Official Title:

The Abuse Liability of a Novel Heated Tobacco Product (IQOS) and Its Feasibility as a Menthol Cigarette Substitute

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1. Objectives:

This project's objective is to determine if menthol cigarette smokers will substitute with a modified risk tobacco product (an HTP known as "IQOS") and whether the availability of a menthol-flavored HTP is important for substitution behaviors in this population. The overarching hypothesis is that, relative to own brand menthol cigarettes (OB), IQOS-menthol's abuse liability profile will differ less than IQOS-tobacco's, suggesting that menthol smokers will be more likely to substitute an HTP for combustible cigarettes when a menthol-flavored HTP option is available. The specific aims of our study are to:

Aim 1. Assess IQOS' abuse liability among menthol smokers in a clinical lab setting. In clinical lab sessions, participants will complete standard controlled product use episodes (10 puffs, 30-sec inter-puff interval) with OB (baseline) and IQOS (intervention). Blood will be sampled to assess nicotine/menthol delivery, puff duration and volume will be measured to assess use behavior, and subjective effects (e.g., cigarette craving) and the Experimental Tobacco Marketplace (ETM) task will assess IQOS' substitutability for OB. H_{1A}: Nicotine delivery will be lower for IQOS-tobacco than IQOS-menthol, but both will deliver less nicotine than OB menthol cigarettes. H_{1B}: Puff duration will be greater for IQOS-menthol than IQOS-tobacco. H_{1C}: IQOS-menthol will reduce craving for cigarettes more completely than IQOS-tobacco. H_{1D}: The cross-price elasticity of IQOS with respect to own-brand menthol cigarettes will be higher in a market with access to both IQOS-menthol and IQOS-tobacco than it will be in a market with access only to IQOS-tobacco. H_{1E}: IQOS-menthol will deliver more menthol than IQOS-tobacco, but both will deliver less menthol than OB menthol cigarettes.

Aim 2. Measure tobacco use patterns across IQOS flavor availability conditions to assess clinical lab result validity. During 7-day naturalistic evaluation outside of the clinical lab, participants will respond to daily Ecological Momentary Assessment (EMA) prompts by reporting OB and IQOS use. H_{2A}: Those in the IQOS-menthol condition will have a larger percentage reduction in average daily cigarettes consumed per day (Tues-Thurs) from the baseline to the intervention week, than those in the IQOS-tobacco condition. H_{2B}: IQOS use/day higher during the intervention week (Tues-Thurs) will be higher in the IQOS-menthol condition compared to the IQOS-tobacco condition. H_{2C}: Those with access to IQOS-menthol will replace a greater percentage of their total tobacco product consumption (cigarettes + IQOS) with IQOS products during the intervention week (Tues-Thurs) than will those with access to IQOS-tobacco.

Hypothesis H_{1A}, H_{1D}, and H_{2A} constitute primary outcomes. All other hypothesis represent secondary outcomes.

Primary Study Endpoints:

Aim 1: For sub-hypothesis A, the outcome is the baseline-adjusted plasma nicotine concentration following a 10-puff directed bout with the participant's randomly assigned IQOS product on Friday of the intervention week. For sub-hypothesis B, the outcome is the average duration of the puffs taken during the 10-puff directed puffing bout with the participant's randomly assigned IQOS product on Friday of the intervention week. For sub-hypothesis C, the outcome will be the degree of cigarette craving suppression from before to after the directed puffing bout with the participant's randomly assigned IQOS product on Friday of the intervention week. Sub-hypothesis D will consider differences in IQOS' cross-price-elasticity obtained during the ETM performed on Friday of the intervention week between those with access to IQOS-M and IQOS-T and those with

access to IQOS-T only. Sub-hypothesis E will compare the baseline-adjusted plasma menthol-glucuronide following a 10-puff directed bout between IQOS-M and IQOS-T groups on Friday of the intervention week.

Aim 2: The primary EMA outcome (H2A) is the percentage reduction in average daily consumption of cigarettes (Tues-Thurs) from the baseline to the intervention week (e.g., 10 cigs/day in baseline week to 2 cigs/day in intervention week = 80% reduction). The outcome for H2B is the average daily number of IQOS HeatSticks used on Tues-Thurs of the intervention week. The outcome for H2C is the percentage of average daily consumption of tobacco products (cigarettes + IQOS) consumed during the intervention week (Tues-Thurs) that are IQOS HeatSticks.

2. Overview of Design. Once enrolled, eligible participants will complete a two-arm, parallel group, 14-day clinical lab study (Aim 1) of IQOS that includes naturalistic assessment (Aim 2; see Table 1). First, participants will complete a 7-day positive-control, own-brand (OB) menthol cigarette baseline. Then, for the second 7-day period, participants will be randomized (1:1 allocation; stratified by gender (Male vs Female) and race (African American/Black vs non-African American/Black) to receive either IQOS-M or IQOS-T and instructed to attempt to use their assigned product as a complete cigarette substitute. The baseline and intervention weeks will feature clinical lab sessions (Monday and Friday) and daily naturalistic use assessments.

3. Participants**.** A total of 50 community volunteers who currently use menthol cigarettes will be randomized in this study (25 per condition; randomization will stratify across gender (Male vs Female) and race (African American/Black vs non-African American/Black).

Inclusion Criteria

- Healthy adults (aged 21 and older)
- Smoke at least 5 cigarettes per day for at least 1 year (i.e., established, daily smokers)
- Regular cigarette brand is flavored to taste like menthol or mint
- Exhaled Carbon Monoxide (CO) reading of > 5 PPM at in-person screening, as well as a 'positive' cotinine cassette result, to verify smoking status/nicotine use at the in-person screening.
- Report no intention to quit smoking in the next 3 months
- Participants must be willing to provide informed consent and abstain from nicotine/tobacco for ≥8 hours prior to each lab session.
- Participants must have access to a computer/smartphone and be willing to receive and respond to daily surveys
- Able to read and write in English

Exclusion Criteria

- Daily use of any tobacco products other than cigarettes
- Self-reported history of unstable or significant medical conditions in the past 12 months. These include: uncontrolled high blood pressure (via self-

report or observed at screening; BP must be less than 160/100 at screening), heart-related conditions (e.g., recent heart attack/stroke, coronary heart disease), severe immune system disorders (e.g., HIV/AIDS, multiple sclerosis), respiratory disorders (e.g., COPD, asthma), kidney diseases, liver diseases (e.g., cirrhosis), or seizures.
        - Individuals with other self-reported current, diagnosed medical conditions (e.g., diabetes, thyroid disease, lyme disease) will be considered for exclusion after consultation with the PI and medical monitor. Participants with any medical condition/medication that may affect participant safety, study outcomes, or biomarker data will be excluded based on these consultations.
    - Individuals with current, diagnosed, psychiatric conditions that are uncontrolled will be excluded. A controlled psychiatric illness is defined as one where the individual is taking medication and/or receiving other treatment (e.g., psychotherapy). In addition, individuals who have been to the ER and/or been hospitalized for a psychiatric condition in the past year will be excluded.
    - Cannabis use >15 days, alcohol use >25 days, and any other illicit drug use (e.g. cocaine, opioids, etc.) in the past 30 days.
    - Women will be excluded if they test positive for pregnancy (by urinalysis) or self-report breastfeeding.

These inclusion and exclusion criteria are consistent with those employed by Dr. Barnes' recently awarded clinical trial (R01DA050996 [HM20022060]) and previous studies conducted at the VCU Center for the Study of Tobacco Products, including 2 F31 awards (F31DA047018 [HM20015258] and F31DA054780 [HM20018418]).

4. **Recruitment and Enrollment.** Participants will be recruited by institutional review board-approved advertisements and by word of mouth. The BHRL and CSTP Tobacco User Registries are available to aid recruitment efforts. Interested individuals will use the BHRL or CSTP website to complete a screening survey online (i.e., "brief pre-screener") or call the BHRL or CSTP to complete the same survey via phone to determine initial eligibility.

5. **Consent process.** Following documentation of initial eligibility, participants will be contacted to confirm their initial interest in the study and invited to an in-person screening session where consent will be obtained. Prior to the in-person session, we will provide all participants with an unsigned copy of the consent form for them to review via email. Researchers will be available in-person and via email/phone to answer any questions participants may have about the study during the consent process. See SmartForm for more detail on the consenting process.

6. **Study Procedures.**

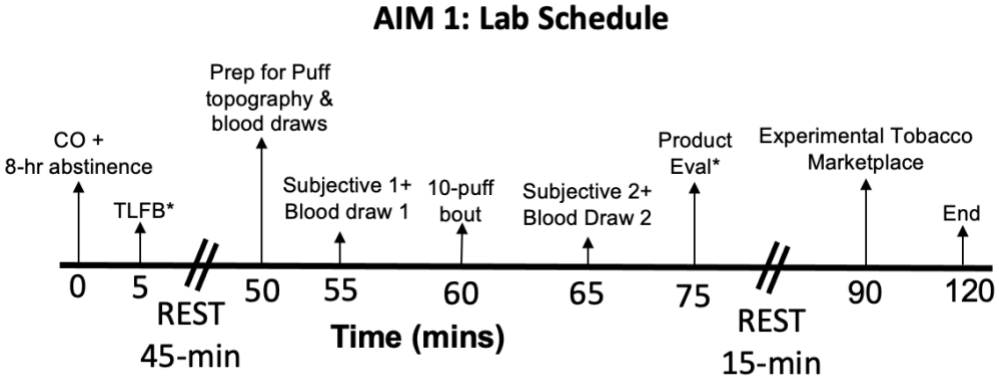
The study is divided into 3 phases: Screening/Enrollment, Baseline Week (use OB menthol cigarettes), and Intervention Week (use randomly-assigned) IQOS product. In the Screening/Enrollment phase, participants will complete the CSTP/BHRL registry to assess initial eligibility for this study and those deemed potentially eligible will be invited to an in-person screening session at the CSTP. At this session, informed consent will be obtained, eligibility confirmed, and baseline/demographic information collected. At the end of the in-person screening session, all eligible and consenting participants will be given an opportunity to take 4 test puffs of the IQOS product (flavor: Tobacco). During the baseline and intervention weeks, participants will complete clinical lab sessions (see "Aim 1" below) and naturalistic use assessments (see "Aim 2" below). Please note, at the start of each in-person activity, participants will answer 4 questions to screen for COVID-19 as with the CSTP's other ongoing projects (all answers must be "no" in order to continue). Randomization will occur at the beginning of the first clinical lab session (Monday, Baseline week) to allow for the proper ETM to be displayed during all subsequent sessions.

	Pre-screen	Screen	Mon	Tues -Thurs	Fri	Sat-Sun	Mon	Tues-Thurs	Fri	Sat-Sun
Week	NA	0	1	1	1	1	2	2	2	2
Phase	**Screening/Enrollment**		**Baseline Week (Own-Brand Menthol Cigarettes)**				**Intervention week (IQOS-menthol or IQOS-tobacco)**			
Main Activity	Online Survey	In-person screening + Test Puffs	Lab Visit 1 + Randomization	Natural Use (EMA)	Lab Visit 2	Natural Use (EMA)	Lab Visit 3 + IQOS Distribution	Natural Use (EMA)	Lab Visit 4	Natural Use (EMA)
Time	10 min	60 min	120 min	3 min/day	120 min	3 min/day	120 min	3 min/day	120 min	3 min/day
Relevant Measures	Baseline Demographics, Health, and Tobacco Use		Aim 1	Aim 2	Aim 1	Aim 2	Aim 1	Aim 2	Aim 1	Aim 2

Aim 1: During the course of the clinical lab study set forth in Aim 1, participants will complete directed puffing bouts (10-puffs, 30 second interpuff interval) with either OB (baseline week) or their randomly-assigned IQOS product (intervention week). The interpuff interval is defined as the time between the start of 1 puff and the beginning of the next (Hiler et al., 2017). This procedure requires physiological monitoring of heart rate and blood pressure (sessions will be stopped if blood pressure ever exceeds 180/120) and venipuncture and/or catheter placement will be completed by Ms. Gaitan, RN. One blood sample (7 mLs) will taken immediately before and immediately after a standard, controlled 10-puff directed puffing bout (total of 14 mL per session). A total of 56 mL of blood will be sampled for the entire study; this amount of blood sampling will occur at 4 sessions over a 12 day period and is less than a standard blood donation that is provided in a single sitting (473 mL). Outcome measures include changes in plasma nicotine and menthol concentration from pre- to post- puffing bout and subjective effects, including cigarette craving suppression as well as the direct effects of OB and IQOS. Following this procedure, participants will then complete an Experimental Tobacco Marketplace (ETM). In the ETM, participants will be asked to make purchasing decisions across an array of tobacco/nicotine products, including IQOS and OB, as their OB become increasingly expensive (prices will be presented in random order at each session [i.e., the order of price-

trials will be randomly determined for each session, but within a session each participant will face the same order of price-trials]). The minimum task time for the ETM will be set to 20 minutes (i.e., if a participant finishes all questions in the ETM before 20 minutes, they'll cannot progress to the next portion of the session until 20 minutes has elapsed). The primary outcome of interest is the cross-price elasticity of demand for IQOS as a function of OB price. Each session will begin by obtaining an exhaled Carbon Monoxide breath sample, as will be done in the in-person screening session, and asking participants whether they've abstained from using tobacco or nicotine products in the last 8 hours. Moreover, on the 2 Friday sessions, participants will complete a short "timeline follow back" assessment to report on their usage of cigarettes, IQOS, and other tobacco products during the preceding 3-days (Tues-Thurs). A timeline of session structure is provided below.

Though every effort will be made to have participants complete the study on the prescribed timeline (in-person screening, 2 baseline week visits [Mon, Fri], 2 intervention week visits [Mon, Fri]), we recognize that things outside the participant's or the researcher's control could impact completion of the study on this schedule. Thus, to handle the event in which a participant misses a session, we have devised the following plan. If an in-person screening session is missed, that session will be rescheduled at the participant's convenience. If the participant misses 1 of the baseline week visits, we will NOT reschedule the missed session – the single baseline visit that was completed will be used as the control comparison in statistical analyses. If both baseline visits are completed, the Friday results will be used as the control comparison. If a participant misses their Monday intervention week visit, we will reschedule for the next Monday on which the participant is available and commence the week as normal from that point. If a participant misses their Friday intervention week visit, we will reschedule for the next business day on which the participant is available. Friday intervention week sessions will not be rescheduled such that the "naturalistic" use period is any less than 3 full days (i.e., the rescheduled session will occur the following week).



Aim 2: In addition to the clinical lab sessions, participants will report usage of OB and their randomly assigned IQOS product daily by responding to ecological

momentary assessment (EMA) prompts (text or email) sent each morning of the 2-week study window. Surveys will be sent at 8 AM each day; if a participant has not responded by noon a reminder text/email will also be sent. Outcomes are primarily concerned with responses to EMA prompts on Tuesday, Wednesday, and Thursday of each week – but prompts will be sent daily to encourage habit formation and compliance. Participants will use their OB during the baseline week.

On Monday of the intervention week, at the conclusion of the clinical lab session, participants will be given an IQOS 2.4 Tobacco Heating System, HeatSticks in their randomly-assigned flavor (Fresh Menthol or Regular Tobacco), and brief instructions for use (including a handout with accompanying video). Participants will be provided with the same number of HeatSticks as cigarettes they reported consuming during the baseline week, plus 20% to account for potential product loss or increases in use. Participants will be instructed "We are providing you with an a heated tobacco product known as IQOS in [condition-specific flavors] over the next week to be used as a substitute or complete replacement for your own brand cigarettes. We want to understand how you use these specific heated tobacco products as well as your own brand cigarettes when they are the only products available to you. Therefore, please refrain from using all other nicotine/tobacco products and other heated tobacco product flavors for the duration of the study. If you use anything else, it is important that you tell us what you used. Additionally, please return all of the IQOS product and any unused HeatSticks at your lab visit on Friday."

7. **Measures.** Participants will complete the measures in the timeline shown below.

Study Period	**Pre-screen**	**In-person Screening**	**Clinical Lab Sessions**	**Daily Surveys**
Study Days	**NA**	**0**	**1, 5, 8, and 12**	**1-14**
Demographics	X	X		
COVID-19 Screening Questionnaire		X	X	
Heart Rate and Blood Pressure Monitoring		X	X	
Urine pregnancy and cotinine tests		X		
Exhaled Carbon Monoxide		X	X	
Tobacco Use History	X	X		
Drug & Alcohol Use		X		
Health and Medical History	X	X		
Reasons for flavored tobacco use		X		
Contact information		X		
Cigarette Dependence (PROMIS 4A and PSNDI)		X		
Stage of Change / Quit Confidence		X		
Test Puffs (4) of IQOS-Tobacco		X		
Adverse Events			X	
3-day Timeline Follow Back			X (Days 5 and 12 only)	

Product Evaluation Questionnaire			X	
Subjective Effects Questionnaire			X	
Plasma Nicotine and Menthol Collection			X	
Puff Topography			X	
Experimental Tobacco Marketplace			X	
Ecological Momentary Assessment				X

Baseline/Screening and Cigarette/Tobacco Measures: We will assess contact information, demographics (e.g., age, gender, race, ethnicity, income, occupation), tobacco use history, other drug/alcohol use, and health and medical history including health/psychiatric conditions (e.g., Medical History Form used in P50DA036105-Project 3), reasons for flavored tobacco use (CASEL Flavors Working Group, 2021), cigarette dependence (PROMIS 4A; Shadel et al. 2014, Penn State Nicotine Dependence Index [PSNDI], Foulds et al., 2015), stages of change/quitting confidence using standardized items from PhenX and national surveys (e.g., PATH; BRFSS; TUS-CPS), and items/measures adapted for menthol cigarettes. Additionally, those that attend the in-person screening but are deemed ineligible because their blood pressure exceeds the limits set in the inclusion/exclusion criteria will be given a letter explaining their test result and directed to resources that can help them in the management of hypertension.

8. **Compensation.** Participants will be compensated for their time: $25 for in-person screening, $2 for each complete EMA assessment (14 total), $50 for each of two Monday sessions, and $100 for each of two Friday sessions. Total possible compensation for this study amounts to $353. We'll also reimburse participants up to $12/session for parking, if needed.

9. **Statistical Analysis Methods and Sample Size/Power.** 50 participants will be needed to obtain power ≥0.80 to detect a difference between subjects on the plasma nicotine outcome, with alpha<0.05 (G*power 3.1.9.7). The power analysis was based on previous studies (Ns ~30) where effect sizes of the main effect of condition were large for ETM outcomes (d>1.16), medium for plasma nicotine (d>0.76), and large for reduction in average daily number of cigarettes (d>2.66).

Aim 1 Analyses.

Plasma Nicotine

The main plasma nicotine outcome was the change in plasma nicotine concentration from before the 10-puff bout to after (i.e., nicotine boost) at the final clinical laboratory session (Fri, week 2; session 4, study day 12). Plasma nicotine boost was calculated for each participant by subtracting their pre-puff plasma nicotine concentration from their post-puff plasma nicotine concentration at each session. Mann-Whitney U tests compared the participant-level nicotine boost estimates across the IQOS-M and IQOS-T groups (Stata 17).

Exploratory analyses compared within-group differences in nicotine boost between sessions 3 (Mon, week 2; study day 8) and 4 (Fri, week 2; study day 12) using Wilcoxon Signed Rank tests. Differences in nicotine boost between OB menthol cigarettes (Fri, week 1; study day 5) and IQOS (Fri, week 2; study day 12) were assessed within each group using Wilcoxon

Signed Rank tests. Pre- and post-puff plasma nicotine concentrations at each session were compared within-group using Wilcoxon Signed Rank tests to determine if pre- and post-puff plasma nicotine concentrations differed.

Puff Topography

The main puff topography outcome was the average puff duration during the 10-puff directed use bout at the final clinical laboratory session (Fri, week 2; session 4, study day 12). Mann-Whitney U tests compared the mean puff duration during the 10-puff directed use bout across the IQOS-M and IQOS-T groups (Stata 17).

To assess whether puff topography patterns changed during the 5-day naturalistic exposure to IQOS, topography outcomes at session 3 (Mon, week 2; study day 8) and session 4 (Fri, week 2; study day 12) were compared within-group using Wilcoxon Signed Rank tests. Difference in topography outcomes between OB menthol cigarettes (Fri, week 1; study day 5) and IQOS (Fri, week 2; study day 12) were assessed within-group using Wilcoxon Signed Rank tests.

Self-Reported Effects

The main self-reported effects outcome was the change in self-reported "craving a cigarette/nicotine" on the MNWS from before the 10-puff directed use bout to after at the final clinical laboratory session (Fri, week 2; session 4, study day 12). The change in "craving a cigarette/nicotine" was calculated for each participant by subtracting the pre-puff measurement from the post-puff measurement (i.e., cigarette craving suppression). Mann-Whitney U tests compared differences in cigarette craving suppression across the IQOS-M and IQOS-T groups (Stata 17).

Differences across experimental groups in pre- to post-puff changes in QSU-B Factor 1, pre- to post-puff changes in QSU-B Factor 2, pre- to post-puff changes in all MNWS items, PEQ subscales, and the study specific questions were explored at session 2 (OB; Fri, week 1), session 3 (IQOS; Mon, week 2), and session 4 (IQOS; Fri, week 2) using Mann-Whitney U tests. Exploratory analyses compared within-group differences in all self-reported effects outcomes at session 3 (IQOS; Mon, week 2; study day 8) to session 4 (IQOS; Fri, week 2; study day 12) using Wilcoxon Signed Rank tests. Wilcoxon Signed Rank tests compared self-reported effects outcomes associated with use of OB menthol cigarettes (Fri, week 1; study day 5) to IQOS (Friday, week 2; study day 12) within each experimental group. Differences in the pre-puff and post-puff values for items on the QSU-B and MNWS were explored within-group using Wilcoxon Signed Rank tests.

Experimental Tobacco Marketplace

The main ETM outcome was IQOS' CPE with respect to OB menthol cigarettes. Demand for all products in the ETM was converted to milligrams (mg) of nicotine to allow for cross-product comparisons (Bickel et al., 2018; Appendix 4) then log transformed (zero consumption values were converted to a nonzero integer by adding 0.1). CPE estimates for each alternative product in the ETM were estimated using an approach based on linear regression (Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2017; Quisenberry, Koffarnus et al., 2016). CPE estimates were generated for each fixed-price alternative, for each individual, by creating a

linear regression of log-transformed fixed-price alternative demand as a function of log-transformed OB menthol cigarette prices,

$$\log(Demand) = \beta_0 + \beta_1 \log(OB\ Menthol\ Cigarette\ Price) + e,$$

where β_0 represented the cross-price intensity of demand, β_1 represented the CPE of the fixed-price alternative as a function of OB menthol cigarette price (main outcome), and e was the error term. Mann-Whitney U tests compared the individual-level CPE estimates for IQOS across participants with access to both flavors of HeatSticks (IQOS-M group) to participants with access to only Regular/Tobacco HeatSticks (IQOS-T group) at the final clinical laboratory session (IQOS; Fri, week 2; session 4, study day 12). As an alternative strategy for calculating CPE estimates, demand for each fixed-price alternative was averaged within-group at each price trial in the ETM then a single regression for each group was fit to Equation 1. The resulting β_1 coefficient estimates were compared across experimental groups using a linear combination of parameters approach.

To ensure data quality and that participants were responding to the price cues within the task, demand for OB menthol cigarettes in the ETM was modeled using an exponentiated demand equation (GraphPad Prism 9; Hursh & Silberberg, 2008),

$$Q = Q_0 + 10 * k\left(e^{(-\alpha(C*Q_0))}\right) - 1),$$

where C represented the cost of the OB menthol cigarettes, Q represented cigarette consumption at price C, Q_0 represented OB menthol cigarette demand intensity (i.e., cigarette consumption at the lowest price trial), k represented the range of cigarette demand across price trials in log units, and α was the free parameter that represented the rate of change in demand elasticity. k was set equal to 4.89 for all participants (Hursh & Roma, 2013; Hursh & Silberberg, 2008; Quisenberry, Koffarnus et al., 2016). Group-level averages for α and R^2 were the outcomes of interest; α was expressed in terms of log(α) because α values tend to be very small. OB menthol cigarette demand was also assessed for each participant using criteria (i.e., trend, bounce, reversal from zero) for identifying nonsystematic demand in purchase tasks (Stein, Koffarnus et al., 2015).

Exploratory analyses compared the observed *cross-price intensity* of IQOS (i.e., demand for IQOS at the lowest price of OB menthol cigarettes [$0.12/cigarette]) across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. CPE estimates for all other alternative products were compared across experimental groups using Mann-Whitney U tests (individual-level analyses) and a linear combination of parameters (group-level analyses). Wilcoxon Signed Rank tests compared ETM outcomes (within-group) across sessions 2 (OB, Fri) and 4 (IQOS, Fri) as well as across sessions 3 (IQOS, Mon) and 4 (IQOS, Fri) to gauge if exposure to IQOS in the clinical laboratory or at home influenced purchasing decisions in the ETM.

Aim 2 Analyses.

Naturalistic Use

The main naturalistic use outcome was the percentage reduction in the mean number of cigarettes smoked per day from the baseline week (Tues-Thurs, week 1) to the intervention week (Tues-Thurs, week 2) based on responses to EMA prompts. The percentage reduction in mean number of cigarettes smoked per day was calculated for each individual as (Stone, DeAtley et al., 2022):

$$\%\ reduction\ in\ cigarettes\ consumed\ per\ day = 100 \times \left(\frac{Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 1,\ Tues-Thurs} - Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 2,\ Tues-Thurs}}{Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 1,\ Tues-Thurs}}\right)$$

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Percentage reductions in OB menthol cigarette consumption from the baseline week to the intervention week were compared across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. As sensitivity analyses, statistical comparisons were repeated using responses to the three-day TLFBs conducted at sessions 2 (OB, Fri) and 4 (IQOS, Fri) and by imputing missing EMA values with multiple imputation by chained equations (i.e., predictive mean matching based on five nearest neighbors across 10 imputed datasets). Exploratory analyses compared mean daily use of IQOS HeatSticks (Tues-Thurs) during the intervention week across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. Within-group differences in total tobacco consumption (i.e., sum of IQOS and OB consumption), OB cigarette consumption, and IQOS consumption during week 1 compared to week 2 were evaluated using Wilcoxon Signed Rank tests.

10. Withdrawing Participants

Participation in this study may be stopped at any time by the investigator without participant consent. The reasons might include:

- the investigator thinks it necessary for the participant's health or safety
- the participant is found to not be eligible for the study
- the sponsor has stopped the study
- the participant has not followed study instructions
- administrative reasons require the participant's withdrawal

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