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IMPACT OF IQOS NON-CIGARETTE TOBACCO PRODUCT ON REINFORCEMENT VALUE AND USE IN CURRENT SMOKERS

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1 ABSTRACT

A novel type of non-cigarette tobacco product was recently approved for sale in the US, the heated tobacco product (HTP) IQOS. IQOS may be less harmful than cigarettes, and there are some reports that it may produce more rewarding subjective effects compared to e-cigarettes. The approval of IQOS provides a unique opportunity to gather preliminary data surrounding IQOS. The goal of this pilot study is to assess the subjective effects and relative reinforcement value of IQOS, including its downstream effects on cigarette smoking. Current smokers will complete a one-week baseline period where they smoke as normal before attending an in-person lab visit. During the in-person lab visit, participants (n=10) will sample a traditional cigarette and a novel IQOS tobacco product. Participants will answer questionnaires about each product they sample and then complete a preference assessment in which they choose between the IQOS and their own cigarette. Finally, participants will take home a tobacco product they sampled to use ad libitum (1-week sampling). During the at-home baseline and sampling weeks, participants will complete electronic daily diaries cataloging their tobacco use. Biomarkers (i.e., expired carbon monoxide, cotinine) will corroborate self-reported indices of use.

2 OBJECTIVES

2.1 OBJECTIVES

To directly compare a novel tobacco product (IQOS) vs. combustible cigarettes on subjective effects and reinforcement value as well as test the impact of IQOS on tobacco use patterns (i.e., cigarettes per day) among current smokers.

Hypothesis: Given that there are no existing data comparing IQOS to traditional cigarettes, we make no *a priori* hypothesis about which product will have greater subjective effects or reinforcement value. We make no *a priori* hypothesis about the impact of IQOS on tobacco use.

3 BACKGROUND AND SIGNIFICANCE

In April of 2019, the FDA approved the sale of IQOS, a novel HTP that has been available for some time in other countries. IQOS heats disposable tobacco sticks (Heat Sticks) which are inserted into a holder and heated with an electric blade at 350ºC[1]. IQOS is currently available in Japan, Italy, Switzerland, South Korea, and has been increasing in prevalence in these countries. IQOS is being marketed as an alternative to smoking for current smokers. Existing data suggest that it likely does provide reduced toxicant exposure compared to smoking for current smokers, although the levels of toxicant exposure may be greater for IQOS than they are for e-cigarettes [2]. If IQOS proves to be a more appealing product than e-cigarettes and produces greater uptake and greater downstream effects on cigarette

smoking, IQOS could have a more positive impact on public health than e-cigarettes, despite the direct health effects of IQOS likely being more harmful than e-cigarettes. However, because IQOS was only recently approved for sale in the US, there is no existing US research on its appeal or reinforcement value.

The proposed pilot is innovative in that it will be the first study to provide the IQOS product to US smokers outside of the tobacco industry and will provide important preliminary data for a future grant application focused on IQOS.

3.1 INTERVENTION TO BE STUDIED (USE OF HTP)

Heated Tobacco Products (HTPs, sometimes called Heat Not Burn or HNB) are quite different from both e-cigarettes and traditional cigarettes. HTPs heat reconstituted tobacco at a temperature below combustion of the tobacco rod as is the case for a conventional cigarette. Because the tobacco is not directly burned, exposure to the many harmful chemicals generated by cigarette smoke is substantially lower for HTPs [3]. Because actual tobacco is used (vs glycerin liquid within e-cigarettes), HTPs products may provide a superior sensory experience to e-cigarettes [3]. However, the tobacco is singed within HTPs, and thus these products most likely result in increased exposure to harmful chemicals compared to e-cigarettes, though still less than combustibles.

Tobacco Products are regulated by the FDA. An Investigational Tobacco Product (ITP) application to the FDA is not required because both products are approved for commercial sale in the US. An Investigational New Drug (IND) application would be required if we were testing the impact of IQOS on smoking cessation but is not required in this case because we are interested in the naturalistic impact of these products on tobacco use generally. We have conducted multiple studies of this type and have strong confidence that we are on safe regulatory ground in conducting the study without an ITP/IND.

Dr. Smith has three recently completed or ongoing trials investigating the impact of providing other non-cigarette products to smokers on tobacco use patterns. These trials are very similar to the proposed project in that smokers are recruited to receive an e-cigarette, which is provided in a naturalistic way to be used as much or as little as the smoker wishes. While Dr. Smith has not led trials of IQOS, neither has any other US investigator.

4 ELIGIBLITY CRITERIA

4.1 INCLUSION CRITERIA

To be eligible for this study, the participant must meet all of the following criteria:

1. have been smoking at least five cigarettes daily for the past year (baseline carbon monoxide > 8ppm)
2. rate their interest in using non-cigarette tobacco products as >5 on a 0-10 scale

3. have a smartphone that can receive text messages and has access to the internet or have an e-mail account they check daily (necessary for daily diary completion).

4.2 EXCLUSION CRITERIA

To be eligible for this study, the participant CANNOT meet any of the following criteria:

1. purchasing a heated tobacco product within the last six months
2. weekly use of heated tobacco product over the last six months
3. any heated tobacco product use in the past 30 days
4. use of tobacco products other than cigarettes on ten or more days in the past 30 days
5. current use of cessation medications
6. pregnant, trying to become pregnant, or breastfeeding
7. recent history of cardiovascular distress in the last three months
8. history of a seizure disorder
9. household member currently enrolled.

5 PROCEDURES

Design Overview: After completing a screening/baseline session, current smokers will complete a one-week baseline period. Participants will then attend a lab-reinforcement session where they will sample the IQOS product and a traditional cigarette. We will provide transportation via a taxi cab company (Yellow Cab) for participants who are eligible, but do not have reliable transportation to in-person visits. We will pay the cab company directly, the participant will not need to contribute. Participants will complete questionnaires that assess subjective effects and reinforcement value of these products. Participants will complete a preference assessment designed to assess the relative reinforcement value of these products (see below for details). At the end of the session participants will receive an IQOS to take home with them for a one-week sampling period. Across the at-home baseline and sampling weeks, participants will complete electronic daily diaries cataloging their tobacco use.

The HTP device used will be the IQOS device. Participants will receive a rechargeable IQOS device and charger. Each Heat Stick is considered to be similar in nicotine delivery to a cigarette. Thus, to ensure participants have a full supply for the one-week period, we will provide 7 packs of Heat Sticks, one for each day. Again, this supply ensures participants could exclusively use IQOS across the entire sampling period, although we expect that the majority of participants will not do so. Heat sticks will be available in both traditional tobacco and menthol flavors (participant's choice).

Experimental Design:

Study design for both studies follows our prior and ongoing studies, and all procedures including diaries, are well established. Prior to attending the in-person screening session, participants will complete an online screening questionnaire to determine preliminary eligibility and may be consented remotely (see below for details). If consent is not completed remotely, it will be completed in person at the Screening/Baseline Session prior to collection of any data.

1) Screening/ Baseline session and Baseline Smoking Phase: Participants will attend an in-person screening session in which they complete a battery of assessments to determine eligibility. Eligible participants will then complete a series of baseline questionnaires. At the end of the baseline session, participants will be instructed to smoke as normal for a one-week baseline period. Participants will enroll in daily electronic diaries documenting their tobacco use and will complete the first diary in the lab with help of study staff. Participants will provide a urine sample for baseline assessment of cotinine (the primary metabolite of nicotine).

2) Laboratory Reinforcement Session: Participants will attend a lab session in which they sample the IQOS product and a traditional cigarette and complete questionnaires about each product they sample (see below).

Sampling and Product Questionnaires:

Participants will sample the IQOS product (n=10) and a traditional cigarette (traditional cigarette first). For each product, participants will take four puffs at their own pace, and then complete a series of questionnaires assessing the subjective effects and reinforcement value of the product (see below). There will be a 15-minute inter-product interval. When participants finish the questionnaires about each product, they will wait for the remainder of the 15 minutes to elapse before trying the next product. Participants can play on their phones or read a magazine during this time. Study staff will be able to see and hear the participant from the control room during this time and will guide the participant through the sampling session by giving directions as to when to try each product and when to start/stop questionnaires.

Preference Assessment:

At the end of the 15-minute period for the last product, participants will begin a preference assessment. For this preference assessment, participants will complete 10 trials with a 4-minute inter-trial interval. For each trial, a member of study staff will ask the participant to choose between the IQOS and a traditional cigarette. Participants will indicate which product they choose and then be allowed to take two puffs of the product at their own pace. For each trial, participants may also choose not to take any puffs.

3) At-home sampling period and Follow-up Session: Participants will be provided with an IQOS product to take home with them for a one-week sampling period. Participants will receive the IQOS product and a supply of Heat Sticks. Participants will be instructed to use their assigned product as much as they would like over the week. Participants will continue to complete the daily electronic diaries during this time period and will report use of their assigned product. The primary purpose of the daily diaries is to capture daily tobacco use more effectively than retrospective recall of tobacco use at a lab session. Participants will return to the lab following the sampling period for a follow-up session to complete additional assessments and collect expired carbon monoxide. A urine sample will be collected for cotinine analysis at this follow-up session.

Compensation: Participants will receive $25 for the screening visit, $75 for the lab reinforcement session, and $50 for the follow-up session ($150 total). Participants can earn up to $25 per week for the daily diaries ($50 total). Participants who complete all sessions and all diaries can earn up to $200. Participants who are not eligible at the screening visit will receive $15 for their time. Participants who are not eligible do not receive the full $25 payment for that visit because the visit will be shorter (no additional baseline measures).

5.1 CONSENT PROCESS

All research personnel have up to date CITI Certification for Protection of Human Subjects and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets (e.g., craigslist, flyers, print ads, Facebook). Participants will complete an online redcap survey to determine initial eligibility. When participants click the link for this survey, they will see a brief description of the research study. Once participants have been determined to be initially eligible, they will be invited to participate in the consent process.

The consent process will take place via one of the following modalities: 1) Remote electronic consent (e-consent) via REDCap facilitated with a discussion over the phone, 2) Remote consent via doxy.me, or 3) in-person consent (in-person visit at start of Visit 1). Options 1 and 2 are functionally the same (remote teleconsent prior to attending Visit 1), but utilize different platforms (doxy.me vs. REDCap), and we have built in the option to use both platforms in case of technicality difficulties with one platform. During the COVID-19 restrictions, all consenting will be done remotely (not in-person). We have included the option for electronic consent to reduce the length of the first in-person visit, while still providing ample time for the consent process. During the teleconsent process, the participant and staff member will be able to talk with each other and review the consent form together. When participants sign the consent form (details below), the form can be downloaded by study staff and saved in a secure REDCap/Box folder (details below).

All participants will be provided with a hard copy and/or electronic copy of the consent form. Participants will be given time to review the consent documents, as well as a detailed overview of the consent documents by study staff. After participants have read the documents and the documents have been described by the study staff, participants will demonstrate that they understand key aspects of the study by verbally answering questions from study staff about participation (e.g., “Can you tell me what the risks of participation are?”). Participants will sign the consent form only after both the participant and the study staff member are confident that the participant understands their participation and the risks associated with participating. Consent/HIPAA signatures may be collected electronically. When consent is collected electronically in person, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap/Box folder if captured electronically. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Dr. Smith will supervise all aspects of the recruiting process. During the COVID-19 restrictions, all consenting will be done remotely through Redcap.

5.2 SETTING

The Medical University of South Carolina will be the only study site. In-person lab sessions will take place in the Health Neuroscience Laboratory located at 30 Bee Street. We currently use this lab space for a number of other lab-based studies. This space includes four testing rooms for conducting participant visits, and these testing rooms are ventilated to allow smoking/tobacco use inside the room. The lab also has a bathroom for collecting urine specimens, and a control room where staff can see and talk to participants while they complete smoking procedures in the testing rooms.

5.3 RECRUITMENT METHODS

Potential participants will be recruited from the Charleston, SC community using standard recruitment methods (craigslist, TV, radio, newspaper, social media) using IRB-approved flyers and ads. Potential participants will be directed to a REDCap screening questionnaire for determination of preliminary eligibility. All appropriate approvals will be obtained if/as needed prior to posting any flyers/advertising in the community.

5.4 SPECIMEN COLLECTION AND BANKING

We will collect spot urine samples at baseline and the follow up visit. These urine samples are collected for the purposes of pregnancy testing, and for testing urinary cotinine (the primary metabolite of nicotine) to assess nicotine exposure. Each specimen will be transferred to the Clinical Neurobiology Laboratory within the Institute of Psychiatry for the cotinine analysis. Specimens will be identified using participant ID, and the lab report will include the specimen ID, which can be linked back to the remainder of the participant data by the statistician. The report will be stored on a password protected server. Urine specimens will be destroyed after cotinine analysis.

5.5 MODIFIED PROCEDURES TO BE IMPLEMENTED DURING COVID-19 RESTRICTIONS:

After passing initial screening, all participants will be consented into the study through our established remote procedures via RedCap, instead of having the option to complete the consent process in person. All in-person screening questionnaires that can be administered over the phone prior to the visit will be completed over the phone (demographics questionnaire, physiological & medical history, & tobacco use history). Participants who are ineligible based on these questionnaires will be paid for the visit, but not required to come into the lab to complete the remaining screening assessments. If the participant is still eligible after completing these questionnaires, we will then schedule them to come into the laboratory to complete the remainder of the visit. For visits 2 and 3, we will complete any questionnaires remotely that we can complete remotely. For interview-administered questionnaires, we will call participants in advance of the visit and complete the questionnaire over the phone via interview with study staff. For questionnaires that are completed independently by the participant, we will send them a RedCAP link prior to the visit and request that they complete the questionnaires on their own. If participants fail to complete these questionnaires on their own or we are unable to reach them to complete the questionnaires, we will ask the participant to complete them at the visit in the lab.

For all visits, participants will be called 24 hours prior to all visits to confirm they are not experiencing any symptoms of COVID-19. All participants for each visit will be required to wear a mask and remain six feet away from the research staff and others when possible. When staff and participants must interact (for CO collection and e-cigarette disbursal), at least six feet of distance will be maintained by placing materials on a desk/table six feet away from the participant and then staff stepping away while the participant approaches to retrieve materials. All surfaces will be sanitized prior to the visit and after the visit.

6 STUDY

Timepoints	Screening / Baseline	Lab Session 2 Reinforcement Session	Lab Session 3 Follow up Session
Assessments			
Informed Consent	**X**		
Demographics	**X**		
Carbon Monoxide	**X**	**X**	**X**
Pregnancy Test	**X**		
Physiological and Medical History	**X**		
Tobacco Use History	**X**		
Adverse Event Monitoring		**X**	**X**
Timeline Followback	**X**	**X**	**X**
Cotinine	**X**		**X**
Stages of Change	**X**		
Fagerstrom Test for Nicotine Dependence	**X**		**X**
Penn State Cigarette Dependence Index	**X**		**X**
Penn State Dependence –Assigned Product			**X**
Brief Wisconsin Inventory of Smoking Dependence Motives	**X**		**X**
Electronic Daily Diaries	**Enroll→**	**→**	**→Unenroll**
***Cigarette Evaluation Scale**		**X**	
***Purchase Task (UB)**		**X**	
***Perceived Health Risks (UB)**		**X**	
***Product Evaluation Scale (IQOS)**		**X**	
***Purchase Task (Cig + IQOS)**		**X**	**X**
***Purchase Task (IQOS)**		**X**	**X**
***Perceived Health Risks (IQOS)**		**X**	**X**
Preference Task		**X**	**X**

7 RISKS AND BENEFITS

The research protocol calls for smokers to use an an IQOS product. Participants are not required to the use the product during the at-home sampling period but are asked to take four puffs of each product during the Lab Reinforcement Session. HTP are no more harmful than conventional cigarettes, and various studies suggest that they may offer reduced harm. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants.

7.1 RISKS TO SUBJECTS

Potential risks are as follows:

1) Use of HTP
2) Concurrent Use of HTP and smoking
3) Potential for undermining cessation
4) Non-smokers in the home (i.e., children) experimenting with non-cigarette tobacco products
5) Loss of confidentiality

Use of HTP. HTP are not fully combusted, and therefore levels of carcinogens are markedly reduced, if not eliminated, comparable to trace levels seen in nicotine replacement products[2][2]. HTP contain reconstituted tobacco, and therefore, toxicant exposure appears to be greater than it is for exclusive use of e-cigarettes [2]. Thus, for current smokers who are provided with an HTP, such as IQOS, use of this product is less harmful than continuing to use their current tobacco product. We will verify smoking status and study onset, and thus, we will not provide an HTP to anyone to whom it would present increased risk.

There is little information about likely AEs for use of HTP or the IQOS product. In a randomized trial conducted by industry scientists, there were fewer AEs among smokers who were randomly assigned to switch to IQOS than among smokers who were randomly assigned to continue smoking their usual brand[4]. However, the incidence of cough was higher among the participants assigned to switch to IQOS (20%)[4].

Concurrent use of HTP and smoking. If smokers engage in dual use, the major concern will be intake of nicotine, and too much of it. Symptoms of nicotine intoxication include nausea, dizziness, headache, and stomachache[5]. In a randomized trial conducted by industry scientists, smokers who were randomly assigned to switch to IQOS sometimes used both IQOS and cigarettes, and there was no reported evidence of nicotine intoxication, nor were there any serious adverse events[4]. The bulk of the evidence surrounding these products suggests that smokers who engage in dual use with HTP are able to titrate their nicotine intake. That is, they reduce their use of one product when they increase use of another product in order to avoid excessive nicotine intake. In the same randomized IQOS trial discussed above, smokers who used both IQOS and smoked cigarettes did not have significantly changed exposure to nicotine [4]. Thus, it is unlikely that concurrent use of cigarettes along with the IQOS product would result in nicotine intoxication.

Undermining cessation. Another potential risk is that the sampling intervention will decrease rather than increase future cessation. We do not know of any studies to examine this research question for IQOS. All participants will be told at the outset that quitting use of all tobacco products

is best for their health, and that quitting smoking by switching to a less harmful product would improve their health.

Use of HTP among non-participants and non-smokers, including children. Whenever a product is given to a smoker to take home and use, there is potential that the product will be used by someone else, inclusive of non-smokers and even children. This would be the case for a local in-person study or a remote study. In Dr. Carpenter's recently completed snus trial in which he mailed tins of smokeless tobacco to smokers all over the country, such "diversion" was not a problem, nor has it been observed in his ongoing R01 of e-cigarettes. We will verify smoking status at the study outset and will advise participants who receive HTP to keep them out of reach of children and pets.

Confidentiality. A final risk is breach of confidentiality.

2. Adequacy of protection against risks.

2.1 Informed consent. All research personnel have up to date CITI Certification for Protection of Human Subjects and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets in each recruitment city (e.g., craigslist, flyers, print ads, tv, Facebook). Participants will be directed to an online REDCap screening questionnaire for determination of initial eligibility. We have a system in place for REDCap to flag potential duplicate entries, ensuring we are able to exclude participants who might try to complete the screener multiple times to gain entry to the study. Participants who are determined to be eligible will be sent the informed consent document to review on their own before scheduling an informed consent teleconsent session or coming to the lab to review the consent document in person. During the consent session, study staff will review the consent document with participants, and answer any questions the participants may have. Participants will demonstrate that they understand key aspects of the study by verbally answering questions from study staff about participation (e.g., "Can you tell me what the risks of participation are?"). Participants will sign the consent form only after both the participant and the study staff member are confident that the participant understands their participation and the risks associated with participating. Consent signatures will be collected electronically during teleconsent or on our study tablet if in person. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap. We will abide by all HIPAA regulations as set forth by our institution. Dr. Smith will supervise all aspects of the recruiting process.

2.2 Protection against risk.

Use of HTP. At screening, participants will be screened for general medical precautions by self-report (cardiovascular disease, seizure disorders), and all participants will be monitored for adverse events during the study period. We will clearly advise against use of any tobacco product during pregnancy and breastfeeding. Participants will be educated about potential risks of tobacco use, including risks specific to HTP, and concurrent use of these products with cigarettes. Any serious or unexpected adverse events will be reported to the IRB. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (<5%) and mild (mouth/throat irritation, cough, headache, nausea, headache), and will be handled quickly (i.e., advice to participant to reduce or stop HTP). Lab studies of toxin exposure (above) suggest that HTP confer no greater risk to health than do conventional cigarettes. It is unlikely that HTP users will become addicted to the product in the 1-week sampling period. All participants will be provided with cessation information (referrals to Quitline) as part of this study.

Concurrent use of HTP and smoking. Per above, the most common effects from too much nicotine are nausea, headache, and disturbed sleep. The sampling period is one week in duration,

and thus we do not expect sustained patterns of dual use. We will track adverse events at every study contact and will have a toll-free number available for participants to call if they experience an adverse event (AE). All study contacts will remind participants of this number. Participants will be encouraged to contact Dr. Smith as soon as possible for serious events. If they wish, they may contact their local MD or give the study physician permission to do so.

Undermining cessation. We emphasize that this is not a cessation trial, though we will collect various cessation outcomes. Nonetheless, it is possible that use of HTP will undermine quitting (though this would be contrary to existing literature). At study outset and at the end of the study, participants will be reminded that quitting all tobacco products is best for their health, although completely switching to a less harmful product is likely to improve their health.

Diversion of or IQOS. We will verify smoking status prior to enrollment in order to ensure that we do not provide IQOS to a non-smoker for whom these products would represent increased health risks. We will strongly advise participants that they are not to share the study product with others, and that they should store the product in a secure area that is out of reach of children and pets. We cannot directly assess any diversion/uptake from the perspective of adolescents, since that would require separate consent, and is a separate research question.

Confidentiality. We will use the participant's name only on the screening and informed consent/HIPAA documents and these will be kept in electronically in REDCap, a secure database. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. REDCap is a secure, password-protected database. Any research materials collected on paper will be kept in locked files at the Cancer Control Program of the Hollings Cancer Center, with limited access to the study personnel. All database files will include password protection to further ensure confidentiality.

7.2 POTENTIAL BENEFITS

There will be no direct benefit to participants in this study. However, the information that we get from the study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health.

8 DEFINITION OF ENDPOINTS

Screening: A variety of questionnaires and assessments will be used for the purpose of determining eligibility. This includes a Demographics Questionnaire, expired breath Carbon Monoxide reading, Physiological and Medical History Questionnaire, urinary pregnancy test, and a detailed Tobacco Use History Questionnaire.

Baseline: For participants who have been determined to be eligible, additional baseline questionnaires will be administered including a Stages of Change Questionnaire which assesses a participant's interest in quitting, smoking dependence questionnaires including Fagerstrom Test for Nicotine Dependence, Penn State Cigarette Dependence Index, and the Brief Wisconsin Inventory of Smoking Dependence Motives.

Daily Diaries: Daily diaries will assess the number of cigarettes used each day, as well as the number of IQOS Heat Sticks used. We will assess which product (cigarette or IQOS) was preferred and which was used first each day. Participants will be enrolled in these daily diaries at the baseline session and will continue to complete them each day until the Follow up session when they are

unenrolled. The primary outcome obtained using the daily diaries is the average number of cigarettes smoked during the baseline and sampling weeks.

Lab Session 2: Sampling: Participants will sample a traditional cigarette and the IQOS product. Participants will sample each product (four puffs at their own pace), and then wait 15 minutes before sampling the next product or beginning the preference assessment (i.e., 15-minute interproduct interval). During the interproduct interval, participants will complete questionnaires about the product they just sampled, each designed to assess the subjective effects and reinforcement value of the product they just sampled. After sampling the traditional cigarette, participants will complete three questionnaires. 1) The Cigarette Evaluation Scale, which assesses the sensory characteristics of the cigarette. Five subscales can be created from this assessment as previously described [6]: Satisfaction subscale, Psychological Reward subscale, Aversion subscale, Enjoyment of the Sensations in the Respiratory Tract subscale, and Craving subscale. 2) the Cigarette Purchase Task which assesses how many cigarettes participants estimate they would smoke at a variety of prices. As previously described [7], the following parameters can be calculated from this questionnaire: Intensity, or the number of cigarettes participants estimate they would smoke if cigarettes were free; Omax, or the maximum amount of money participants report they would spend in a single day; Pmax, or the price that produces Omax, Breakpoint, or the highest price at which participants report they would continue to smoke, and alpha, or the elasticity of demand for smoking. 3) the Perceived Health Risks scale, which assesses personal health risks associated with smoking. After sampling the IQOS product participants will complete four questionnaires.: 1) the Product Evaluation Scale, adapted from the Cigarette Evaluation Scale, which asks participants to rate the product on sensory characteristics (e.g., tasted good, immediately reduced craving for cigarettes). This questionnaire is analyzed in the same way as the Cigarette Evaluation Scale. 2) a modified Cigarette Purchase Task, in which participants estimate how many cigarettes they would smoke at a variety of prices if IQOS were also available (a test of whether the product reduces the reinforcement value of cigarettes), 3) a Product Purchase Task in which participants estimate how many Heat Sticks they would use across a series of prices if it were the only tobacco product available (a test of the reinforcement value of IQOS. Both the modified Cigarette Purchase Task and the Product Purchase Task are analyzed in the same way as the Cigarette Purchase Task. 4) a Perceived Health Risks scale, which assesses personal health risks associated with IQOS, and is the same scale used for traditional cigarettes.

Lab Session 2: Preference Assessment: After completing the sampling portion of this session, participants will complete the preference assessment. Preference Assessments have been used in a variety of contexts to determine reinforcement value. Across a series of trials, participants will have the option to choose either a traditional cigarette or IQOS. The primary outcome is the product most preferred.

Lab Session 3: Follow-up Questionnaires: After participants have taken home and sampled their assigned product for one week, they will return to the lab to complete a variety of follow-up questionnaires. This includes expired carbon monoxide (an objective marker of changes in smoke exposure compared to baseline), and the four questionnaires they completed about each product during the sampling session, this time completed about the product they took home with them for the week (Product Evaluation Scale, modified Cigarette Purchase Task, Product Purchase Task, Perceived Health Risks).

9 STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

9.1 DETERMINATION OF SAMPLE SIZE

The primary purpose of the proposal is to collect pilot data to lead to a larger grant submission. No formal power analysis has been conducted, and the sample size was chosen based on feasibility. A prior ITC pilot study conducted by Dr. Smith recruited 30 participants using a similar design with more restrictive inclusion criteria, and we anticipate being able to recruit 10 participants in the time proposed.

9.2 DATA ANALYSIS

For each of the questionnaires completed during Visit 2 sampling, the IQOS device will be compared to traditional cigarettes using paired-sample t-tests. A chi-square test will determine whether there are differences in the percentage of participants who preferred the IQOS and the percentage who preferred traditional cigarettes during the preference assessment. For the at-home sampling phase, a within-subjects t-test will determine whether there are differences in the average number of cigarettes smoked during baseline and the sampling week.

10 DATA COLLECTION AND MANAGMENT

Research material obtained from the participants include responses to surveys, collected directly by our research team and entered into REDCap, responses to surveys entered directly into REDCap by the participant themselves, and responses to electronic daily diaries, stored directly into REDCap. We will also collect CO, entered by study staff into REDCap at the visit. Research data will be obtained specifically for research purposes. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA.

11 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

This project involves three laboratory visits across two weeks. Participants will receive an IQOS to take home with them over a one-week time period.

Dr. Tracy Smith has used a similar protocol before and she will train and closely monitor research assistants. She will discuss issues with research assistants at least weekly.

Any unexpected death or unanticipated problem involving risks to subjects or others will be reported to the IRB. Consistent with MUSC policy, we will report deaths within 1 day and unanticipated problems within 10 days. We have identified clear risks associated with the trial, which are related to potential breaches of confidentiality and use of HTP.

Risks associated with this study include:

1) Use of HTP
2) Concurrent Use of HTP and smoking
3) Potential for undermining cessation
4) Non-smokers in the home (i.e., children) experimenting with non-cigarette tobacco products

5) Loss of confidentiality

When a serious AE occurs, Dr. Smith will review it prior to the participant's next scheduled visit. If a death occurs, study staff will notify Dr. Smith immediately and she will notify the IRB.

12 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

12.1 INFORMED CONSENT

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

12.2 INSTITUTIONAL REVIEW

Adverse events will be handled in accordance with MUSC Human Research Protection Program (HRPP) policies. Any event that is unexpected, related or possibly related, and suggest that the research places participants at greater risk than was previously known will be reported to MUSC IRB. Serious adverse events (SAEs) are defined in Section 4.7 of MUSC HRPP as any adverse event temporarily associated with a participant's participation in research that results in death, is life-threatening, requires inpatient hospitalization, results in significant disability/incapacity, results in a congenital anomaly, or any other adverse event that requires immediate medical or surgical intervention. Consistent with IRB policy, any unexpected death will be reported within 24 hours and any unanticipated problem involving risk to subjects or others will be reported within 10 days.

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