 8) Urine Pregnancy test (if applicable)

5806 **The following assessments will be administered as an interview and will be entered into**
5807 **REDCap by the interviewer at the end of the visit:**

- 5808 1) Concomitant Medications

- 5809 2) Medical Event Form, if applicable
 5810 3) Health Changes Questionnaire
 5811 4) Time Since Last Cigarette Questionnaire

5812 **The following assessments will be completed by the participant directly in REDCap:**

- 5813 1) BDI
 5814 2) OASIS
 5815 3) COVID19 Symptom Questionnaire
 5816 4) Respiratory Symptom Questionnaire
 5817 5) MNWS
 5818 6) QSU (usual brand)
 5819 7) QSU (study cigarette)
 5820 8) Vaping Craving Questionnaire
 5821 9) CES (usual brand)
 5822 10) CES (study cigarette)
 5823 11) Vaping Evaluation Scale
 5824 12) PANAS
 5825 13) Cigarette Purchase Task - Usual Brand Cigarette Version (weeks 4, 8, 12 and 16
 5826 only)
 5827 14) Cigarette Purchase Task – Study Cigarette Version (weeks 4, 8, 12 and 16 only)
 5828 15) Cross-price Elasticity Task⁸⁴- e-cigarettes and combustible cigarettes (weeks 4, 8, 12
 5829 and 16 only) (for e-cigarette experimental conditions only)
 5830 16) Penn State Electronic Cigarette Dependence Index (weeks 8 and 16 only)
 5831 17) Respiratory Health Questionnaire (weeks 8 and 16 only)
 5832 18) FTND (weeks 8 and 16 only)
 5833 19) Perceived Health Risks Questionnaire (weeks 8 and 16 only)
 5834 20) Smoking Stages of Change Algorithm and Contemplation Ladder (weeks 8 and 16
 5835 only)
 5836 21) WISDM – Brief Scale
 5837 22) Drug Use Questionnaire – 1 month version (weeks 8 and 16 only)
 5838 23) Perceived Stress Scale (weeks 8 and 16 only)
 5839 24) Alcohol Use Questionnaire – 1 month version (weeks 8 and 16 only)
 5840 25) E-cigarette flavor rating questionnaire (weeks 4, 8, 12 and 16 only)
 5841 a. Participants will rate only of the flavors that they have been using over the
 5842 past week and that have been dispensed by study staff.
 5843

5844 In the event that the REDCap website is not functioning, the assessments will be
 5845 administered aloud and participant answers will be recorded securely. The interviewer will enter
 5846 the data into REDCap when it resumes functioning properly. This information should be recorded
 5847 in the 'End of Visit Evaluation Form'.
 5848

5849 **Biological Samples to be collected:**

- 5850 1) First void urine sample (Weeks 8 and 16 only)
 5851

5852 **7.4. Interactive Voice Response System:**

5853 Participants will continue to use the IVR system on a daily basis throughout the experimental
 5854 period to record the number of study cigarettes smoked per day, measurement of e-cig use and
 5855 use of non-study cigarettes or other tobacco products. Measurement of e- cig use will be
 5856 collected by asking two questions: how many daily e-cigarette episodes occurred, where one
 5857 episode consists of around 10-15 puffs or up to approximately 10 minutes, and what proportion
 5858 of pods and/or cartridges were used per day. Participants will also be asked to log how many
 5859 flavors of e-cigs they used per day. During the first week after Baseline 1, the IVR system will
 5860 collect information about mood and withdrawal symptoms.
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7.5. Variable Incentive Program:

An incentive program has been developed with the goal of improving attendance at scheduled assessment sessions, compliance with using only study-provided tobacco products, and encouraging honest self-reports regarding all nicotine/tobacco use.

Briefly, participants will receive a total of seven tickets for each weekly visit they attend after randomization (Visits 03-18, weeks 1-16). In total, participants could earn 112 valid tickets across the 16 visits. Participants will be instructed that these tickets correspond to attendance (one ticket), honest reporting (one ticket), compliance in bringing back used and unused pods/cartridges (two tickets) and adherence to using only the assigned study product (three tickets). Participants who do not bring back all of their unused study product and used packaging will be told that they may not be eligible to earn the two compliance tickets. Participants will be further instructed that all of the tickets that they receive “could” be eligible for entry into a monthly drawing for prizes, but that only tickets that are “validated” will be eligible for prizes.

Since it is prohibitively expensive to test urine samples each week for each participant and because it is currently not feasible to detect with reasonable precision non-compliance based on biomarkers in the two higher nicotine group, we plan to only validate the attendance tickets. Hence, each participant who attends their regularly scheduled weekly session will have a total of seven validated tickets entered into the monthly drawing.

To convey the message that we may be validating honest reporting and use of only study-provided products, in a bogus pipeline of sorts, we will tell the participants that a composite assessment of the measures that we collect MAY be used to validate the amount of nicotine and tobacco products that they are using. So there is some minor deception involved, but technically we could conduct urine toxicology testing for both purposes. Hence, if the urine toxicology testing is presented as something that MAY be done for validation purposes, we feel that any deception is relatively minor. For scientific/economic reasons we are just electing to restrict validation to attendance. Nevertheless, we will debrief all participants upon the completion of the trial. We will inform them that the incentive program was based exclusively on attendance due to the relatively high cost of urine toxicology testing and other practical problems with shipping the urines for prompt testing.

Drawings will be conducted on the 1st of each month. Validation will be performed by staff who have no participant interaction and are not blind to condition. Any ticket drawn will be eligible for an incentive as the only true contingency is for attendance. There will be no mention of the basis for earning incentives (i.e., whether the ticket was for attendance, honesty, adherence). Participants will simply be informed that he or she earned an incentive from the drawing.

Each drawing will be independent (without replacement); consequently, some participants will not win a prize and others may win more than one during the study if more than one of their tickets is drawn. After confirming winners, the remaining tickets from each month will be discarded (i.e., tickets will only be entered into one drawing). The monthly prize amounts are detailed below.

We estimate based on the 2 ½ years we think it will take to complete this study, that participants will win an average of approximately \$65 in prizes or an additional \$5.50 per week per participant.

Grand Prize (1): \$500 cash

Second Prize (1): \$200 cash

Third Prize (5): \$10 cash

7.6. Product and Procedures Compliance Review Sessions:

At each visit, Baseline 2 through Week 16, participants will be counseled about their use of the study cigarettes and assigned e-cigarette (if applicable). Participants will be asked about any concerns or obstacles associated with use of the study cigarettes and assigned e-cigarette (if applicable). The importance of honest self-reporting will be stressed. Participants will be told that they will not be penalized for use of other nicotine or tobacco products and that it is crucial for them to report any use of these products. If difficulties are encountered, participants will be

5916 asked why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to
5917 problem-solve how to deal with these difficulties in order to meet the protocol requirements.
5918 Additionally, participants will be counseled about their IVR completion, visit attendance, task
5919 engagement and product accountability. Refer to the '*Product and Procedures Compliance*
5920 *Review Sessions SOP*' for more information.

5921 **7.7. Quit Attempts During the Study Protocol:**

5922 At each weekly session, we will ask each participant if s/he is currently abstaining from
5923 smoking with the intention of quitting and whether s/he is planning to quit smoking prior to his/her
5924 next scheduled visit. If a participant is currently abstaining from smoking with the intention to quit,
5925 we will encourage the participant to continue abstaining, schedule them for weekly visits , and
5926 provide them with NCI's Clearing the Air manual and local smoking cessation resources. We will
5927 give them the option of taking study product(s) home but not require that they take them, and if
5928 they do take the product(s) home we will suggest that they put the product(s) away at home so as
5929 to remove these cues from view. We will ask the participant to contact staff if they lapse and
5930 would like to receive study product(s) prior to his/her next visit. If a participant is planning to quit
5931 but has not initiated a quit attempt, we will ask if s/he has identified a quit date and if so what the
5932 date is, provide them with the Clearing the Air manual and local smoking cessation resources,
5933 provide them with the study product(s), and recommend that they put the product(s) away out of
5934 view on the quit date.

5935 For those in a condition including e-cigarettes, we will defer to the participant's interests in
5936 continuing to use e-cigarettes as part of their quit attempt. Those who indicate that they will
5937 continue to use them will be given their same weekly supplies base on their baseline smoking
5938 rate. Those who indicate that they are planning to abstain from both combusted and non-
5939 combusted tobacco, we will honor that request. As we state above about combusted cigarettes, if
5940 participant changes his or her mind about resuming e- cigarette use, they can contact us and
5941 obtain their weekly supply.

5942 **7.7.A. If a participant is currently abstaining from smoking with the intention to quit:**

- 5943 • Encourage participant to continue abstaining from smoking
- 5944 • Schedule the participant for normal weekly visits
- 5945 • Provide the participant with the '*Clearing the Air*' manual and local smoking cessation
5946 resources
- 5947 • Give the participant the option to receive product rather than require him/her to take
5948 the product
- 5949 • If the participant choses to receive the study product have him/her sign a form
5950 acknowledging that cigarette availability could be detrimental to the quit attempt.
5951 Recommend that he/she put the product "away" at home as to avoid unwanted cues
5952 to smoke.
- 5953 • If the participant chooses not to receive the study product, have him/her contact the
5954 lab if he/she lapses and would like to pick up or be mailed the study product prior to
5955 his/her next visit.

5956 **7.7.B. If a participant is planning to quit smoking, but has not initiated the quit attempt:**

- 5957 • Ask if he/she has identified a target quit date and, if so, what that target date is
- 5958 • Provide the participant with the '*Clearing the Air*' manual and local smoking cessation
5959 resources
- 5960 • Provide the participant with the study product as usual. Recommend that on the target
5961 date he/she put the product "away" at home as to avoid unwanted cues to smoke.

5962 **7.8 Abstinence Assessment Session:**

5963 After the week 16 visit, participants will be required to attend one additional visit the following day.
5964 During this visit, participants will have been encouraged to abstain from smoking until their next
5965 scheduled visit (approximately 24 hours later). The abstinence assessment session should be
5966

5967 scheduled no less than 18 hours and no more than 30 hours after the Week 16 visit. Abstinence
5968 will be verified by an expired breath carbon monoxide level of 6 parts per million (ppm) or under.
5969 This session will allow us to determine whether the experimental cigarettes and e-cigarette use
5970 (for the e-cigarette conditions) have reduced the effects of abstinence on these measures relative
5971 to the control conditions. If the participant does NOT meet abstinence criteria, he/she will only
5972 receive \$20 for the visit.

5973 **7.8.A Participants Who Meet Criteria for Abstinence**

5974 **7.8.A.1 Measures/Assessments**

5975 **Physiological measures collected and entered directly into REDCap by the**
5976 **interviewer:**

- 5977 1) CO
- 5978 2) Blood Pressure
- 5979 3) Heart Rate
- 5980 4) Body temperature
- 5981 5) Oxygen saturation
- 5982 6) Respiratory rate
- 5983 7) Urine or Saliva Toxicology

5984 **The following assessments will be administered as an interview and entered directly into**
5985 **REDCap by the interviewer:**

- 5986 1) Concomitant Medications
- 5987 2) Medical Event Form, if applicable
- 5988 3) Health Changes Questionnaire
- 5989 4) Time Since Last Cigarette Questionnaire

5990 **The following assessments will be completed by the participant directly in REDCap:**

- 5991 1) BDI
- 5992 2) OASIS
- 5993 3) COVID19 Symptom Questionnaire
- 5994 4) Respiratory Symptom Questionnaire
- 5995 5) MNWS
- 5996 6) PANAS
- 5997 7) QSU-brief - Usual Cigarette
- 5998 8) QSU-brief - Study Cigarette
- 5999 9) Vaping Craving Questionnaire
- 6000 10) Cigarette Purchase Task - Usual Brand Cigarette Version
- 6001 11) Cigarette Purchase Task - Study Cigarette Version
- 6002 12) E-cigarette Purchase Task- E-cigarette Version

6003
6004 In the event that the REDCap website is not functioning, the assessments will be administered
6005 aloud and participant answers will be recorded securely. The interviewer will enter the data into
6006 REDCap when it resumes functioning properly. This information should be recorded in the 'End
6007 of Visit Evaluation Form'.

6008 **7.8.B. Participants Who Do Not Meet Criteria for Abstinence**

6009 **7.8.B.1 Measures/Assessments**

6010
6011 **Participants who do NOT meet abstinence criteria will be required to complete the**
6012 **following assessments:**
6013
6014

6015

- 6016 1) CO
- 6017 2) Blood Pressure
- 6018 3) Heart Rate
- 6019 4) Body temperature
- 6020 5) Oxygen saturation
- 6021 6) Respiratory rate
- 6022 7) Urine or Saliva Toxicology

6023 **The following assessments will be administered as an interview and entered directly into**
6024 **REDCap by the interviewer:**

- 6025 1) Concomitant Medications
- 6026 2) Health Changes Questionnaire
- 6027 3) Medical Event Form, if applicable
- 6028 4) TLFB

6029 **The following assessments will be completed by the participant directly in REDCap:**

- 6030 1) BDI
- 6031 2) OASIS
- 6032 3) COVID19 Symptom Questionnaire
- 6033 4) Respiratory Symptom Questionnaire

6034 **7.9 Participant Compensation:**

6035 Participants will receive \$25 plus a \$25 bonus for completing each screening visit on time as
6036 scheduled. Payment for the first screening session will be made upon its completion. Payment for
6037 the second screening session will be made regardless of enrollment as long as the participant
6038 passes the drug test and meets the minimum requirements for carbon monoxide or urinary
6039 cotinine levels. Participants who do not pass the drug test or who are visibly intoxicated as
6040 determined by slurred speech, swaying, or stumbling will not be able to complete the visit and will
6041 be asked to take another test several days after the first positive. If they are negative for the
6042 second test, they will be eligible to participate, and if they are positive the for the second text they
6043 will be excluded. Participants will receive \$100 for each study visit from Baseline 1 to Week 16.
6044 Participants will also have a chance to earn an additional \$20 bonus for every study visit that is
6045 completed on time as scheduled starting at Week 1 and ending at Week 15. Participants can
6046 receive up to \$120.00 for the abstinence session (\$20 if participant does not achieve abstinence,
6047 \$120 if participant reaches abstinence), \$40 for biochemical verification of abstinence at 30 day
6048 follow up visit, and up to \$306 for completing daily IVR reports of study cigarette and other
6049 nicotine and tobacco use. There will also be a \$150 bonus distributed at Week 16 for completing
6050 the study.

6051 Participants who do not complete the entire study will receive compensation for the sessions
6052 that they do complete. Total compensation for completing Study 3, including study visit
6053 payments, daily IVR calls and end of study bonus is \$2816. As mentioned above, participants will
6054 have a chance to earn additional incentives for compliance, honesty and attendance through
6055 urine testing. Participants will be given a debit card at the beginning of the study (during the
6056 second portion of the screening visit) and compensation for each visit will be automatically
6057 transferred to the card after they complete that visit. If debit cards are unavailable, participants
6058 will be paid via an alternate method (i.e. cash or check).

6059 **7.10 End of Study:**

6060 After a participant has completed all study procedures and has been paid for participation the
6061 research assistant will read the following script and give the participant the Clearing the Air
6062 Manual.

6063 *“If you’ve reduced your smoking during this study, we encourage you to continue these*
6064 *reductions or even consider quitting. We would like to provide you with some resources should*
6065 *you decide to try to abstain from smoking (give “Clearing the Air” and hotline information). Please*
6066 *also feel free to consult with your physician and use any medications he/she deems appropriate.*
6067 *We will call you in approximately 30 days to ask about your smoking since leaving the study.*
6068 *There is no right answer and we know how difficult quitting can be. Please just answer honestly.*
6069 *The call will take less than 5 minutes. Thanks again for your participation.”*

6070 **The following assessments will be administered using REDCap:**

6071 1) End of Study Questionnaire

6072 **7.11 30 Day Follow up Phone Call:**

6073 Participants will receive a follow-up phone call or text between 25 and 35 days after the
6074 abstinence assessment session to assess their smoking patterns. The phone questionnaire will
6075 last less than five minutes. The questionnaire will ask if the participant is still smoking, how much
6076 and whether he/she has attempted to quit smoking since the end of the study.

6077 Participants will receive 5 variable incentive program lottery tickets for completing the call as
6078 compensation. Those who report abstinence will be invited to complete biochemical verification
6079 and be compensated \$40 for doing so. Abstinence will be achieved by a carbon monoxide
6080 reading of 6 parts per million (ppm) or under. A urine sample will may also be collected to be
6081 sent to the lab for analysis. Additionally, any Medical Event Forms that remain open from the last
6082 session will be discussed. If the participant became pregnant during the study, this would have
6083 been recorded as a medical event. During this phone call, the research assistant will confirm her
6084 due date. This event will remain open until delivery. At that time the licensed medical professional
6085 will contact the participant to ask a few questions about the baby’s health and will update the
6086 Medical Event Form.

6087 Once a participant has completed all study procedures and all open events have been closed,
6088 the PI or Project Manager will review the participant’s record and sign a form indicating study
6089 completion for that participant.

6090 **8.0 Study Randomization**

6092 **8.1 Randomization Process**

6093 The lead statistician will create a randomization schedule for each of the two sites, amounting
6094 to 150% of expected enrollment at each site. The excess randomization codes will be used in the
6095 event that a site will have to enroll extra participants due to unexpectedly slow enrollment at
6096 another site. The nicotine doses will be identified by letter code and only Administrative Core
6097 personnel with no participant contact will have the link between the statistician’s letter code and
6098 dose assignments. There will be no blinding of e-cigarette conditions. The Administrative Core
6099 will maintain the randomization schedule and the link between the alphabetic code and treatment
6100 assignment securely. A second sealed copy will be secured in a separate building to protect
6101 against loss related to fire or other unforeseen events.

6102 The University of Vermont will be responsible for removing all identifying information from
6103 cigarettes received from the Research Triangle Institute (RTI), labeling each carton with a blind
6104 code, assigning product using this blind code based on the randomization schedule being
6105 provided by the UVM Biostatistics Core, and shipping cigarettes and e- cigarettes to each site as
6106 needed based on recruitment. Each site will be responsible for tracking product received and
6107 distributed to participants, collecting unused product from participants, and returning unused
6108 cigarettes and e-cigarettes to UVM. The participants, investigators and study staff will not have
6109 knowledge of which product is given to a participant or whether different participants received the
6110 same or different product.

6111 **8.2 Study Product Administration**

6112 During the experimental period, participants will be provided with a 14-day supply of research

6113 cigarettes equivalent to 150% of their daily smoking rate. Those in the e-cigarette conditions will
6114 also be provided with a 14-day supply of e-cigarettes equivalent to their daily smoking rate. This
6115 rate will be calculated at Baseline 2 and will be an average daily smoking rate based on the IVR
6116 data that reports on the usage for the first seven days following the day of the first baseline visit.
6117 This will ensure adequate availability of cigarettes in the numerous locations participants may
6118 typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if
6119 they miss a scheduled visit. Participants will be instructed to use the research cigarettes for 16
6120 weeks, at which point they are to discontinue product use.
6121 If there is prior knowledge a participant will be missing a visit (i.e. planned vacation, laboratory
6122 closure, etc.), then the participant will be provided with an adequate supply of cigarettes to make
6123 up for the missed visit(s). The participant will be given a 21-day supply if one visit is going to be
6124 missed and a 28-day supply if two visits are going to be missed.

6125 **8.3 Guidelines for Reporting other Nicotine Product Use**

6126 Participants will be asked to refrain from use of other non-study cigarettes during the study
6127 period. If participants have to use another nicotine product, they will be told to use a non-
6128 combustible product (gum, patch, etc.). Additionally, they will be told there is not a penalty for
6129 use of non-study products, and that it is crucial for them to report any use of non- study tobacco
6130 products. Throughout the baseline and experimental periods, an Interactive Voice Response
6131 (IVR) system will be used on a daily basis to record the number of study cigarettes and non-
6132 study cigarettes used the previous day. During the baseline and first experimental week,
6133 participants will also answer daily IVR questions about their mood. Participants will be seen
6134 weekly for assessments. Brief standardized review sessions focusing on compliance with the
6135 study cigarettes and other study procedures will be provided at each visit.

6136 **8.4 Product Accountability:**

6137 Participants will be required to keep track of all the products provided to them. Therefore,
6138 they will be instructed to return all unused products and empty cigarette packs e- liquid
6139 pods/cartridges to the laboratory each week. Research staff will complete the 'Product
6140 Accountability Log' as they process participants' product. Any discrepancies in the product
6141 dispensed versus product returned will be discussed and recorded in the log. Research staff will
6142 weigh all opened e-cigarette pods/cartridges that the participant returns at all visits to determine
6143 how much e-liquid was used since the participant was last seen. Empty cigarette packs and e-
6144 liquid pods/cartridges will not be saved. Unused cigarette packs and e-liquid pods/cartridges will
6145 be re-distributed to the participants during Weeks 1-15. During Week 16, remaining unused
6146 cigarettes and e-cigarette pods/cartridges returned by the participants will be collected by the
6147 research staff.

6148 Participants who report running out of cigarettes or e-liquid pods/cartridges prior to a
6149 scheduled weekly visit will be allowed to come in for an unscheduled visit to obtain more
6150 research cigarettes. To determine whether a rate change for cigarettes is necessary, we will look
6151 at the past two CO levels as compared to the Baseline 2 CO. If the CO trend is consistent with
6152 the self-report of smoking all of the allotted cigarettes then a rate increase will be granted. The
6153 participant will then receive cigarettes at a rate of 175% of their daily smoking rate. The
6154 maximum increase is 200% of their daily smoking rate. To determine whether a rate change for
6155 e-cigarettes is necessary, we will monitor the amount of e- cigarette use the participant is
6156 reporting and showing through product return along with any unscheduled visits. The investigator
6157 may grant an e-cigarette rate increase in increments of 25%. The maximum increase for e-
6158 cigarettes will be 200% of their baseline weekly e- cigarette dispensation rate.

6159 If participants lose more than two packs of cigarettes and/or pods/cartridges and require an
6160 unscheduled visit to the laboratory to supplement their supply, they will be told the next time they
6161 lose more than two packs they will have to wait until their next scheduled appointment to receive
6162 more cigarettes.

6163 **9. Study 3 Statistical Methods and Sample Size**

6164

9.1 Statistical Methods

Continuous outcomes will be summarized by mean, standard deviation, median and range. Categorical outcomes will be summarized by frequencies and percentages. Skewed continuous outcomes will be log- or square-root transformed as appropriate. Variables measured at each baseline visit will be averaged and the average will be used as the baseline measurement. As we expect conditions to be balanced on important baseline characteristics due to randomization, our primary analysis for all endpoints will not be adjusted for potential confounders. However, a secondary analysis will be completed for all outcomes adjusting for demographic characteristics (e.g., age) that we have found to be important in prior studies. Potential moderators (e.g., SSRI vs. non-SSRI antidepressant, depression vs. anxiety disorders, BMI above or below 30) will be explored by adding that term and the moderator-by-condition term to the model. We will examine age group and gender as potential moderators in a similar fashion.

Participants will be randomized in equal probability to one of the four conditions, with randomization stratified by site and menthol cigarette status. All analyses will follow the intent-to-treat principle (i.e. subjects will be analyzed according to condition assignment, regardless of compliance). The Primary Aim will examine the effects of condition on total CPD (study product and non-study product). CPD will be analyzed by week (mean over all days in a seven-day period) using a mixed model to account for repeated measures from the same individual. Models will include baseline CPD as a covariate. Using a mixed model also allows us to include the effect of study site as a random effect. Additional analyses conducted using data collected at the end of the study will use orthogonal comparisons to test for a linear trend in the decrease in CPD, such that VLNCC + PF e-cig > VLNCC + TO e-cig > VLNCC > NNCC, with the largest reduction in the VLNCC + PF e-cig condition. As we expect that differences among conditions for some of the outcomes may not follow a linear pattern, we will use related planned comparisons to test for threshold effects, specifically contrasting the NNCC condition to all three VLNCC conditions, and NNCC to the two VLNCC + e-cigarette conditions. Analysis of cigarette demand, smoke exposure and tobacco carcinogens (Aim 2) as well as additional outcomes, including subjective effects, will be analyzed in a similar manner. Because Exploratory Aim 3 is based on abstinence-induced effects and will be examined using data collected at a single visit at Week 17, analysis will be based on an analysis of co-variance model. In addition to the effect of condition, we will include important covariates noted above. Exploratory analyses will also be conducted combining data collected from three of the vulnerable populations (disadvantaged women of childbearing age, opioid dependent individuals, individuals with AD) to explore potential differences in effects of study condition across these populations.

This will be done with the addition of the effects of population and population-by-condition terms to the models described above. Study staff will make every effort to minimize missing data, and results of our ongoing trial suggest that this will be minimal. We will examine the missing data pattern, and if it is missing at random, will use all data available, without imputation.

9.2 Sample Size

Sample size was determined using NQuery Advisor based on hypothesis tests related to Aim 1, specifically to detect a significant difference between the study conditions (NNCC, VLNCC, VLNCC + TO e-cigs, VLNCC + PF e-cigs) on total CPD. The primary statistical approach will be repeated measures ANOVAs but required sample sizes were calculated focusing on expected outcomes at Week 16. This sample size estimate is intentionally conservative and calculated based on one outcome at one time point; however, given the repeated measures nature of our data, we will have correlated observations within subjects. Thus, with the given sample sizes we will achieve the stated power to detect differences of even lesser magnitude than stated or planned. Our sample size determination is based on preliminary results from our current trial

Table 2. Observed effect sizes

Outcome	Observed between-group ES (15.8 vs 0.4 mg/g)
CPD	0.70
Craving	0.40
FTND	0.12
Breath CO	0.38

6219 and results from the Donny et al. study⁹⁸ of VLNC and NNC cigarettes. Note that the between-
6220 group effect size is defined as the difference of study condition means divided by the common
6221 standard deviation. A sample size of 53 participants per condition will provide 80% power to
6222 detect an effect size of 0.60 for all pair-wise comparisons, with a two-sided type 1 error rate of
6223 0.05. This is smaller than that found in our on-going study to date for CPD and smaller than the
6224 effect sizes reported by Hatsukami et al. 2010³⁸ for all measures except breath CO. In addition,
6225 this sample size provides greater than 95% power to detect a linear dose-response effect
6226 across the four experimental conditions. Because we have relied only on outcomes at Week 16,
6227 our proposed sample sizes are somewhat conservative, but we believe this is appropriate for
6228 this study given that the effects of VLNC cigarettes in this population, particularly in combination
6229 with e-cigarettes, are completely unknown. The sample size above assumes a 15% loss to
6230 follow-up, consistent with our experience in the current study.

6231 10. Potential Risks of Participation

6232 10.1 Risks of Participation

- 6233 1) Survey Questionnaires. Surveys include questions about participants' medical and
6234 psychiatric histories, drug and alcohol use and history, breath tests for cigarette and
6235 alcohol use, urine or salivary tests of illicit drug use and pregnancy, and questionnaires
6236 about mood. Answering these personal questions can make participants
6237 uncomfortable. If a participant reports thoughts of killing themselves or other indicators
6238 of suicidality, a study clinician will come to talk to the participant. The participant may
6239 also request to see a study clinician if he or she is in discomfort and would like help
6240 and/or referrals for mental health resources.
- 6241 2) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find
6242 out the results.
- 6243 3) Undue Influence: Undue influence is a possible risk due to monetary compensation for
6244 participating in these studies. The likelihood of this risk is low because the
6245 compensation is commensurate with the amount of time and effort required for these
6246 studies.
- 6247 4) Drug Testing: A breach of confidentiality could occur and other people could learn of
6248 the participant's drug use.
- 6249 5) Obtaining Blood Pressure and Heart Rate. The blood pressure cuff may cause minimal
6250 discomfort. In obtaining blood pressure we may find a participant to have abnormal
6251 blood pressure and/or heart rate. If participant's blood pressure is abnormal, we will
6252 inform the participant of this, and participant may be advised to see a doctor, and may
6253 also be contacted by our study doctor. Also, smoking and nicotine can affect the
6254 cardiovascular system, which may result in changes in blood pressure and/or heart
6255 rate.
- 6256 6) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to
6257 significant medical problems including:
 - 6258 a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral
6259 vascular disease, reduced blood circulation, abdominal aortic aneurysm
 - 6260 b. Respiratory Diseases: Emphysema, bronchitis, and chronic airway obstruction
 - 6261 c. Cancers: Cancer of the lung, bladder, cervix, esophagus, kidney, larynx, mouth,
6262 pancreas, throat, and stomach; leukemia
 - 6263 d. Metabolic Diseases: Type 2 Diabetes
 - 6264 e. Other Health Risks Associated with Smoking: Including but not limited to infertility,
6265 lower bone density in postmenopausal women, and hip fracture in women
 - 6266 f. Death
- 6267 7) Smoking Study Cigarettes. All cigarettes are harmful to a person's health and can lead
6268

6270 to cardiovascular (heart) disease, respiratory (lung) disease, cancer and other health
6271 problems. In addition to the above medical problems, participants may experience
6272 some minor negative health effects such as headaches. Participants may also
6273 experience smoking withdrawal symptoms, which are listed below. In addition, due to
6274 the altered nicotine levels, there could be a change in a participant's use of cigarettes
6275 including the manner in which he or she inhales the smoke. Smoking the study
6276 cigarette does not necessarily provide any less risk than the participant's usual brand of
6277 cigarette and could pose increased health risks.

6278 8) Using Study E-cigarettes. E-cigarettes are devices that heat nicotine to produce an
6279 aerosol. The health effects of e-cigarettes are still unclear, but appear to be less than that
6280 for tobacco cigarettes. Most e-cigarette users have lower nicotine levels than when they
6281 smoked regular cigarettes. Some e-cigarette users, especially those who use both e-
6282 cigarettes and regular tobacco cigarettes as well as youth and young adults, can have
6283 increased nicotine levels. In some rare cases, these use patterns have been associated
6284 with seizures. Whether this would occur with the concurrent use of very low nicotine
6285 cigarettes is unclear. E-cigarettes users very often maintain addiction to nicotine, but
6286 this addiction appears to be somewhat less than that from tobacco cigarettes. Abruptly
6287 quitting e-cigarettes could cause withdrawal symptoms similar to those from quitting
6288 tobacco cigarettes (see below) but slightly less severe. The most common side effects
6289 include dry mouth, irritation of the throat and mouth, and mild cough. The JUUL and
6290 Vuse e-cigarettes we will be providing have not been well-studied but appear to be of
6291 similar risk to other e-cigarettes. Participants may have heard that e-cigarettes, or
6292 "vapes," can explode and seriously injure people. Study staff should instruct participants
6293 that although they appear rare, these explosions are dangerous. The exact causes of
6294 these incidents are not yet clear, but some evidence suggests that battery-related issues
6295 may lead to vape explosions. In order to prevent e-cigarette related injuries, instruct
6296 participants to keep their e-cig away from other metal objects, never charge the e-cig
6297 with a phone or tablet charger, don't charge the e-cig overnight or leave it charging
6298 unattended, and to stop using the e-cig if the batteries get damaged or wet. The
6299 participant will be instructed to always keep e-cig liquid out of kids' and pets' reach and
6300 sight after use. If we study staff learns about additional risks of e-cigarettes during the
6301 study, participants will be informed of these risks.

6302 9) Mood and Psychiatric Symptom Changes. Participants may experience smoking
6303 withdrawal symptoms during this study. These symptoms can include anger,
6304 anxiousness, craving for a cigarette, depressed mood, difficulty concentrating,
6305 frustration, increased appetite, impatience/impulsivity, irritability, restlessness, sleep
6306 problems, and weight gain. These feelings can be uncomfortable and can last a couple
6307 of weeks, but usually are of minimal risk. In addition, if participants have a past history
6308 of anxiety, depression, or alcoholism, it is possible withdrawal could cause substantial
6309 increases in depression and anxiety symptoms, but this appears to be rare. At each visit,
6310 study staff will ask participants how they feel. If either study staff or the participant thinks
6311 that being in this study is putting the participant's mental health at risk, staff may have the
6312 participant meet with an on-site clinician and/or stop participating in the study. Further, if
6313 a participant report thoughts of killing oneself or other indicators of suicidality, a study
6314 clinician will come to talk to the participant. Participants may also request to see a study
6315 clinician if he or she is in discomfort and would like help and/or referrals for mental health
6316 resources.

6317 10) Returning to Regular Smoking: It is possible that if participants return to smoking their
6318 usual brand of cigarette at the end of the study they may experience mild and transient
6319 nausea, dizziness, and lightheadedness.

6320

- 6321 11) Risk to Fetus. To avoid risks to a fetus, it is important that participants are not
6322 pregnant during this study. Avoiding sexual activity is the only certain method to
6323 prevent pregnancy. However, if participants choose to be sexually active,
6324 participants should be using approved forms of birth control if applicable determined
6325 by the Project Medical Director. including but not limited to prescribed birth control
6326 pills, patch, ring, injections, implants or intrauterine device (IUD) or an appropriate
6327 “double barrier” method. If you choose to be sexually active during this study,
6328 pregnancy could still result even with the use of these birth control methods.
6329

6330 **10.2 Avoiding Risks to Fetus**

6331 If participants choose to be sexually active, they should use an appropriate “double barrier”
6332 method of birth control (such as female use of a diaphragm, or contraceptive sponge, in
6333 addition to male use of a condom) or the female should be using prescribed “birth control” pills,
6334 patch, ring, injections, implants or intrauterine device (IUD) if applicable determined by the
6335 Project Medical Director. If a participant endorses a “double barrier” method, our medical
6336 professional will speak to the participant to confirm which methods will be used during the
6337 duration of the study. Participants will be tested for pregnancy every two weeks beginning at
6338 screening through the last study visit. If a participant becomes pregnant during the study, she
6339 will be withdrawn from the study. Approximately 30 days after being withdrawn or having a
6340 positive pregnancy test at the last study visit, the research staff will call the participant to
6341 confirm her due date. The licensed medical professional will follow-up with the participant after
6342 delivery to ask questions about the baby’s health.
6343

6344 **10.3 Expected benefits of participation**

6345 There are no benefits from participating in the study. The information obtained from this
6346 study may ultimately help the Food and Drug Administration decide how best to regulate
6347 nicotine and tobacco products with the goal of improving public health.
6348

6349 **11. Protection Against Risk**

6350 **11.1 Data Collection Protections**

6351 Research data without identifiers will be maintained in a locked file cabinet and on
6352 password-protected computers in the research staff workplace, with only code numbers
6353 identifying subjects. Study consent forms and the linkage between the participants’ names and
6354 codes will be stored in a locked file cabinet inside a locked office. Interviews with participants
6355 will be conducted in private rooms. Urine or saliva samples for drug and pregnancy tests and
6356 tobacco exposure biomarkers will be obtained in a private bathroom within the laboratory suite.
6357 Subjective measures will be administered electronically. The biostatistics and data-
6358 management team will provide consistent data-management practices for all data in the Center.
6359 Using REDCap, which is housed on the University of Vermont Medical Center’s HIPAA-
6360 compliant computing system, will maximize validity and reliability of data. REDCap is a secure,
6361 web-based system that accommodates local and remote data collection by each project team,
6362 and allows for data entry work-flow monitoring and data quality control monitoring by biometry
6363 staff. The RedCap database for this project will be hosted on the UVMCOM servers. In
6364 addition, data will be collected from participants on a daily basis using an interactive voice
6365 recognition system (IVR) developed and hosted by TeleSage Inc (www.telesage.com, Chapel
6366 Hill, NC). TeleSage is a company with expertise on gathering patient-centered outcomes
6367 tracking data for mental health clinical and research institutions. TeleSage has developed
6368 and hosted behavioral health-related research software systems using IVR and Web-
6369 based technologies and is leader in behavioral health outcomes tracking technologies. For
6370 data integrity, data entry windows will follow the structure of paper forms as much as possible to
6371 allow for ease of entry, and will use predefined choices to minimize errors when possible. Data
6372 quality monitoring will be facilitated with periodic down loads and analysis using a variety of
6373 common statistical program format such as SAS, Stata, R, and SPSS. Quality control
6374

6375 procedures will be conducted for all data collected, including analysis of missing data and logic
6376 checks for out of range and other anomalous values. This secure electronic data gathering and
6377 transmission plan, overseen by the experienced biostatistical team, will minimize opportunities
6378 for breaches of confidentiality. Biological samples for nicotine and carcinogen biomarker
6379 analysis will be marked with participant ID, stored in the locked laboratory suite, and sent to a
6380 laboratory for analysis on a quarterly basis.

6381 All information collected as part of this study will be accessible only to research staff. No
6382 information will be shared with participants' clinicians unless the participant requests this in
6383 writing. All investigators and staff have undergone (and any new staff will undergo) human
6384 subjects' ethics training as required by UVM and are fully conversant with relevant ethical
6385 principals around confidentiality. Assessments, consenting and study procedures will be closely
6386 supervised by the PI.

6387 The sponsors (NIDA/FDA) as well as the Institutional Review Board and regulatory
6388 authorities could be granted direct access to original medical and research records for
6389 verification of clinical trial procedures and/or data. If this is required, it will be done under
6390 conditions that will protect privacy to the fullest extent possible consistent with laws relating to
6391 public disclosure of information and the law-enforcement responsibilities of the agency.

6392 **11.2 Data Storage:**

6393 Data will be stored locally at each site. Long-term storage of all study data, for at least 7
6394 years after study completion, will be at the University of Vermont.

6395 **12. Adverse Events**

6396 The research assistant will ask about adverse events at each session, using a form that
6397 assesses the nature, severity, duration, action taken, and outcome of study-related adverse
6398 events. AEs will be captured from the time of first study cigarette. Participants will be given
6399 contact cards to inform us of events that occur between study contacts. Any AE that remains
6400 open will be reviewed and closed at an interview conducted 30 days after the study completion
6401 date (completers) or when the study should have ended had the participant completed the study
6402 (dropouts and those withdrawn by investigator).

6403 All procedures will be monitored to ensure that they conform to the approved protocol. In
6404 addition, monitoring will be done of all unforeseen circumstances that might arise and affect
6405 safety; of all reports of serious adverse events as defined in 38 CFR 46 (death, new or
6406 prolonged hospitalization, persistent or significant disability/incapacity); of other significant
6407 adverse events (adverse events that lead to drop out by the participant or termination by the
6408 investigator); of unexpected adverse events resulting from the study, and of expected adverse
6409 events.

6410 Any SAE will be brought to the attention of the site PIs as soon as possible and not longer
6411 than 24 hours. Any AE or SAE that is both unexpected and related to study participation will be
6412 reported to the IRB within 7 days of the event. The local IRB will make a determination as to
6413 whether additional reporting requirements are needed. IRB actions will be reported to the
6414 funding agency by the PIs no less than annually and more frequently as recommended by the
6415 local IRB. Any SAEs will be summarized in the yearly Progress Reports to the funding agency,
6416 including a review of frequency and severity. All SAEs will be followed through ongoing
6417 consultation with the physician caring for the patient until they resolve, result in death, or
6418 stabilize and are not expected to improve. The study staff will be in close contact with
6419 participants and health care providers throughout the study to monitor for potential
6420 unanticipated problems. Any unanticipated problems will be discussed at the weekly research
6421 staff meetings and reported as required to the local IRB.

6423 **13. Withdrawal or Monitoring of Participants**

6424 **For the participant's protection, participants will be withdrawn immediately from the**
6425 **study if any of the following occur:**
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- 1) Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
 - 2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
 - 3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
 - 4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
 - 5) Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at any time during the study, she will be withdrawn from the study, and this event will remain open until delivery. At that time the licensed medical professional will contact the participant to ask a few questions about the baby's health and will update the open 'Medical Event Form'. A positive pregnancy test at Week 16 will trigger a 'Medical Event Form' to be completed but will not result in withdrawal since she is no longer receiving study product.
 - 6) Expired breath carbon monoxide increase: A participant will be withdrawn from the study if the average of two consecutive CO readings during the same visit is 100 ppm or greater.
 - 7) Marked increase in smoking: A participant will be withdrawn from the study if he/she meets **BOTH** of the following criteria for two consecutive weeks
 - a. Cigarette per day increase: The average CPD increases by more than 100% from the average CPD during baseline.
 - b. Expired breath carbon monoxide increase: If the average of two consecutive CO measurements in the same visit is
 - i. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
 - ii. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
 - iii. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
 - iv. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
 - v. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
 - c. Note: If the second consecutive visit is the last study visit, then the participant would not be withdrawn from the study.
 - 8) If a participant is discharged from or discontinues his or her methadone or buprenorphine treatment, they will be discontinued from the study.

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The following will be monitored and can lead to the participant being withdrawn by the PI or Licensed Medical Professional:

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- 1) Cigarettes per day increase: Continued participation will be evaluated by the site PI if the average number of cigarettes per day (CPD) increases by more than 100% from the average CPD during baseline as determined by CPD at Baseline 2.
 - 2) Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-enrollment: 1) BP is at or above 160/100 or below 90/50, or 2) HR is at or above 115 bpm or below 45 bpm a manual blood pressure and heart rate measurement will be taken after 10 minutes have passed. If the manual reading is still out of range, a 'Blood Pressure and Heart Rate Symptom Checklist' and 'Medical Event Form' will be completed, and the participant will be monitored by the medical professional.
 - 3) Expired breath Carbon Monoxide increase: If the average of two consecutive CO measurements meets the criteria below then the 'Medical Event Form' will be completed and the participant will be monitored by the medical professional.

- 6478 a. CO is greater than 50 ppm if CO at Baseline 1 is <20 ppm.
6479 b. CO is greater than 60 ppm if CO at Baseline 1 is 20 – 34 ppm.
6480 c. CO is greater than 70 ppm if CO at Baseline 1 is 35 – 49 ppm.
6481 d. CO is greater than 80 ppm if CO at Baseline 1 is 50 – 64 ppm.
6482 e. CO is greater than 90 ppm if CO at Baseline 1 is 65 – 80 ppm.
- 6483 4) Any hospitalization or debilitation in which participation in the study could be detrimental
6484 to the recovery process. This will be self-reported by the participant and will be reviewed
6485 by the site PI and medical professional to determine whether continued participation in
6486 the study is appropriate.
- 6487 5) If a participant is behaving in an inappropriate or threatening manner, admits to lying
6488 about eligibility criteria, is participating in other smoking research studies that could
6489 affect the primary outcome measures, etc., then the PI can withdraw him/her from the
6490 study at the PI's discretion.
- 6491 6) If a participant fails to attend regularly scheduled research assessment visits or comply
6492 with the research procedures or schedule, then the PI can withdraw him/her from the
6493 study at the PI's discretion.
- 6494 7) Increase in psychiatric symptoms: Exacerbation in symptoms noted during the study
6495 (i.e., change in BDI category from mild to moderate or moderate to severe) will trigger
6496 review by the study's licensed medical professional. The PI will withdraw the participant
6497 upon the licensed medical professional's recommendation.
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14. Data Safety Monitoring Board

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6501 A Data and Safety Monitoring Board (DSMB) has been established to monitor safety
6502 outcomes and will be comprised of four members. The DSMB will be chaired by Kevin Delucchi,
6503 PhD., Professor in Residence of Biostatistics in Psychiatry at the University of California San
6504 Francisco and Director of the Quantitative Core of the San Francisco Treatment Research
6505 Center; Eden Evins, MD, MPH., Cox Family Professor of Psychiatry at Harvard Medical School
6506 and Director of Center for Addiction Medicine at Massachusetts General Hospital; Ari
6507 Kirshenbaum, PhD, Professor of Psychology at Saint Michael's College who he teaches
6508 courses in psychopharmacology and neuroscience, and currently has grants from NIH and NSF
6509 for work in human behavioral pharmacology and his grant-funded work focuses on cognitive
6510 and behavioral responses to nicotine and cannabinoids; and Elisabeth Johnson, Ph.D., who has
6511 over twenty years of clinical experience in women's health and pediatrics, including caring for
6512 women with substance use disorders.
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Conflict of Interest

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6515 None of the board members will be otherwise affiliated with the center and each member will
6516 complete a conflict of interest disclosure form prior to each meeting. Ad hoc specialists may be
6517 invited to participate as non-voting members at any time if additional expertise is desired.
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Monitoring Activities and Frequency of Meetings

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6520 The DSMB will set their own agenda and decisions about monitoring; e.g. how frequently to
6521 monitor, what threshold requires changes to protocol or stopping the study, and whether to view
6522 raw or analyzed data. The DSMB will be given FDA and EMEA guidelines for DSMBs and
6523 recent reviews on DSMBs. A brief report will be generated from each meeting for the study
6524 record and forwarded to each of the study site's Institutional Review Boards (IRB) and NIDA's
6525 Program Officer with the progress report. The DSMB will be available to convene outside of the
6526 regular meetings, if necessary. If concerns should arise regarding a particular subject, or any
6527 troublesome trends in the experiences of participants, they will make appropriate
6528 recommendations for changes in protocol, as needed. The project investigators will continue to
6529 examine safety data, blind to study condition, in case they wish to make study modifications.
6530 Before modifications are made, they will inform the DSMB and request their comments.
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6532 **Communication Plan to IRB, NIDA, and FDA (if applicable)**

6533 All IRBs, the FDA and the NIDA's Program Officer will be informed of any significant action
6534 taken as a result of the Data and Monitoring Board's findings. Study Participants will be
6535 informed of any changes in risk.
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6537 **Protection of Confidentiality**

6538 For DSMB meetings only de-identified data, including blinded study site and condition type,
6539 will be provided to the board. All data and discussion during the meeting will be confidential.
6540

6541 **15. Investigational Tobacco Product**

6542 The University of Vermont Center on Tobacco Regulatory Science will complete an
6543 Investigational Tobacco Product (ITP) application with the FDA to cover the experimental
6544 cigarettes being used in this study. This application encompasses both Project 1 sites.
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6547 **16. Certificate of Confidentiality**

6548 To help protect the participant's privacy, Dr. Stephen Higgins, PhD, will obtain a Certificate
6549 of Confidentiality from the national Institute on Drug Abuse. With this certificate, the researchers
6550 cannot be forced to disclose information that may identify the participants, even by a court
6551 subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other
6552 proceedings. The researchers will use the Certificate to resist any demands for information that
6553 would identify the participants, except as explained below. The Certificate cannot be used to
6554 resist a demand for information from personnel of the United States Government that is used
6555 for auditing or evaluation of federally funded projects or for information that must be disclosed in
6556 order to meet the requirements of the Federal Food and Drug Administration (FDA).
6557

6558 The Certificate of Confidentiality does not prevent the participant or a member of their family
6559 from voluntarily releasing information about themselves and their involvement in the research. If
6560 an insurer, employer or other person obtains the participant's written consent to receive
6561 research information, then the researcher may not use the Certificate to withhold that
6562 information.

6563 The Certificate of Confidentiality does not prevent the researchers from disclosing
6564 voluntarily, without consent, information that would identify the individual as a participant of the
6565 research project in instances such as evidence of child abuse or a participant's threatened
6566 violence to self or others.


6567 **17. Outcome Variables**

6568 **Primary Endpoints for Study 3:**

- 6569 1) Cigarette Smoked per Day (CPD)
6570 2) Nicotine Dependence Severity
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6572 **Secondary Endpoints for Study 3:**

- 6573 1) Measures of adherence: non-study cigarette use, drop-out rate
6574 2) Measures of psychiatric symptoms: BDI, OASIS
6575 3) Measures of discomfort/dysfunction: MNWS, QSU
6576 4) Measures of other health-related behaviors: breath alcohol, urine or salivary drug
6577 screen, TLFB-drug use, Alcohol Use Questionnaire, Drug Use Questionnaire, weight
6578 5) Measures of nicotine/tobacco dependence: FTND, WISDM
6579 6) Measures of tobacco exposure: CO, total nicotine equivalents, NNN, NNAL, minor
6580 alkaloids
6581 7) Measures of intention to quit: Stages of Change, Contemplation Ladder
6582 8) Measures of compensatory smoking: puff topography, filter analysis
6583 9) Measures of other tobacco use: TLFB-other tobacco

- 6584 10) Measures of cigarette characteristics: CES, Cigarette Purchase Task
 - 6585 11) Measures of cardiovascular function: heart rate, blood pressure, urine 11-
 - 6586 dehydroTXB2
 - 6587 12) Measures of perceived risk: Perceived Health Risk Questionnaire
 - 6588 13) Safety outcome variables: Adverse Events (AEs), Serious Adverse Events (SAEs)
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