Penn Medicine
University of Pennsylvania School of Medicine

CLINICAL RESEARCH PROTOCOL

The Effects of IQOS Use on Cigarette Smoking Behaviors

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1 Study Summary

Title	The Effects of IQOS Use on Cigarette Smoking Behaviors
Short Title	IQOS
IRB Number	843646
Methodology	This within-subjects study aims to evaluate the effects of IQOS use on combustible cigarette smoking behaviors among 160 cigarette smokers. After measuring baseline cigarette smoking rate, participants will receive an IQOS device and be instructed to use it (versus cigarettes) over a 14-day period. We will also examine which objective and subjective effects of IQOS use predict a complete and incomplete switch from cigarettes to IQOS.
Study Center(s)	Single-center
Objectives	**Aim 1:** To evaluate the effects of IQOS use on cigarette smoking behaviors. **Aim 2**: To examine which subjective and objective effects of IQOS predict cigarette smoking.
Number of Participants	Forty participants
Main Inclusion and Exclusion Criteria	Main Inclusion: 1. Male and female current cigarette smokers who are between 18 and 65 years old and self-report smoking at least 5 cigarettes per day for at least the last 12 months. 2. Not currently undergoing smoking cessation treatment or planning to quit smoking within the next 30 days. 3. Report an interest in quitting smoking within the next 6 months. Main Exclusion: 1. Regular use of nicotine containing products other than cigarettes. 2. Current enrollment or plan to enroll in a smoking cessation program over the duration of the study. 3. History of substance abuse (other than nicotine dependence) in the past 12 months and/or currently receiving medical treatment for substance abuse. 4. Alcohol use greater than 20 standard drinks/week. 5. Women who are pregnant, breast feeding, or planning a pregnancy over the duration of the study period. 6. Serious or unstable disease within the past year (e.g. cancer, heart disease). 7. Lifetime history of schizoprenia or psychosis. **The complete list of study inclusion and exclusion criteria is included within the Characteristics of the Study Population section of this protocol.**

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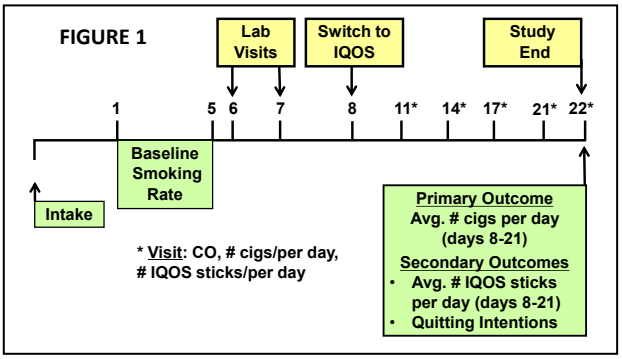
2 Introduction

This document is a protocol for a human research study. This study is to be conducted in compliance with this research protocol, as well as according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.



2.1 Background

Combustible cigarette smoking results in the rapid delivery of nicotine, contributing to smoking persistence, as well as long-term exposure to numerous toxins and carcinogens. Heat-not-burn (HNB) tobacco products are an emerging nicotine delivery innovation designed to deliver nicotine without the toxins associated with combustion. In 2019, the FDA approved the sale of IQOS, the first HNB tobacco product available in the U.S. Manufactured by Philip Morris International, IQOS is a rechargeable electronic device that produces a nicotine-containing aerosol by heating a disposable tobacco stick called HEETS or HeatSticks.

Since entering the market in 2014, global sales of IQOS have increased with millions of users across 50 countries. In 2017, 1 in 10 smokers in the U.S. was aware of HNB tobacco products such as IQOS. Awareness increased by 33% across the following 12 months. Among those aware, 18% had ever used IQOS, while almost 9% were current users, a 50% increase from the previous year. Current smokers had six times the odds of ever use compared to never smokers, suggesting the potential for dual product use. Tobacco scientists and market analysts forecast rapid growth in IQOS sales in the U.S. over the next few years.

While demand for IQOS is expected to increase among cigarette smokers, the lack of scientific studies evaluating the impact of IQOS use on cigarette smoking behaviors renders us unable to predict how an increase in IQOS sales will affect public health and regulatory actions. The proposed research will examine: 1) whether cigarette smokers switch completely to IQOS or dual-use two tobacco products; 2) whether IQOS use affects smokers' motivation to quit smoking cigarettes; and 3) how risk perceptions of IQOS and IQOS use impact cigarette smoking behaviors.

The proposed study will fill gaps in the evidence base by recruiting combustible cigarette smokers to a 21-day protocol using a within-subjects design. Baseline smoking rate will be established during days 1-5. After overnight cigarette smoking abstinence, laboratory visits on days 6 and 7 will assess IQOS-associated craving relief, withdrawal relief, subjective reward, and the reinforcing value of IQOS relative to combustible cigarettes. Participants will switch from cigarette smoking to IQOS use for the following 14 days (days 8-21). Participants will collect their spent cigarette filters and their used IQOS HeatSticks daily in order to assess consumption of cigarettes per day (cpd) and tobacco HeatSticks per day (spd). The primary outcome measure will be the longitudinal daily count of cigarettes from baseline to the end of the 14-day IQOS switch phase. Changes in motivation to quit smoking will be a secondary outcome.

3 Study Objectives

Aim 1: To evaluate the effects of IQOS use on cigarette smoking behaviors.

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H1a: IQOS use will decrease the number of cigarettes smoked per day relative to baseline. We do not expect IQOS to replace all cigarettes, and we will measure IQOS only use (complete switching), cigarette smoking only, and dual use.

H1b: The reduction in number of cigarettes smoked per day will be associated with the number of IQOS sticks used.

H1c: IQOS use will decrease smokers' motivation to quit cigarette smoking.

Aim 2: To examine which subjective and objective effects of IQOS predict cigarette smoking.

H2: Participants with lower IQOS risk perceptions, greater craving and withdrawal relief, greater IQOS subjective reward, and a higher relative reinforcing value of IQOS will smoke fewer cigarettes per day during the 14-day switching phase.

This will be the first independent and prospective study to examine the subjective, objective, and behavioral effects of IQOS use on cigarette smoking behaviors (i.e., switching, dual use and smoking cessation-related behaviors). As the only HNB tobacco product available in the US, demand for IQOS presents tobacco control challenges such as encouraging the long-term use of combustible cigarettes and foregoing the benefits of cessation, while risking the unknown effects of dual use. A greater understanding of IQOS use and its relationship to cigarette smoking will be fundamental to address these challenges and to inform appropriate public health and regulatory actions. The findings will directly address CTP's Rapid Response priority #4 (Behavior) to assess the likely impact of heated tobacco products on cigarette smoking behaviors (i.e., switching, use, dual use and smoking cessation-related behaviors).

4 Study Design

4.1 General Design

We propose to conduct a within-subjects study of the impact of IQOS use on smoking behavior among 160 combustible cigarette smokers. Eligible smokers will participate in 8 visits across a 21-day protocol. Participants who are eligible based on telephone screening will complete an in-person Intake Visit (**day 0**). Those eligible will complete measures of demographics, smoking history, and motivation to quit smoking. Baseline cigarette smoking rate will be established during **days 1-5** by instructing participants to smoke as usual for the following five days (**days 1-5**), while collecting their spent cigarette filters each day. Participants will return to the lab on **day 6** after overnight smoking abstinence (CO < 10). Participants will be required to use the IQOS device in the lab, then complete an assessment of IQOS-associated craving relief, withdrawal relief, subjective rewarding value of IQOS, and IQOS-associated risk perceptions. Participants will also return to the Center on **day 7** after overnight smoking abstinence (CO value 50% of Intake visit's CO value) for an assessment of the Relative Reinforcing Value of IQOS (RRVI) after required use of the IQOS device in the lab. **See Figure 1.**

Participants will then be instructed to use IQOS (versus cigarettes) for the following 14 days (**days 8-21).** Participants will collect their used cigarette filters and their used IQOS HeatSticks daily in order to assess consumption of cigarettes per day and sticks per day. Participants will return to the Center on days 11, 14, 17, and 21 to have their carbon monoxide (CO, exhaled breath) measured, and to return their used tobacco sticks and any spent cigarette filters. Cigarette smoking status will be assessed via self-report, spent cigarette filters, and biochemically verified (CO value 50% of Intake visit's CO value). Changes in motivation to quit smoking will be measured at study end, and all remaining used sticks and spent cigarette filters will be returned on Day 22.

On Day 22, participants will be: (1) informed of the lack of data supporting IQOS as a smoking cessation aid or harm reduction tool; (2) cautioned on the likelihood of dual use and the risks

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associated with dual use; (3) advised to either quit using IQOS or to quit smoking cigarettes if they are using both; and (4) referred to a smoking cessation program if interested in quitting smoking. The **primary outcome** measure will be the longitudinal daily count of cigarettes from baseline to the end of the 14-day IQOS switch phase. Changes in motivation to quit smoking from baseline to study end will be a **secondary outcome**.

4.2 Study Duration

Recruitment/enrollment for the pilot version of this study began in November 2020 and and will continue until July 2021. Recruitment/enrollment for the full version of this study is anticipated to begin in August 2021 and will continue until January 2024. We estimate that up to 40 participants will have completed the pilot version of the study by July 2021, and we estimate that up to 120 participants will have completed the study by August 2024, for a total of 160 participants completing the study. Each participant will be considered "active" within the study for 21 days per the study design.

4.3 Rationale

4.1.1 Rationale for within-subject design

We chose a within-subjects design for several reasons. First, our proposed aims and hypotheses reflect intra-individual change across time. Baseline smoking rate will be established across five days of ad-libitum smoking. Cigarette smoking subsequent to the introduction of IQOS will be compared to each participant's baseline smoking rate (Day 1-5 vs. Day 8-21, see Figure 1). Randomly assigning smokers to continue to smoke their own cigarettes or to switch to IQOS in a between-subjects design is inconsistent with our aims. Second, we do not expect daily cigarette consumption to change in a group of smokers instructed to continue smoking as usual. Third, utilizing a within-subjects design allows us to maximize statistical power and take advantage of the high within-individual correlation of the primary outcome measure so that we can detect differences in smoking behaviors as participants switch to IQOS.

4.1.2 Rationale for nontreatment-seeking smokers

Consistent with previous studies of IQOS use among cigarette smokers, we will recruit smokers who are <u>not</u> seeking smoking cessation treatment. The goals of this study are to evaluate the effects of IQOS use on cigarette smoking behaviors and to examine which subjective and objective effects of IQOS predict greater IQOS use relative to cigarette smoking. Because the proposed study is not a smoking cessation treatment study, and we are thus not providing treatment, it would be inappropriate to recruit smokers wishing to quit. However, to increase the likelihood that participants will represent smokers likely to use IQOS, eligible smokers will include smokers who would like to quit smoking cigarettes within the next six months, but not within the next 30 days. Smokers reporting a desire to quit in the next 30 days are typically treatment seekers.

4.1.3 Rationale for study duration

We have previously conducted research on the effects of progressively decreasing nicotine levels on cigarette smoking behaviors and subjective effects across 10-day duration periods. Significant decreases in smoking behavior and subjective ratings of cigarette characteristics were observed within this 10-day period. We have also observed significant effects on smoking behaviors in menthol cigarette smokers who switched to a non-menthol brand across a 15-day period, especially between days 10-12. In previous studies, we observed that most daily cigarette change occurs within the first 12 days of product use and then remains unchanged for at least the next 4 weeks. Phillip Morris conducted the only longitudinal study of IQOS use among cigarette smokers under naturalistic conditions. Across six weeks of observation, the majority of change occurred in

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the first weeks of IQOS use, with little to no change thereafter. Given these findings, we expect to detect the majority of change in IQOS use and cigarette smoking across 14 days.

4.1.4 Rationale for providing IQOS, but not smokers' own brand of cigarettes

IQOS will be provided to participants at no cost, but cigarettes will not. This decision is based on methodological, budgetary, and logistical reasons. One, it is not feasible to maintain every variety of cigarette brand that smokers use. Two, we are interested in how IQOS use impacts smoking behavior. By providing cigarettes, we may alter cigarette smoking behavior by implying that we expect participants to smoke their usual brand in addition to IQOS. Three, smokers who purchase IQOS in the natural environment are likely to have a limited supply of cigarettes available, because their intent is to switch to IQOS. As such, not providing a 14-day supply of cigarettes maximizes external validity.

5 CHARACTERISTICS OF THE STUDY POPULATION

5.1 Target Population

Participants will be males and females between the ages of 18-65 who report smoking at least 5 cigarettes/day for at least the past 12 months.

5.2 Accrual

We propose to recruit 160 total participants (40 pilot study participants, 120 full study participants) to complete a 21-day duration protocol over an 8 month period. Their six laboratory visits will occur about every three days. This will allow approximately four to five participants to be recruited every month, accounting for scheduling of visits at about the same time of day (within 1 hour), as there is diurnal variation in smoking behaviors. We will use several, proven strategies to encourage completion of the study, such as providing: (1) each participant with a calendar of their appointments throughout the study; (2) reminder calls the day prior to coming in; (3) incentives for each visit; and (4) a bonus for completion of the entire study such that total compensation equals $500.

5.3 Inclusion Criteria

1. Able to communicate fluently in English (i.e. speaking, writing, and reading).
2. Male and female smokers who are between 18 and 65 years of age and self-report smoking at least 5 cigarettes (menthol and/or non-menthol) per day for at least the last 12 months.
3. Not currently undergoing smoking cessation treatment or planning to quit smoking within the next 30 days.
4. Report an interest in quitting smoking within the next 6 months.
5. Plan to live in the area for the duration of the study
6. Willing to use study provided IQOS devices and HeatSticks during 2 laboratory visits and throughout study participation.
7. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent and HIPAA form.

5.4 Exclusion Criteria

Subjects who present and/or self-report with the following criteria will not be eligible to participate in the study:

<u>Smoking Behavior</u>

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1. Regular use of nicotine containing products other than cigarettes (e.g. chewing tobacco, snuff, snus, cigars, e-cigs, etc.). Participants agreeing to abstain from using nicotine containing products other than cigarettes for the duration of study will be considered eligible.
2. Current enrollment or plans to enroll in a smoking cessation program over the duration of the study (i.e. 21 days/3 weeks).
3. Provide a CO breath test reading less than 10 ppm at Intake.

Alcohol and Drug

1. History of substance abuse (other than nicotine dependence) in the past 12 months and/or currently receiving medical treatment for substance abuse. Counseling and support groups (e.g. Alcoholics Anonymous and Narcotics Anonymous) will not be considered medical treatment for the purposes of this protocol.
2. Current alcohol consumption that exceeds 20 standard drinks/week.
3. Breath alcohol reading (BrAC) greater than .000 at Intake.

Medical

1. Women, including all individuals assigned as “female” at birth, who are pregnant, breast feeding, or planning a pregnancy over the duration of the study period.
2. Serious or unstable disease within the past year (e.g. cancer, heart disease). Applicable conditions will be evaluated on a case-by-case basis by the Principal Investigator.

Psychiatric

1. Lifetime history of schizophrenia or psychosis.
2. Lifetime history or current diagnosis of active major depression. Participants who maintain a diagnosis of major depression who have not experienced any major depressive episodes in the past 6 months and are stable on antidepressant medication(s) are eligible to participate.
3. Lifetime history of a suicide attempt.

General Exclusion

1. Past, current, anticipated, or pending enrollment in another research program over the study period that could potentially impact subject safety, study data, and/or the study design as determined by the Principal Investigator.
2. Any medical condition, illness, disorder, adverse event (AE), or concomitant medication that could compromise participant safety or significantly impact study performance as determined by the Principal Investigator. Subjects may be deemed ineligible for any of the aforementioned reasons at any point throughout the study, as well as during the initial telephone screen.
3. Significant non-compliance with protocol and/or study design as determined by the Principal Investigator and/o. Subjects may be deemed ineligible at any point throughout the study.

5.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the current study will be independent of the participant’s work or school activities.

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5.6 Subject Recruitment

Participants may be recruited from print, traditional, and social media advertisements, referrals, and/or from our database of previous participants who have agreed to be re-contacted for future studies. All advertising materials will be submitted to the UPENN IRB for approval prior to distribution/posting. Interested participants will first complete a telephone screen to assess their initial eligibility. Participants who are initially eligible will be screened against our registration database to confirm that they are not currently participating in another research study at our Center and have not previously reported a condition or circumstance that would make them ineligible for the current study. These participants who remain initially eligible will then be invited to attend an Intake Visit at our Center during which they will be presented with the IRB-approved combined informed consent and HIPAA Form and have their final eligibility confirmed. Initially eligible participants will also have the option to review and sign the combined informed consent and HIPAA Form electronically via REDCap prior to completing the rest of the Intake Visit at our Center.

5.7 Early Withdrawal of Subjects

5.7.1 When and How to Withdraw Subjects

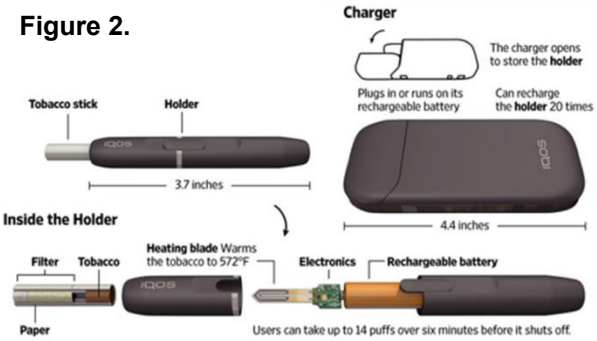
Participants are free to withdraw from the study on their own accord at any time. In addition, participants may be withdrawn by the Principal Investigator at any time per the exclusion criteria listed previously. No follow-up data collection is required for participants who withdraw or are deemed ineligible throughout the study.

6. Study-Provided IQOS Device and HeatSticks

6.1 Description

Heat-not-burn (HNB) tobacco products are an emerging nicotine delivery innovation designed to deliver nicotine without the toxins associated with combustion. Powered by a rechargeable battery, HNB devices heat (~662 degrees Fahrenheit) rather than combust (~1,112 degrees Fahrenheit) leaf tobacco to produce a nicotine-containing aerosol for inhalation. In 2019, the Food and Drug Administration (FDA) approved the sale of IQOS, the first HNB tobacco product available in the U.S. [4]. Manufactured by Philip Morris International, IQOS consists of three components: (1) a disposable tobacco stick – HeatSticks or HEETS; (2) a holder that heats the tobacco stick via an electronically charged heating blade; and (3) a charger to recharge the holder after each use. To use IQOS, a tobacco stick is inserted into the heating blade within the holder, the holder is turned on, the heating blade is activated, and then the tobacco stick is heated producing a nicotine-containing aerosol. The tobacco stick is heated for approximately six minutes, allowing up to 14 puffs to be taken, offering smokers the opportunity to self-administer nicotine without combustion. **See Figures 2, 3.**

Figure 2.



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6.2 Distribution Schedule

At the Day 7 Visit, participants will be provided with an IQOS 3.0 holder and charger, a 7-day supply of regular and/or menthol HeatSticks, and fourteen date-stamped zipped baggies for daily collection (7 for spent cigarette filters, 7 for used HeatSticks). At Figure 3. visit, participants will be provided with their second seven-day supply of Marlboro HeatSticks, as well as fourteen additional date-stamped zipped baggies (7 for spent cigarette filters, 7 for used HeatSticks). The Principal Investigator may approve a change to the distribution schedule on a case-by-case basis due to extenuating circumstances.

Figure 2

6.3 Participant Compliance Monitoring

Participants will be required to keep track of the IQOS device and all the HeatSticks provided to them. Therefore, participants will be instructed to return all used HeatSticks, unused HeatSticks within their original packaging, and empty HeatStick packages to the Center at each lab visit. Research staff will fill in a "Product Accountability Log" with the participants at each visit. Any discrepancy between the products dispensed versus the products returned will be discussed and recorded in the log. All unused study HeatSticks will be collected from participants at all visits. Unused HeatSticks returned by a given participant may be re-distributed to the same participant. At the Day 22 Visit, any remaining unused HeatSticks returned by the participants will be collected by the research staff for destruction.

6.4 Receipt, Storage, Dispensing and Return

6.4.1 Receipt of IQOS and Marlboro HeatSticks

IQOS devices and HeatSticks will be shipped directly to the CIRNA and/or purchased from a commercial vendor. Upon receipt of IQOS devices and HeatSticks to the CIRNA, an inventory will be performed and a product receipt log will be filled out and signed by the person accepting the shipment/delivery. Study staff will verify that the shipment/delivery contains all the items noted in the shipment/delivery inventory. Any damaged or unusable IQOS devices and/or HeatSticks in a given shipment/delivery will be documented in the study files.

6.4.2 Storage

IQOS devices and HeatSticks will be held at room temperature in a double-locked location (e.g., a locked cabinet in a locked room).

6.4.3 IQOS and HeatStick Accountability

A master product accountability log will be maintained throughout the study. All product received, distributed to each unique participant, and destroyed will be documented per standardized product accountability procedures.

6.4.4 Return or Destruction of IQOS and HeatSticks (trial completion)

At the completion of the study, there will be a final reconciliation of IQOS devices and HeatSticks purchased, IQOS devices and HeatSticks dispensed, and IQOS devices and HeatSticks remaining. This reconciliation will be logged on a study completion reconciliation form. Any notable discrepancies will be investigated, documented, and resolved if possible.

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7 Study Procedures

7.1 Telephone Eligibility Screen

Individuals interested in study participation will be screened by a qualified member of the research team to determine initial study eligibility. If the participant meets preliminary eligibility, they will be invited to schedule an Intake Visit at which their final eligibility will be confirmed.

7.2 In-Center Visits

7.2.1 Visit Reminders

Participants will typically receive study visit reminders 24 hours prior to their scheduled study visits via phone call, email, and text message (if applicable).

7.2.2 Intake Visit

During Intake, (Duration: ~1.5 hours) participants will:

1. Either hear an informed consent and HIPAA presentation where all the study procedures and institutional policies will be reviewed OR complete a virtual IRB-approved informed consent and HIPAA presentation via REDCap where all the study procedures and institutional policies will be reviewed prior to coming in to complete the remainder of their Intake Visit. The Principal Investigator will determine whether in-person or electronic consent will be collected based on University COVID-19-related guidelines. The in-person consent procedures will proceed as follows: the combined informed consent and HIPAA form will be read verbatim. All participant questions will be answered as appropriate after which the combined informed consent and HIPAA form will be completed (signed and dated) by both the participant and a qualified member of the research team. The electronic consent process will involve the following procedures:
    a. The participant will be required to view the entire combined informed consent and HIPAA form on REDCap prior to signing the document. Upon completing their reading of the consent, the participant will be offered the opportunity to indicate if they have any questions and a staff member will call the participant to complete a consent discussion via the telephone. All participant questions will be recorded and answered as appropriate after which the combined informed consent and HIPAA form will be completed (virtually signed and dated) by both the participant and a qualified member of the research team.
    b. The staff will print a signed copies of this completed record, and provide one copy to the participant and save one copy for our records.
2. Confirm the accuracy of information (i.e. name, address, phone number, email [if applicable], date of birth, age, gender, ethnicity, and race) provided during the initial Telephone Eligibility Screen.
3. Complete a UDS (at least 30ml [two tablespoons] of urine). The UDS will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol and Drug).
4. Participants who test positive for any exclusionary medications or recreational drugs per this protocol will be deemed ineligible.
5. Female participants only: Self-administer a CLIA-waived urine pregnancy test.
6. Female participants are advised that participation of pregnant women in this study is prohibited and that they may withdraw at any time.
7. Have height and weight measured.
8. Perform a BrAC assessment to control for alcohol consumption.
9. Participants with a BrAC greater than 0.000 at Intake Visit will be ineligible.

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10. Perform a CO breath assessment and collect self-report smoking behavior over the past 24 hours to control for prior tobacco exposure.
11. Participants with a CO reading less than 10 ppm will be deemed ineligible.
12. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
13. Complete a Medical History Form with a member of the research team to review for applicable contraindications, including psychiatric exclusions, previously listed under Inclusion and Exclusion Criteria (section 4.3 and 4.4).
14. Complete a baseline concomitant medication review (if applicable).
15. Complete questionnaires:
16. Demographics
17. Smoking History (e.g., duration, rate, regular and/or menthol)
18. Nicotine Dependence (FTND)
19. Motivation to quit smoking (Contemplation Ladder)
20. Provide instructions to smoke as usual for the first five days of the study protocol (assessment of baseline smoking rate).
21. Be provided with five date-stamped zipped baggies by the research staff.
22. Review a written instruction card for the collection and storage of used cigarette filters with the research staff.
23. Be instructed to engage in overnight smoking abstinence (10-hours) the night of Day 5 in preparation for the Day 6 Visit.
24. Tentatively schedule study visits with a member of the research team.

7.2.3 Day 6 Visit

During the Day 6 Visit, (Duration: ~1.25 hours) participants will:

1. Arrive at the Center at 9:00 AM after having abstained from smoking overnight.
2. Perform a CO breath assessment and concomitant medication review.
3. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
4. Have their overnight smoking abstinence (10-hours) verified by a CO measurement of 50% of Intake visit's CO value
5. Return five date-stamped zipped baggies containing all spent cigarette filters from Days 1-5.
6. Receive instructions on how to use the IQOS prior to two IQOS HeatStick exposures (one regular, one menthol).
7. Be required to use the IQOS device in the lab, where they will be exposed to two IQOS HeatSticks (one regular, one menthol)
    - Participants will take 14 puffs from the regular HeatStick, then take 14 puffs from the menthol HeatStick. These two exposures will be separated by 45 minutes.

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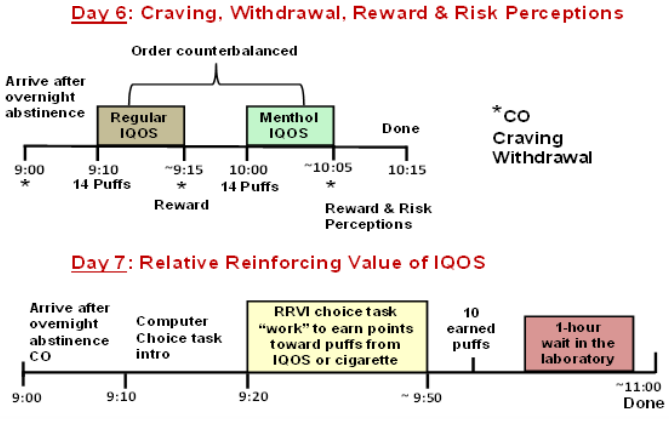
8. Complete questionnaires after each exposure:
    - Adverse Events Form (Open-Ended AEs)
    - Questionnaire of Smoking
    - Withdrawal Symptoms (MNWS)
    - IQOS Risk Perceptions
    - Subjective Reward of IQOS (CES adapted for IQOS use)
9. Be reminded to engage in overnight smoking abstinence (10-hours) in preparation for the Day 7 Visit.

Figure 4.



7.2.4 Day 7 Visit

During the Day 7 Visit, (Duration: ~2 hours) participants will:

1. Arrive at the Center at 9:00 AM after having abstained from smoking overnight.
2. Perform a CO breath assessment and concomitant medication review.
3. Have their overnight smoking abstinence (10-hours) verified by a CO measurement of 50% of Intake visit's CO value
4. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
5. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
6. Be introduced to and briefly practice the Relative Reinforcing Value of IQOS (RRVI) computerized lab task.
7. Complete computerized lab task: Relative Reinforcing Value of IQOS (RRVI).
8. Complete a standardized one-hour wait period in the laboratory, then complete required IQOS use in the lab.
9. Review instructions for IQOS use with a member of the research staff.
10. Receive an IQOS 3.0 holder and charger, a 7-day supply of regular and/or menthol HeatSticks, and 14 date-stamped zipped baggies for daily collection of spent filters and HeatSticks (7 for spent cigarette filters, 7 for used HeatSticks).
11. Be provided with instructions to switch completely from smoking combustible cigarettes to using IQOS.
12. Review written instructions for the collection and storage of used tobacco HeatSticks with a member of the research staff.

7.2.5 Day 11 Visit

During the Day 11 Visit (duration: ~30 min), participants will:

1. Perform a CO breath assessment and concomitant medication review.
2. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
3. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
4. Return used HeatSticks (and cigarette filters, if applicable) in date-stamped zipped baggies provided by the research staff.

7.2.6 Day 14 Visit

During the Day 14 visit (duration: ~30 min) participants will:

1. Perform a CO breath assessment and concomitant medication review.

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2. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
3. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
4. Return used HeatSticks (and cigarette filters, if applicable) in date-stamped zipped baggies provided by the research staff.
5. Receive second seven-day supply of HeatSticks, and 14 date-stamped zipped baggies for daily collection of spent filters and HeatSticks (7 for spent cigarette filters, 7 for used HeatSticks).

7.2.7 Day 17 Visit

During the Day 17 visit (duration: ~30 min) participants will:

1. Perform a CO breath assessment and concomitant medication review.
2. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
3. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
4. Return used HeatSticks (and cigarette filters, if applicable) in date-stamped zipped baggies provided by the research staff.

7.2.8 Day 21 Visit

During the Day 21 visit (duration: ~30 min) participants will:

1. Perform a CO breath assessment and concomitant medication review.
2. Be asked questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
3. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
4. Return used HeatSticks (and cigarette filters, if applicable) in date-stamped zipped baggies provided by the research staff.

7.2.9 Day 22 Visit

During the Day 22 visit (Duration: ~30 min) participants will:

1. Complete questionnaires:
    - Adverse Events Form (Open-Ended AEs)
    - Concomitant medication review
    - Changes in motivation to quit smoking (Contemplation Ladder)
2. Return all remaining used HeatSticks and spent cigarette filters
3. Be informed of the lack of data supporting IQOS as a smoking cessation aid or harm reduction tool
4. Cautioned on the likelihood of dual use and the risks associated with dual use
5. Advised to either quit using IQOS or quit smoking cigarettes if they are using both
6. Referred to a smoking cessation program if interested in quitting smoking

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7.3 Table 1. Study Measures and Time Points

Table 1. Measures	**Bio-behavioral Laboratory Visits**							
Description of Time Point	**Intake**			**Days 8-21: Switch to IQOS**				**End of study**
Day #	**Day 0**	**Day 6**	**Day 7**	**Day 11**	**Day 14**	**Day 17**	**Day 21**	**Day 22**
Demographic & Baseline Covariates								
Demographics	X							
Smoking History	X							
Nicotine Dependence	X							
Cigarettes per day (days 1-5)		X						
CO	X	X	X	X	X	X	X	
Predictor Variables								
Craving Relief		X						
Withdrawal Relief		X						
Subjective Reward of IQOS		X						
IQOS Risk Perceptions		X						
Relative Reinforcing Value of IQOS			X					
IQOS sticks per day				X	X	X	X	X
Outcome Variables								
Cigarettes per day				X	X	X	X	X
Quitting Motivation	X							X

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7.4 Description of Study Measures

7.4.1 Screening/Covariates

Urine Drug Screen: A urine sample (~20-30ml) will be collected at the Intake Visit to conduct a urine drug screen. The urine drug screen indicates whether the subject has recently taken any of the following recreational drugs or medications: THC, cocaine, opiates, amphetamines, methamphetamines, phencyclidine (PCP), ecstasy (MDMA), barbiturates, benzodiazepines, methadone, tricyclic antidepressants, and/or oxycodone. Participants with a positive urine drug screen for any substance listed above other than THC or tricyclic antidepressants will be deemed ineligible. A urine sample that doesn't register a temperature reading of at least 90 degrees Fahrenheit will not be considered a valid sample. In an effort to remain CLIA-compliant, results from urine drug screen will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results. In order to document inclusion/exclusion criteria for regulatory purposes, results of the urine drug screens (test cup) will be retained in research charts and in an electronic research record within our local data management system (Access). These results are not and will not be entered into a participant's electronic medical record.

Urine Pregnancy Test: At the Intake Visit, female participants will be supplied with a simple, CLIA-waived hCG pregnancy test strip and a urine sample cup. Female participants will be informed that pregnant women are not advised to participate in this research study. Participants will then be instructed to self-administer the pregnancy test and inform the study staff if they would like to continue participation after they have reviewed the results of the pregnancy test. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still receive travel reimbursement for the visit.

Breath Alcohol Concentration (BrAC): Participants will complete a BrAC assessment at the Intake Visit. Participants will be made aware of the BrAC assessment prior to the visit and asked to avoid alcohol and alcohol-based products (e.g. mouthwash, breath spray, etc.) the evening and morning before the Intake Visit. The BrAC monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading greater than 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than 0.000 at the Intake Visit will be deemed ineligible.

Medical History Form: A medical history form (led by the research staff) will be completed to review for applicable contraindications previously listed under Key Inclusion/Exclusion Criteria at the Intake Visit.

Demographics and Smoking History (FTND): Standard surveys will collect demographics information such as age, sex, race, ethnicity, education level, and income [7,10,12]. Standard survey questions will assess smoking history (e.g., age at initiation, current smoking rate). Nicotine dependence will be assessed with the Fagerstrom Test for Nicotine Dependence (FTND). This 6-item measure has good internal consistency ($\alpha = .64$) and high test-retest reliability ($r = .88$) [44].

Smoking Urges/Craving (QSU-B): The well-validated and reliable 10-item brief Questionnaire of Smoking Urges will assess ***craving*** for cigarettes. The QSU-B utilizes a "right now" frame of reference.

Adverse Events Form (Open-Ended AEs): Participants will be asked an open-ended question about any symptom or medical event that may be related to their study participation. These events will documented as **unanticipated (unexpected)** AEs unless they are otherwise outlined in the protocol and/or consent form (i.e. related to withdrawal, assessments, etc.). The reporting period for each

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assessment will inquire about any event(s) or symptom(s) experienced since the last in-person visit. If a participant reports a symptom or medical event, they will be asked to rate the severity of the event utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Issue does not interfere with usual daily activities), 2 (Moderate=Issue does interfere with some activities), and 3 (Severe=No normal activities are possible). See section 8.2.1: AE Collection Methods for further details.

Carbon Monoxide (CO) will be measured using a Vitolograph CO monitor (Lenexa, KS). A CO > 5 is indicative of combustible cigarette smoking [25,45,46]. HNB products are expected to result in significantly lower increases in CO compared to a combustible cigarettes [47]. Five minutes of IQOS use did not result in clinically significant increases in CO (0.3 ppm) after overnight abstinence compared to five minutes of combustible cigarette [27]. We will include CO as a covariate in our statistical models.

Concomitant Medications: At the Intake Visit, participants will be asked to list all medications (prescription or non-prescription) and NRTs currently taken and/or recently discontinued (within the past 14 days) as a baseline collection. All information will be collected on a Concomitant Medication Log that will be maintained within the participant's study chart. At every subsequent in-person visit, participants will be asked if they have taken any additional medications (prescription or non-prescription), NRTs, and/or changed the dosage or stopped taking any previously reported medications since their last in-person visit. Participants who report taking contraindicated medication(s) over the course of the study period may only remain eligible if the Principal Investigator determine that the contraindicated medication(s) did not impact the study design, data quality, and/or participant safety and welfare.

7.4.2 Predictor variables

Motivation to Quit Smoking (Contemplation Ladder): The contemplation ladder will be used to assess readiness to consider smoking cessation [59]. The contemplation ladder is designed to measure a smokers position on an 11-point scale (0-10) range, from having no thought of quitting to taking action to quit, and has been successfully employed in several diverse smoking populations [60-62]. We will assess changes in quitting motivation from Intake to Day 22 (end of study).

Craving: Craving will be measured on Day 6 with the well-validated and reliable 10-item brief Questionnaire of Smoking Urges [48-50]. Items are scored from (1=strongly disagree to 7=strongly agree).

Withdrawal symptoms will be measured on Day 6 with the Minnesota Nicotine Withdrawal Scale [51]. This 15-item scale assess withdrawal symptoms with respect to a specific frame of time (0=none to 4=severe).

Subjective rewarding value of IQOS will be measured on Day 6 with the Cigarette Evaluation Scale (CES) adapted for IQOS use [15-18,27]. The CES is an 11 item Likert-format (1=not at all to 7=extremely) self-report instrument with established validity and reliability ($\alpha > .80$) [22,23,32,33,52]. We will focus on the Satisfaction Subscale for the measurment of subjective reward [23].

IQOS Risk perceptions will be measured on Day 6 with 12 items. Four items drawn from prior studies will assess absolute health risk and addictive potential [53-56]. Response options include 1=no risk, 2=low risk, 3=moderate risk, 4= high risk, and 5=very high risk. Eight previously validated tobacco use risk perception items will assess risk relative to combustible cigarettes [57,58]. Instructions are "Compared to your own cigarettes that you usually smoke, IQOS is lower in nicotine, lower in tar, are less addictive, are less likely to cause cancer, have fewer chemicals, are healthier, make tobacco use safer, and help people quit smoking." The Likert-style response options range from 1=definitely untrue to 5=definitely true [57,58].

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Relative reinforcing value of IQOS will be measured on Day 7 with a validated choice paradigm, evaluating the preference for IQOS versus cigarettes [34,36,37]. RRVI will be defined in relation to responding for cigarette puffs. Working for cigarette puffs on ≤ 5 trials out of the 10 trials is indicative of reinforcer indifference or less reinforcing value of cigarette puffs relative to IQOS puffs [41,42]. We will also measure overall responding for IQOS versus cigarette puffs [41,42].

IQOS Use will be determined by counting the daily spent tobacco HeatSticks returned for each of the 14 days (days 8 – 21) [12] [24,25]. HeatSticks per day will be included as a time-varying covariate in the Aim 1 models.

7.4.3 Outcome variables

Cigarette Consumption (primary outcome): The primary outcome is the longitudinal daily count of cigarettes from Intake to the end of the IQOS switch phase. Daily cigarette consumption will be determined by counting the daily spent cigarette filters returned for each of the 14 days (days 8-21).

Motivation for smoking cessation (secondary outcome): The contemplation ladder will be used to assess readiness to consider smoking cessation. The contemplation latter is designed to measure a smoker's position on an 11-point scale (0-10) range, from having no thought of quitting to taking action to quit, and has been successfully employed in several diverse smoking populations [60, 62]. We will assess changes in quitting motivation from baseline to day 21 (end of study).

7.5 Analytic Plan

Sample size. Hypotheses will be tested with 80% power using a two-sided type-1 error of 5%. The primary outcome is the longitudinal daily count of cigarettes from baseline to the end of the IQOS switch phase. Using simulation methods, with correlated negative-binomial random numbers (r=0.6 within subject) and a longitudinal (GEE) negative binomial model, we calculated that we can detect a slope (change per day) of 0.1 cigarettes, or a change of 1.5 cigarettes per day across the two-week switch period. With a lower correlation (r=0.3), that detectable effect becomes a slope of 0.15 (change per day) or 2.0 cigarettes per day across the switch period. The secondary outcome is motivation to quit smoking (contemplation ladder), which will also be modeled longitudinally. The contemplation ladder itself has a historical standard deviation of approximately 3.0, and a correlation of 0.3. Our sample of 100 will allow us to detect a change of 0.7 in the contemplation scale in a baseline to end of study comparison.

Data analysis. Prior to analyses, we will: (a) screen the data for data entry errors, (b) check for outliers, and (c) assess the extent and type of missing data, and select the most appropriate method for dealing with the missing data. We will create all summary scores needed for the analysis, and check that the distributional assumptions are met. We will assess for participation biases and differences between participants retained and lost. Analyses will be conducted using Stata software (StataCorp, College Station, Texas).

The primary outcome is a daily count variable, the number of cigarettes smoked each day. The distribution of cigarettes smoked per day is expected to be over-dispersed (and perhaps zero inflated), because of the study instructions for participants to switch to IQOS heat-sticks for a 14-day period, and the expectation that the majority of participants will have various levels of dual use. The number of IQOS HeatSticks used each day is also a count variable. Participants may have days where they only use IQOS HeatSticks, only smoke cigarettes, and days where they use both. We will accomplish the measurement portion of Aim 1 by summarizing the daily frequencies of cigarettes only, partial switching, and complete switching. Distributional assumptions of all regression methods will be examined in the data set ahead of the analysis to ensure that the best and most representative error model is used. We will examine demographic and other variables for any association with the outcomes or predictors. Those found to be

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associated with outcomes (p=0.2) will be included in the model either to correct for confounding or to control error.

The goal of Aim 1 is to evaluate the effects of IQOS use on cigarette smoking behaviors. For the primary analysis, we will analyze the longitudinal counts of cigarettes using mixed models (Gaussian or negative binomial as appropriate). The model will include predictors of time (continuous or discrete), and study phase (baseline versus switch period). We will also include candidate controlling variables (demographic and clinical).

H.1.a. states that IQOS use will decrease the number of cigarettes smoked per day relative to baseline. We do not expect IQOS to replace all cigarettes, and we will measure the use of cigarette smoking only, dual use, and IQOS only use (complete switching). H.1.a. will be tested using the z-score corresponding to the contrast between baseline and switch periods (phase). **H.1.b.** states that the reduction in number of cigarettes smoked per day will be associated with the number of IQOS HeatSticks used. For H.1.b., we will add the daily IQOS use to the model predicting cigarette use, and test using the z-score corresponding to the daily IQOS HeatStick count by phase interaction.

H.1.c. will test whether IQOS use decreases smokers' motivation to quit cigarette smoking. This hypothesis will be examined using mixed models. Predictors will include time (baseline, end of study), and H1c will be tested using the z-score corresponding to the baseline to end of study comparison. Secondarily, we will test cumulative IQOS use as the predictor for change in motivation to quit smoking as measured by the contemplation ladder.

The goal of Aim 2 is to examine which subjective and objective effects of IQOS predict cigarette smoking. **H.2.** will test whether participants who report lower IQOS risk perceptions, greater craving relief, greater withdrawal relief, greater IQOS subjective reward, and have a higher relative reinforcing value of IQOS will smoke fewer cigarettes per day during the 14-day switching period. For H.2., we will remove the daily IQOS counts from the model to avoid confounding, and evaluate the laboratory measures from days 6 and 7 (i.e., IQOS risk perceptions, craving relief, withdrawal relief, subjective reward, and reinforcing value of IQOS relative to cigarettes) for entry in to the model as predictors, using the significance of the corresponding z-score.

8 Risks / Benefits

8.1 Potential Study Risks

The potential risks to participants, their likelihood and seriousness, and strategies to mitigate risks are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions/AEs will be collected, assessed, and reported as per the study protocol (see section 8: Safety and Adverse Events), federal law, and University of Pennsylvania regulations.
Reproductive Risks: Smoking can cause serious harm to unborn children or children who are breast-feeding. Female participants are asked to use a medically accepted method of birth control (such as IUD, birth control pills, condoms, etc.) while participating in the study. Further, female participants, and those assigned as female at birth, will be asked to administer a simple, one-step hCG pregnancy test and informed that if they are (or believe they may be) pregnant that they will not be eligible to participate in the research study. If a female participant becomes pregnant over the course of the trial, they will be immediately withdrawn. It will also be recommended that the participant seek consult from an obstetrician or maternal-fetal specialist about the dangers of smoking while pregnant.

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Withdrawal Symptoms: Participants may experience uncomfortable withdrawal symptoms during their overnight smoking abstinence. In preparation for the overnight abstinence, participants will receive tips for remaining abstinent (e.g., coping with withdrawal and craving, smoking triggers, coping with stress). Participants will also be reminded that these symptoms will be short-lived and that they will be able to self administer nicotine in the laboratory the following morning.

Assessments: Some participants may experience some emotional distress during the assessments due to learning their carbon monoxide levels or seeing how many cigarettes and/or HeatSticks they smoke. These events happen very rarely and in almost all cases are short-lived and of low intensity. If a participant does exhibit a high level of emotional distress, however, they will be offered contact information for mental health services in the area.

Cigarette Smoking and IQOS use: Although cigarette smoking is associated with many diseases, we do not believe the risk is beyond every day risk as all participants must be current cigarette smokers to be eligible. We will inform participants that cigarette smoking has been shown to cause diseases such as emphysema and cancer. There will be a phase of the study where participants will be instructed to switch completely to IQOS. If participants don't completely switch from smoking cigarettes to using IQOS, their risks from smoking will remain the same.

Important safety information regarding IQOS: **IQOS works exclusively with HeatSticks**. Never use IQOS with a cigarette or any other tobacco sticks or accessories. Do not remove a tobacco stick (HeatStick) while in use. Tobacco sticks (HeatSticks) are single use only and should never be reused. Tobacco sticks (HeatSticks) should never be lit with a match, lighter, or any other flame source. **Keep tobacco sticks out of reach of children and pets.** If tobacco sticks are swallowed, seek medical attention immediately due to risk of nicotine ingestion. **Store your tobacco sticks in a cool, dry place.** Do not expose product to high humidity conditions or direct sunlight. Do not use IQOS during hot conditions or in periods of high humidity. **Pay attention to signs that your battery may be leaking**. The IQOS Holder and Pocket Charger are powered with sealed Lithium-ion batteries. Under normal conditions of use, the battery is sealed. If you notice fluid leaking from the battery, follow these precautions, discontinue using the product immediately and contact *Shannon* at *215-746-7164*, or *Stephen* at *215-746-2100*. In case of contact with skin, wash hands and do not touch eyes. In case of contact with eyes, immediately flush with running water for at least 15 minutes and seek medical attention. If fluid is inhaled, get fresh air and seek medical attention. If you swallow fluid, seek medical attention immediately. Do not induce vomiting or ingest food or drink. **Stop using IQOS and seek medical attention immediately if you experience any symptoms that may indicate a serious allergic reaction**: swelling of the face, lips, tongue, gums, throat, or body; difficulty breathing, or wheezing.

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related participation via email. Email is not a secure means of communication. Email messages travel across the Internet passing through multiple computers before reaching their final destination. It is not possible to know whether an email a participant sends will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have an archive of everything that is sent. If someone gets access to an email account (for example, a participant's family member), they could see archived messages. There are many other ways in which emails are not secure—these are only selected examples. To manage this risk the informed consent form will include specific language to educate research participants on the privacy risks involved in email communications. Participants will also be

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explicitly instructed to only use email communications for routine matters and never for personal or confidential messages or questions.

Confidentiality and Loss of Privacy: See section 9.6.1 and 9.6.2 for methods in which Confidentiality and Subject Privacy/Protected Health Information will be secured and maintained.

8.2 Potential Study Benefits

Cigarette smokers may benefit from participation by knowing that they are contributing to research that can help determine if (1) IQOS is an acceptable alternative to combustible cigarette smoking among smokers like themselves, (2) IQOS fully replace cigarettes, and (3) IQOS lessens motivation to quit smoking. The proposed study is expected to yield new knowledge regarding the subjective, objective, and behavioral impact of IQOS on cigarette smoking behaviors. The findings will inform public health interventions and regulatory actions to educate and protect smokers if they choose to use IQOS.

8.3 Risk/Benefit Assessment

The potential benefits of this study outweigh the potential risks. There is only a minimal risk of experiencing study-related AEs or SAEs by enrolling in this trial. The findings from this study will inform public health interventions and regulatory actions to educate and protect smokers if they choose to use IQOS.

8.3.1 Adequacy of Protection against Risks

Informed Consent. Informed consent/HIPPA forms will be signed electronically on REDCap or at the Intake Visit before any research activities are completed. Trained staff will provide a study overview, including the risk and benefits of being in the study. Staff will respond to all questions and inform potential participants that participation is voluntary. Preliminarily eligible smokers adults will be asked to provide informed consent for participation. After receiving informed consent, participants will provide a urine sample to assess drug use and/or pregnancy, which are exclusions for participation. Participants will receive a copy of their signed consent form.

Oversight and Monitoring. The Institutional Review Board at the University of Pennsylvania will monitor the protection of human subjects and the safe and secure collection and storage of data. This committee will assess the study before initiation and then annually at the time of Continuing Review. The IRB will ensure the scientific, technical, and statistical soundness of the research and guarantee that methods for the ethical and safe treatment of human subjects are in place.

Participant Safety. Eligibility criteria for this study will exclude any individual who would be at risk of adverse effects from participation in this study. Participant safety begins with the PI's thorough training and ongoing supervision of the project staff and study procedures. Weekly meetings will ensure an understanding and adherence to the study goals and data collection and management procedures. Personnel training by the PI will be considered to be of the highest priority and will be addressed prior to the start of the study and on an ongoing basis. Training will help ensure that all processes and procedures for data collection and management are correctly applied and utilized. Specifically, but not exclusively, this training will ensure that research personnel understand the study's goals and objectives, data collection process, confidentiality, participant safety, all case report forms (CRFs), the manual of procedures (MOP), database software and the data management system (DMS), and all applicable standard operating procedures (SOPs) to attest that the study is conducted in a proper manner. Training will span study recruitment approaches, screening, assessment, follow-up of rescheduled participants, data entry and storage, and tracking study incentives.

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Data Management. The CIRNA Data Management Core will be responsible for the data management system, the operational facets of this study, quality assurance, and data storage.

Data Collection, Processing, and Management. All data collection, processing, and management procedures will be standardized in a detailed Manual of Procedures (MOP). Hard-copy surveys will serve as source documents. All data are entered into a database located upon the secure server with dedicated uninterrupted power at the CIRNA. All indicated data entry and processing operations will be performed using Data Management System (DMS) software. Study personnel will access the menu driven DMS software to perform specific operations. For example, the DMS functionality will include subject tracking, data entry, data validation, and query tracking, standard reports, and tracking of all major study milestones (e.g., assessment and visit disposition), and the counterbalanced sequence of the order of IQOS flavors on the day 6 laboratory visit.

Quality and Data Safety Assurance Practices. The PI will conduct training to ensure that all processes and procedures for data collection and procedures for data collection, processing, and storage are correctly applied and utilized. Confidential participant information will be collected and entered into the database. When this information exists on paper (e.g., updated contact information, alternative contact information) it will always be filed under lock and key. Upon entry of this data into the database, an auto-study ID will be generated. The auto-study ID will then generate and be linked to a participant ID in a separate table. Thus, contact information will never exist in the same DMS table as a participant ID. No one can gain access to an individual database unless they have been explicitly granted a user ID and password. The Center's database server and individual study databases have never been compromised as a result of the extremely rigorous and secure network firewall technologies. The secure servers are located in a specially designed, highly secured facility with dedicated uninterrupted power supply. Access to this server facility is strictly limited.

Adverse Event Reporting. In accordance with NIH and IRB guidelines, this protocol will employ the following mechanisms for adverse event reporting: (1) alert the IRB of any and all reports of serious adverse events; (2) inform all members of the study team of any and all reports of serious adverse events; (3) notify the NIH of any actions taken by IRB with regard to data safety monitoring.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others:
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event:
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study (regardless if study-related). Intercurrent illnesses or

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injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A ***serious adverse event*** (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period:
The study period during which AEs/SAEs will be reported is from the initiation of any study procedures until the end of the study. Any event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in the study after the final time point will be assessed and reported as appropriate.

Preexisting Condition:
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Post-study Adverse Event:
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery:
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

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- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Collection and Recording of Adverse Events

9.2.1 AE Collection Methods

All AEs and SAEs occurring during the study period will be captured through the methods described below:

1. Open-Ended AE Form: Participants will be asked an open-ended question about any symptom or medical event that may be related to their study participation. These events will be documented as **unanticipated (unexpected)** AEs unless they are otherwise outlined in the protocol or consent (i.e. related to withdrawal, assessments, etc.). The reporting period for each assessment will inquire about any event(s) or symptom(s) experienced since the last in-person visit. If a participant reports a symptom or medical event, they will be asked to rate the severity of the event utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Issue does not interfere with usual daily activities), 2 (Moderate=Issue does interfere with some activities), and 3 (Severe=No normal activities are possible). Any report on the Open-Ended AE Form will require additional follow up per the AE documentation and internal reporting procedures outlined below in section 8.2.2.
2. Spontaneous Assessment: Once enrolled, participants will be instructed to inform the research team about any notable symptom or medical event/concern throughout their participation in the study. A participant may also request the Principal Investigator be consulted about any reported medical event or concern of any severity at any time throughout their participation.
3. An “AE Note” template will be available to the research staff to collect supporting AE information and will function as the source document. However, research staff may collect AE information on any source document available to them and transfer the relevant information to a formal AE Note at a later time. Any notable AE reported spontaneously will require additional follow up per the AE documentation and internal reporting procedures outlined below in section 8.2.2.

9.2.2 AE/SAE Documentation and Internal Reporting Procedures

AE/SAE Documentation: At a minimum, follow-up information will include AE/SAE onset/resolution, description of event/course, severity, action taken, outcome, and possible relation to study participation.

Information surrounding AEs and SAEs will be initially recorded on the appropriate source document such as the SEC Form, an “AE Note” or SAE Form, and/or any document in which the AE/SAE information was originally recorded. All applicable AEs and SAEs will then be documented on a cumulative AE and SAE log maintained within the regulatory binder.

Completed documentation of applicable AEs will include the following information:

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- Protocol Title and IRB#
- Subject Identifier
- Event Title
- Date Site Notified
- Event Start Date and Time
- Event Stop Date and Time
- Description of Event/Course (including sequelae)
- Severity:
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Expectedness per protocol and/or consent
    - Expected/Anticipated
    - Unexpected/Unanticipated
- Action(s) taken (if appropriate)
- Outcome (if appropriate)

Documentation of SAEs will include the following information on a standardized SAE Form:

- Protocol name and number
- Subject identifiers
- Demographic data
- Date Site Notified
- Date and time of SAE onset
- Date and time of SAE resolution, if available
- Course/Description of Event (including sequelae)
- Action Taken
- Outcome
- Follow-up plan
- Serious Status (What makes the event an SAE)
- Severity of the event
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI):
    - Unrelated = Definitely not related

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  - Unlikely = Doubtfully related
  - Possibly = May be related
  - Probably = Likely related
  - Definitely = Related
- Clinical assessment of subject conducted at time of SAE (if appropriate)
- Results of any laboratory tests and/or diagnostic procedures (if appropriate)
- Autopsy findings (if appropriate)
- Concomitant medications and therapies (excluding treatment of event)
- Relevant Medical History (if appropriate)

Internal Reporting Procedures: All relevant follow-up information outlined above (see AE/SAE documentation) concerning applicable AEs, including all information regarding the occurrence of previously reported event(s), will be reported to the Study Coordinator (or other senior personnel) and Principal Investigator to determine a course of action (e.g. continue to monitor, reduce medication dose, stop medication), relatedness (causality) to the study, and expectedness (if not already established). This consult will be documented via email. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not (or unlikely) to be the cause.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome unless it has been determined that the study treatment or participation is not the cause. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately per this protocol.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

The reporting requirements of applicable SAEs and/or Unanticipated Problems including reportable AEs (see section 8.1 for definitions) to external entities are detailed in the following sub-sections:

9.3.1 Investigator reporting: notifying NCI and FDA

The following events/reports will be submitted to the FDA and NCI Project/Program Officer in a narrative format or on FDA Form 3500A:

- Unexpected fatal or life-threatening suspected adverse reactions (in relation to study-provided IQOS and HeatSticks) will be reported as soon as possible, but in no case later than 7 calendar days after the initial receipt of the information.

9.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any AE (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the Principal Investigator is:

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Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (According to the Penn IRB standard operating procedures [SOPs], an event is "related to the research procedures" if the event is deemed **probably or definitely related** to the procedures.")

Reporting Process:
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths (more rapid reporting requirements):
Deaths that occur during the course of a research study and that are:

- Unexpected; AND
- Related to the research study; AND
- When other participants are believed to be at an increased risk of harm

Must be reported to the IRB within 3 days from the time the investigator becomes aware of the death.

9.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of AEs/SAEs as noted above, as well as adherence to the study data and safety monitoring plan outlined in sections 8 and 10.

10 Data Management

The CIRNA Data Management Team has developed a data management system (DMS) that will facilitate the operational facets of this study, including determination of entry eligibility, production of lists of subjects for telephone contacts for scheduling, and data entry. The DMS uses the relational database product Microsoft Access as the primary software platform for data entry and validation, storage, retrieval, modification, and security. The DMS ensures data integrity through range and validity checks during the data entry process. Daily backups are performed to protect data against accidental destruction or corruption.

10.1 Data Management System Development

The CIRNA Data Manager will work closely with the trial investigators to develop an understanding of the data collection, storage, and quality assessment needs for the trial. This includes the design and development of the trial data collection forms and any additional administrative CRFs, to ensure that standardized, uniform data collection and data management

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procedures are implemented and sustained throughout the trial. The data collection forms will serve as templates for designing the data entry screens. The Data Manager will work closely with trial investigators and senior personnel to design, develop, and test an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents are incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

Prior to deployment and use by the research staff, the database and DMS will be subjected to extensive functional testing. This testing is conducted according to a written test plan and is intended to verify the proper functioning of all components of the DMS. Any components that do not function as they were intended will be identified and evaluated by the development team to determine appropriate corrective action. Testing will also include an evaluation by user representatives for adherence to the requirements established by the intended users for the DMS. Successful completion of these user acceptance tests will mark the end of development and predicate the deployment of the DMS for use in storing and managing active trial data. Any modifications made to the DMS will be conducted in accordance with change control procedures.

10.2 Data Security

All research data for the trial will be stored in an electronic Access database that is managed by the Data Manger. The database will be hosted on a secure computing server and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. The Data Manager will maintain the database in an appropriate manner for the retention period required by regulation. Database administration includes user account maintenance, database security, performance monitoring, and database change management.

10.3 Data Processing

The data entry screens will resemble the data collection forms as closely as possible to allow visual referencing during data entry. This data entry module will be configured for single data entry. Participant data will be collected by research staff, recorded on study-specific CRFs, and scanned in or entered directly into the appropriate DMS module. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and/or skip pattern enforcement. Following telephone eligibility screening, research staff will perform subject registration. Following the Intake Visit, research staff will randomize eligible subjects. The randomization module will allow the research staff to randomize subjects into one of the two trial arms. At the randomization attempt, the DMS will check the eligibility data to confirm that randomization is valid. A randomization assignment will then be provided.

10.4 *Data Quality Assurance*

A data quality module will be developed to assess data entered into the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by the data manager, working closely with trial investigators, to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. The research staff will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data items

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will be managed by the research staff. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

Monitoring of trial progress will be accomplished, in part, through the use of standard reports. The Data Manager will program a set of standard enrollment, tracking, quality review, and safety monitoring reports. Data audits will occur after the first few participants are enrolled and periodically during the trial to detect errors in data entry. Eligible participants will have 100% of their source document information compared with the data entered in the database. Any errors will be investigated, resolved, and a plan will be implemented to prevent further errors should concerning patterns emerge.

10.5 Subject and Specimen Tracking

The Data Manager will develop a module to assist research staff in recruitment and retention tracking for trial subjects. This module will accept and store contact information for potential subjects and will include data items to indicate the completion status of significant events. The tracking module will include information about contact and visit schedules to assist in preparing communications to potential subjects and trial participants concerning scheduled events. The module will also allow for incentive-related inventory management.

10.6 Data Handling and Record Keeping

10.6.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI. Note in the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Confidentially of study data will be maintained in the following manner:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, personnel will be required to review and sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.
- Precautions are in place to ensure the data is secure by using passwords and encryption.

Since self-report data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the data management system has set up several safeguards to prevent unauthorized access to participant data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying

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subject information is directly linked to bio-samples or results. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All subject data that can be linked to the study ID will be stored in the secure data management system, which has limited, password-required access. The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 9.6.2 below.

10.6.2 Subject Privacy/Protected Health Information

The following protected health information (PHI) may be collected as part of this study:

1. Name
2. Street address, city, county, zip code
3. All elements of dates (except year) for dates directly related to an individual and all ages over 89
4. Date of birth
5. Social Security Number
6. Telephone number, email address
7. Any other unique identifying number, characteristic, or code
8. Results from all questionnaires, tests, and procedures

Potential participants will be contacted over the phone after responding to recruitment efforts or having agreed to be contacted for future studies. Only individuals who have responded to recruitment efforts or who have agreed to be contacted regarding research studies at our Center will be contacted. If an individual cannot be reached immediately, staff members will identify themselves only as calling from the University of Pennsylvania; no mention will be made of the inquiry regarding study participation. Participants will undergo an initial telephone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they be asked to attend an in-person Intake Visit to confirm eligibility. All data collected over the phone and during in-person visits will be collected by research staff that have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Once enrolled, information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. All analyses will be conducted on de-identified data.

Data will be accessible only to the Study Investigators, study staff, applicable Center staff, UPenn IRB, Office of Clinical Research, authorized UPENN staff (e.g. accounting and billing matters, provide treatment, etc.), National Cancer Institute, and the FDA.

11 Data and Safety Monitoring

11.1 Research Roles

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, research staff, and the IRB. The research staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms (CRFs), ensuring all fields are completed appropriately, and all error corrections are done according to GCPs. Any inconsistencies/deviations will be documented and addressed as appropriate. The research staff will perform regular chart reviews to verify data integrity. The Study Coordinator (or senior personnel) and Principal Investigator will maintain the study regulatory binder/essential documents per GCP. Research staff will meet and communicate on a regular basis to reconcile data queries and safety concerns. The IRB will

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review the trial on an on-going basis per institutional and federal regulations until the study is formally closed-out.

11.2 Staff Training

Staff training will consist of an initial explanation and review of the protocol, informed consent form, CRFs and laboratory tasks, sample collection protocols, data management system, adverse event collection and reporting, and all study-specific SOPs. In addition, during a standardized training period, the duties of each staff member will be clearly outlined and all applicable regulations will be reviewed. Training interactions will be documented in a training log, which will be maintained within the regulatory binder. Senior personnel will supervise junior staff and provide re-training as needed.

All personnel working on this project will complete required training in the protection of human subjects and the protection of personal identifiable information (i.e. HIPAA) before interacting with study data or research participants. All human subject and privacy protections certifications will be maintained in the regulatory binder.

11.3 Monitoring Activities

11.3.1 AE/SAE Monitoring

Monitoring and management of AEs/SAEs will be conducted in real-time by the Principal Investigator and the research team at regular time points as per the methods and procedures detailed in section 8: Safety and Adverse Events.

11.3.2 Initial Assessment (Intake) Monitoring

The study staff will conduct a manual review of source documents and CRFs for all subjects determined to be eligible at telephone screen and again prior to the Intake Visit. Eligibility data will be reviewed in real-time at the Intake Visit by the research staff. In addition, The Study Coordinator (or senior personnel) will verify that all data have been collected and, when applicable, meet the eligibility criteria on a "Final Eligibility Checklist." The Final Eligibility Checklist will be signed and dated by the Study Coordinator (or senior personnel) to formally document review. In addition to confirming eligibility, a brief, internal report describing the findings will be compiled and distributed to study staff (if applicable). If the Study Coordinator (or senior personnel) notes a pattern of improper data collection or deviations, additional trainings will occur.

11.3.3 Protocol Monitoring

Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as identifying, reporting, and rectifying protocols deviations, reviewing for violations of inclusion/exclusion criteria, and ensuring the adherence to study-specific SOPs, GCP, and other federal and institutional regulations. Protocol monitoring will be performed on an ongoing basis through the following methods:

1. Checklists will be utilized at all time points to ensure all data is collected per protocol and procedures are followed as appropriate.
2. A Final Eligibility Checklist will be completed after the Intake Visit for all participants who enroll (i.e. sign consent) in the study. The Final Eligibility Checklist will serve as final confirmation of eligibility status.
3. A complete chart review of a randomly selected participant charts. The chart review procedure is a thorough review of all source documentation to ensure the integrity of the data, all study paperwork is present, all fields are completed per GCP, and all study-specific SOPs have been followed appropriately.

11.3.4 Database Auditing

As outlined in Section 9: Data Management, the study DMS will be equipped with internal validation checks to ensure data is entered within reasonable ranges. Error messages will be

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displayed in real-time if data appears inaccurate. Staff will have to respond to these error messages before data can be saved. In addition, The Study Coordinator (or senior personnel) will perform regular milestone quality assurance checks.

11.3.5 Data Security

As outlined in section 9: Data Management, study data will be secured through controlled user access and accessible to authorized personnel only. Source documents will be secured in locked filing cabinets.

11.4 Frequency of Data and Safety Monitoring

Data will be reviewed internally on a regular basis. Specifically:

1. At data capture, the research staff will review data for completeness and integrity.
2. At data entry, the DMS will include multiple internal validity checks which will prompt the staff if an entry was made that is out of range or in an unacceptable format.
3. Eligibility data will be reviewed in real-time at the Intake Visit. In addition, the Study Coordinator (or senior personnel) will review and verify that all data have been collected and, when applicable, meets the eligibility criteria on a "Final Eligibility Checklist."
4. On a regular basis, the project staff will review data through an internal chart review procedure supported by the DMS. A random subset of eligible participants will be reviewed.
5. All CRFs for eligible subjects are 100% source-data verified through an internal data management system (Data Entry/Quality Assurance) on an ongoing basis.
6. The study statistician will review data prior to analysis to ensure integrity and validity.

11.5 Auditing and Inspecting

The Principal Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Informed Consent

A fully trained staff member will obtain informed consent using the combined consent and HIPAA form approved by the IRB (UPENN). The consent process will take place prior to the initiation of any study procedures. The consent process will occur electronically via REDCap OR in person at the CIRNA and will involve a discussion of the study requirements and procedures. During in-person consent, the combined consent and HIPAA form will be read verbatim to participants.

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During electronic consent, the combined consent and HIPAA form will be completed virtually via REDCap. Participants will be required to read the entire consent in order to participate in the research study. Participants will have an opportunity to ask any questions and/or express concerns. Participants can elect not to participate and may withdraw at any time without penalty. Participants will receive a copy of the combined consent and HIPAA form for their records. In addition, participants will be given the Principal Investigator's contact information (located on pg.1 of the consent) should they wish to speak to the Investigator during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all participants will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for). The consent form must be signed and dated by the participant and the investigator-designated research professional obtaining the consent. The original signed combined consent and HIPAA form will be centrally stored in regulatory binders (consent).

13 RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

13.1 Research Staff

The following research staff will be directly involved with the implementation and execution of the current study:

- Janet Audrain-McGovern, Ph.D., Principal Investigator
- Andrew A. Strasser, Ph.D., Collaborating Investigator
- Melissa Mercincavage, Ph.D., Collaborating Investigator
- Shannon Testa, Research Staff
- Stephen Pianin, Research Staff
- Stephanie Messiha, Research Staff
- Fodie Koita, Research Staff
- Susan Ware, Database Developer/Manager
- Paul Sanborn, Research Staff

13.2 Study Facilities

This project will be conducted at and through the CIRNA. The CIRNA has successfully conducted similar protocols and has well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large and small conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities.

If participants require referral for psychological services, information about such programs at 3535 Market Street and/or the Philadelphia area will be provided; we have a form with specific information about such programs already in use in other CIRNA studies.

14 Study Finances

14.1 Funding Source

This study is financed through a grant from the U.S. National Cancer Institute.

14.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict

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reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14.3 Subject Compensation

Participants will be compensated for each in-person visit they attend and can receive up to $500.00 (including travel reimbursement) for successfully completing all of the study requirements in their entirety as per the Study Compensation table (Table 2) below.

All cases of non-compliance in regards to task and visit completion compensation will be reviewed on a case-by-case basis by senior personnel. A detailed compensation breakdown will be reviewed during the informed consent presentation and throughout the course of the trial.

Participants will be asked to complete a W-9 tax form (includes social security number) at the conclusion of Intake because the University of Pennsylvania is required to report to the Internal Revenue Service (IRS) any cumulative payments for participation in research studies at the University of Pennsylvania that exceed a total of $600.00 in a calendar year. A W-9 will aid the Center and University in tracking and reporting those who participate in multiple projects and accrue over $600.00 in a calendar year. Further, a social security number is required to register each participant for a Greenphire ClinCard (described below).

At the end of the Intake Visit, eligible participants will be issued a Greenphire ClinCard, which is a reloadable, pre-paid card for the purposes of study compensation. Compensation will be loaded onto the ClinCard at the end of successfully completed visits. Participants may opt to receive a text message alert when a payment has been loaded onto the ClinCard.

14.3.1 Table 2. Study Compensation

Visit	Visit Compensation	Compensation for Used Cigarettes/HeatSticks	Travel Reimbursement	Total
Intake	$10.00	N/A	N/A	$10.00
Day 6 Visit	$35.00	$35.00	$5.00	$75.00
Day 7 Visit	$40.00	N/A	$5.00	$45.00
Day 11 Visit	$20.00	$45.00	$5.00	$70.00
Day 14 Visit	$20.00	$45.00	$5.00	$70.00
Day 17 Visit	$20.00	$45.00	$5.00	$70.00
Day 21 Visit	$20.00	$60.00	$5.00	$85.00
Day 22 Visit	$55.00 BONUS	$15.00	$5.00	$75.00
			Study Total:	$500.00

15 References

See the NCI grant proposal for references.