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Research Article

IQOS® Cross-Sectional and Cohort US Study Documentation

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Background: The FDA's modified risk authorization for IQOS® is contingent upon approved post-market surveillance studies. The IQOS® Cross-Sectional Post-Market Adult Consumer Study (hereinafter termed IQOS® CS PACS) and the IQOS® Longitudinal Cohort Post-Market Adult Consumer Study (hereinafter termed IQOS® LC PACS) are contiguous surveys designed to fulfill this proviso.

Objectives: IQOS® CS PACS seeks to assess tobacco use patterns in IQOS® users, risk perceptions of IQOS®, and tobacco transition and cessation behaviors related to IQOS®. The IQOS® LC PACS aims to follow over time, and in comparison with cigarette users, these same parameters with additional emphasis on transitions and health outcomes.

Methods and Results: The IQOS® CS PACS is a repeated cross-sectional study to be conducted annually for four years. The IQOS® LC PACS is a longitudinal study, planned to follow a cohort of new IQOS® users for two years. Potential adult IQOS® consumers aged 21 and older will be recruited from an IQOS® consumer database. Both studies will use self-administered online screening and survey assessment. At least 250 adult ever established IQOS® users (current and former) constitute the target sample size for each administration of the IQOS® CS PACS. The target sample size for the IQOS® LC PACS is 2,100 adult IQOS® users and 1,600 adult cigarette smokers as control. Data analysis includes descriptive statistics for pre-defined outcomes and inferential statistics (e.g., generalized estimating equations and propensity scoring) to compare outcomes among IQOS® and cigarette smokers.

The IQOS® CS PACS is designed to commence one year after IQOS® modified risk tobacco product authorization (MRTPA) and will recur annually over the course of four years. The IQOS® LC PACS will begin two years after issuance of the IQOS® modified risk order and has been designed to follow up with participants at 3-, 6-, 12-, 18-, and 24-months from initiation. Final reports will be generated and shared with the FDA when the studies are completed.

Conclusions: Postmarket studies can help inform outcomes related to risk perceptions, tobacco use patterns, and health status related to IQOS® use in a real-world setting.

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Declarations

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Conflict of Interests

All authors are employees of Altria Client Services LLC. The authors have no conflicts of interest related to the contents of this article.

Introduction

Cigarettes are the most frequently used tobacco product globally and in the US, 40 million adults are cigarette smokers ^[1]. Mortality estimates predict 500,000 deaths per year from smoking-related illnesses or secondhand smoke exposure, and an annual expenditure exceeding 170 billion dollars in medical costs for the treatment of smoking-related lung and cardiovascular illnesses ^[2]. While cigarettes deliver nicotine efficiently, they also generate harmful and potentially harmful constituents (HPHCs) during combustion and quitting smoking is the only complete tobacco health-risk mitigation strategy. However, there are many barriers to smoking cessation, including the fact that many adult tobacco users are not amenable to quitting tobacco use, underlining the need for reduced risk (RR) non-combustible tobacco offerings geared towards harm reduction.

Tobacco harm reduction (THR) is a multi-faceted public health initiative aimed at reducing health costs and negative health impact associated with tobacco use; the concept accepts that while complete abstinence is the most viable risk alleviation option, the many barriers to complete eradication of nicotine and tobacco necessitate recourse to other strategies (**Reviewed in** ^[3]). Therefore, approaches to THR involve underage prevention, public health education on the relative risks of tobacco products, cessation support, and the availability of RR products that do not burn tobacco (**Reviewed in** ^[3]). Thus, transitioning adult smokers who are unable or unwilling to quit tobacco to RR profile non-combustible tobacco products is intimately intertwined with the mission of public health protection ^{[4][5][6][7][8]}. Heated tobacco products, though

not entirely risk free, represent potential opportunities to reduce health risks related to HPHC exposure while providing nicotine at a similar level as cigarettes ^{[9][10][11][12][13][14][15]}.

In alignment with tobacco harm reduction efforts, Philip Morris Products S.A. (PMP S.A.) has developed a novel heated tobacco product, the IQOS[®] Tobacco Heating System[®] and Marlboro HeatSticks[®] (hereinafter referred to as IQOS[®]) ^{[16][17]}. IQOS[®] and predecessor products generate aerosols by heating tobacco to a lower temperature than traditional combustible cigarettes, thereby limiting the generation of, and user exposure to, deleterious constituents ^{[10][14]}.

PMP S.A. submitted Modified Risk Tobacco Product Applications (MRTPA) for IQOS[®] to the US Food and Drug Administration (FDA) seeking authorization to communicate modified risk claims. IQOS[®] was introduced in the US in limited markets with Philip Morris USA as the exclusive distributor and having corresponding responsibilities for conducting post-market surveillance studies (PMSS). On July 7, 2020, the FDA granted the MRTPA marketing order authorizing the reduced exposure claim¹. The IQOS[®] MRTPA authorization is conditioned on the agreement that the PMSS are conducted according to FDA approved protocols. In particular, the FDA requires the PMSS to evaluate the effects of the MRTP claim on consumer perception, behavior, and health under authentic IQOS[®] usage conditions. There is precedent for the utility of such research – cross-sectional and longitudinal studies in international markets have helped characterize product adoption, prevalence, usage patterns, and risk perceptions of IQOS[®] ^{[16][18][19][20][21]}. These studies also probe consumer satisfaction along with motivations for transitions, provide context for population risk-benefit analysis, and help prioritize regulatory decision-making in the protection of public health. Therefore, after the introduction of IQOS[®] in the US and FDA's authorization of MRTP, FDA approved two survey studies to fulfill MRTPA requirements. The IQOS[®] Cross-Sectional Postmarket Adult Consumer Study (IQOS[®] CS PACS) was launched one year after issuance of the IQOS[®] modified risk granted order with a planned annual recurrence over a four-year period from commencement. The IQOS[®] Longitudinal Cohort Postmarket Adult Consumer Study (IQOS[®] LC PACS) planned to begin enrollment two years after issuance of the IQOS[®] modified risk granted order with a follow-up period of two years.

Objectives

The objectives of the IQOS[®] CS PACS are (i) to characterize adult ever established IQOS[®] users and their tobacco use patterns; (ii) to characterize risk perceptions of IQOS[®] and the modified risk tobacco product (MRTP) claim understanding; (iii) to describe initiation, complete switching from cigarette smoking to IQOS[®] use, transitions to/back to cigarette smoking, and quitting and cessation behaviors relevant to IQOS[®] use.

The IQOS[®] LC PACS seeks to comparatively assess over time (i) tobacco use patterns among IQOS[®] users and cigarette smokers; (ii) transitions in IQOS[®] users and cigarette smokers; (iii) self-reported measures of health and disease-related outcomes pertinent to tobacco use; and (iv) assess risk perceptions and MRTP claim understanding among established IQOS[®] and cigarette users.

Materials and Methods

Study Design

Overview of study design

The IQOS[®] CS study will be conducted annually over a four-year period among adults (21 years of age or older) who use IQOS[®]. The IQOS[®] LC PACS will be conducted over a closed 24-month period among a cohort of adults who started using IQOS[®] fairly recently (i.e., within 6 months prior to the recruitment) and a group of adults who smoke cigarettes. Participants will be recruited from an adult tobacco consumer database maintained by Philip Morris USA (PMUSA) through e-mail and traditional mail contact. Both studies will determine eligibility using a computerized Participant Screener Survey prior to administering the Main Survey to consenting adult participants at the designated time points. The IQOS[®] CS PACS is designed to collect data on tobacco use patterns, risk perceptions of IQOS[®], and behaviors pertaining to tobacco use transitions and cessations at each wave of data collection; the IQOS[®] LC PACS will interrogate these same objectives over time and in comparison with a reference group of cigarette smokers, with additional emphasis on quality of life and health outcomes related to IQOS[®] transitions.

Study design objectives and survey instrument

The IQOS[®] CS PACS survey consists of modules to assess tobacco use patterns, risk perceptions of IQOS[®], behaviors pertaining to IQOS[®] initiation, switching, cessation, dual use, and transition to/from cigarettes among current established IQOS[®] users and former established IQOS[®] users. Pertinent survey questions were based on, or adapted from, national surveys and previous studies [22][23][24]. Furthermore, ALCS updated items after commissioning cognitive testing of survey instrument in 2020.

The IQOS[®] LC PACS survey is made up of modular units administered at designated timepoints, pertaining to gathering data on demographics, tobacco use behaviors, tobacco dependence, quitting behaviors, risk perceptions, perception and understanding of IQOS[®] and exposure reduction, and quality of life, signs, symptoms, and diagnoses. Study groups consisting of current established IQOS[®] users and reference cigarette smokers will be queried at every survey on some measures such as tobacco use behaviors, tobacco dependence, quitting behaviors, perception and understanding of IQOS[®], and quality of life signs and symptoms. However, responses to risk perceptions and diagnoses will be mined only during the annual modules. Survey questions utilized for each study are summarized in the supplementary data section (**Appendix 1 for the IQOS[®] CS PACS questionnaire and Appendices 2 and 3 for the for the IQOS[®] LC PACS, denoting baseline, and follow-up survey questionnaires, respectively**).

Study duration, frequency, and length

The IQOS[®] CS PACS will be conducted annually over a four-year time period. Each annual data collection period is expected to last approximately 12 weeks. The Participant Screener and Main Survey are estimated to take 20 minutes for completion, depending on the individual's use of the number of tobacco products. Upon completion, participants will be provided with options to redeem an e-card of their choice.

The IQOS[®] LC PACS will follow cohorts over a 24-month timeframe (See **Figure 1** for milestones). When considering the initial 12-week enrollment period, including first participant in and last participant out, the study will span the entirety of 27 months. The 24-month study period consists of a total of six sequential survey modules. Three survey modules will be administered to participants every three months for the

first six months (Module 1 commencing at the start of survey; module 2 at three months; module 3 at six months); the other three modules will be administered every six months of the remainder of the study timeframe (Module 4 at 12 months; module 5 at 18 months; module 6 at 24 months). The six survey modules and schedules are described in detail (Figure 2).

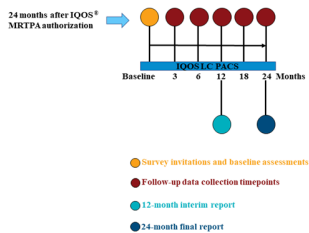


Figure 1. Projected Survey Plan for IQOS® Longitudinal Cohort Post-Market Adult Consumer Study (IQOS® LC PACS) 24 Months after a Modified Risk Tobacco Product Authorization. Survey invitation and baseline assessments will take place over a 12-week period. All survey data assessments and analysis at three- and six-month intervals over a 24-month period will be subject to analysis at the conclusion of the designated survey timepoints. The findings will eventually be presented to the FDA as interim and final reports and subsequently made available for public dissemination.

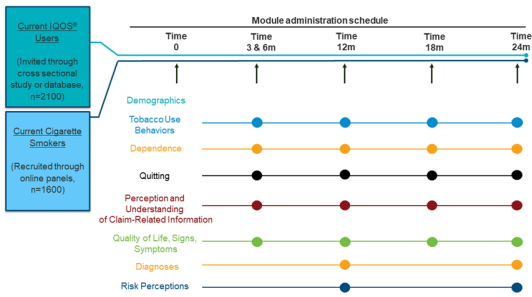


Figure 2. Proposed Design of Survey Modules and Schedules. The survey modules are expected to span a 24-month time course with timepoint-specific survey modules to assess tobacco use behaviors, transitions, risk perceptions, and quality of health outcomes.

Each module needs to be completed online within a 30-day window and will require approximately 15-25 minutes to complete. All eligible participants will be

compensated with cash equivalents, such as electronic gift cards, for survey completion commensurate with length and complexity of survey participation.

Study Population

Study groups

The IQOS® CS PACS will include adult ever established IQOS® users who are 21 years of age or older. Ever established IQOS® users will be defined as individuals who have used at least 100 Marlboro HeatSticks® in his/her lifetime. Ever established IQOS® users include current and former established IQOS® users defined as:

Current established IQOS® users: A participant who has used at least 100 Marlboro HeatSticks® in his/her lifetime and reports now using IQOS® “every day” or “some days”.

Former established IQOS® users: A participant who has used at least 100 Marlboro HeatSticks® in his/her lifetime and reports “not at all” using IQOS® now.

The IQOS® LC PACS will include both current established IQOS® users and cigarette smokers from IQOS® sale geographies. At the time of recruitment, the groups will be defined as test and reference groups elaborated below.

IQOS® User Group: The IQOS® user group will consist of adults who report: (1) using IQOS® “every day” or “some days”, (2) having used IQOS® during the past 30 days, (3) having used IQOS® for a period of six months or less (irrespective of use of any other tobacco product), and (4) having used at least 100 Marlboro HeatSticks® in their lifetime.

Cigarette Smokers (Reference Group): The cigarette smoker group will consist of adults who report: (1) never trying IQOS®, (2) having smoked at least 100 cigarettes in their lifetime, (3) smoke “every day” or “some days”, and (4) having smoked cigarettes in the past 30 days (irrespective of use of any other tobacco product).

For those qualified participants from the IQOS® CS PACS who are also amenable to participating in the LC PACS, all study data will transfer and serve as initial baseline data for IQOS® users with continued participation.

Sample size and power considerations

A sample size of n=250 is deemed sufficient for the requirements of precision and statistical power for the IQOS[®] CS PACS. This calculation (**Supplementary Table 1**) can accommodate a 95% confidence interval (CI) width of 0.127 for the estimates of proportions [25]. The study will commence when the minimum sample size for established IQOS[®] users can be met, assuming a 5% response rate.

In the case of the IQOS[®] LC PACS, a sample size of n=2,100 participants is anticipated for the test group of current established IQOS[®] users and n=1,600 for the reference category of cigarette smokers. These sample sizes and 24 month study duration were devised to account for significant differences in quitting smoking between the IQOS[®] user and cigarette smoker categories with over 90% power; the quit rates were assumed to be a constant over a two year timeframe, extrapolating from published literature [26]. Informed by discontinuation rates of 12%–66% from prior studies of IQOS[®] cohorts from other countries [27][28][29][30][31][32][33][34][35][36], the current study sample sizes for both the IQOS[®] CS PACS and the IQOS[®] LC PACS were intended to accommodate survey attrition rates without loss of power. The power analysis was conducted for a two-sided Pearson's Chi-square Test for Proportion Difference [37]. If sample size requirements for the IQOS[®] user group cannot be satisfied through the IQOS[®] CS PACS alone, then additional study respondents will be sought using the IQOS[®] consumer database.

Study inclusion and exclusion criteria

The following inclusion criteria were set for enrollment into both studies: at the time of screening, study participants must be US residents aged 21 or older; provide voluntary consent for participation and must comply with all study requirements listed in the informed consent statement (ICS); acknowledge and digitally sign the ICS; meet the 100 Marlboro HeatSticks[®] lifetime use threshold for enrollment as a current or former established IQOS[®] user.

The following criteria constituted grounds for exclusion for both studies: participants unable to read, speak, or understand English; participant, or a first-degree relative, or household member, is a current or former employee of the tobacco industry, any market research firm; participant or first-degree relative currently

involved in litigation against any tobacco industry entity; participants recruited from the IQOS[®] user database had been respondents in any of the prior year IQOS[®] CS PACS.

Study Procedures

Study settings, recruitment, and implementation:

All study participant recruitments for the IQOS[®] CS and LC PACS will occur in the US in restricted IQOS[®] markets with a sampling approach relying on a mixed recruitment model. First, invitations to participate will be issued to adult IQOS[®] consumers enrolled in the IQOS[®] consumer database maintained by PMUSA. In 2021 prior to the first IQOS[®] CS PACS recruitment, an estimated 70% of IQOS[®] consumers were enrolled in the database. Second, third-party recruitment via commercial online panels in IQOS[®] sales geographies may be used to enroll potential participants if consumer database recruiting is not projected to fulfill the sample size requirement. IQOS[®] sales geographies were confined to limited southeastern US markets. Recruitment will continue until fulfillment of all sampling size requirements. All participants, regardless of recruitment approach, will complete the same online survey.

Eligible participants will be required to sign an ICS before participating in the study. The ICS includes a study summary, study objectives, voluntary nature of study participation, data confidentiality and privacy guidelines, and information on monetary or equivalent forms of compensation commensurate with study participation and length. A Participant Screener Survey will be administered to determine eligibility and include age verification. The Main Survey will then be administered to eligible participants to collect information detailed above.

An external market research firm, under the guidance of ALCS, will coordinate study recruitment, survey administration, and data collection for both IQOS[®] CS PACS and IQOS[®] LC PACS. The IQOS[®] CS PACS and IQOS[®] LC PACS were scheduled to begin one and two years after issuance of the modified risk granted order, respectively and will be reliant on continued distribution and sales of IQOS[®]. Adverse event reporting for both studies will comply with Good Epidemiological Practices (GEP) and ALCS established consumer research procedures.

Participant discontinuation and replacement

Participants are informed of the voluntary nature of their decision to participate and that they are free to discontinue at any time. There will be no penalties imposed on discontinuing participants for withdrawal and no loss of benefits to which participants are entitled. The number of qualified participants who consent to the study and then prematurely withdraw will be recorded. The study sponsor reserves the right to terminate the study at any time.

Given the cross-sectional nature of the IQOS® CS PACS, replacement of study participants is not feasible. For the IQOS® LC PACS, adult participants who discontinue before survey completion will be permitted to return and complete the survey within their allotted completion time. In the event the participant misses a survey, there will be no catch-up surveys or deviations permitted in the study schedule; however, participants will be allowed to progress to the next scheduled survey module. Only completed surveys will be used for data analysis and reporting, with comprehensive survey attrition analysis to rule out any resultant bias. Weights may be used to account for attrition. If weights are used, the weighted generalized estimating equations (GEE) approach [38] for logistic regression will be used to estimate the probability that a subject's survey is missing at a given wave and weights the data based on the inverse of these probabilities.

Study Outcome Measures

The study outcomes for the IQOS® CS PACS will include the following:

1. Tobacco use patterns

- i. Types of tobacco products² ever tried, used to lifetime criterion, and currently using
- ii. Types of tobacco products ever used (even one time), used to lifetime criterion, and were currently using prior to first trying IQOS®
- iii. Exclusive or dual/poly tobacco use with IQOS®
- iv. Number of days of use of IQOS® and cigarettes in the past 30 days
- v. Amount of Marlboro HeatSticks® and cigarettes used in the past 30 days
- vi. Amount of tobacco product use before trying IQOS® relative to current tobacco product use
- vii. Use of IQOS® not as intended

2. Risk perceptions of IQOS®

- i. Risk perceptions of IQOS® and cigarettes
- ii. Perception of harmful or potentially harmful chemical exposure when switching from cigarettes to IQOS®
- iii. Understanding of the behavior smokers must demonstrate to reduce HPHC exposure

3. Initiation, switching to IQOS®, transitions to/back to cigarette smoking, and quitting behaviors

- i. IQOS® as the first tobacco product ever tried
- ii. Initiation of IQOS® as long-term former smokers and long-term former tobacco users
- iii. Complete switching from cigarettes smoking/all tobacco to IQOS®
- iv. Relapse to cigarette smoking after first trying IQOS® (among those who had smoked cigarettes, but had not smoked cigarettes for less than 12 months prior to first trying IQOS®)
- v. Re-initiation of cigarette smoking after first trying IQOS® (among those who had smoked cigarettes, but had not smoked cigarettes for at least 12 months prior to first trying IQOS®)
- vi. Initiation of established cigarette smoking after first trying IQOS® (among those who never smoked cigarettes prior to first trying IQOS®)
- vii. Complete switching from IQOS® to cigarette smoking

Quitting Behaviors

- i. Past 12-month cigarette smoking quit attempt (s)
- ii. Motivation to stop smoking cigarettes [39]
- iii. Quitting cigarettes after first trying IQOS®
- iv. Quitting all tobacco products after first trying IQOS®
- v. Use of tobacco cessation treatments
- vi. Quitting IQOS®
- vii. Quitting IQOS® for 12 months or longer

Sample size permitting, all outcomes of initiation, complete switching from cigarettes to IQOS®, dual use, quitting, and quitting attempts will be stratified by menthol vs non-menthol Marlboro HeatSticks® use as well as menthol vs non-menthol cigarette use.

4. Characterization of study participants with respect to demographics, background, and health information

- i. Demographic, background, and health-related information characterization for all participants: sex, age, race, ethnicity, education, employment

status, region, income, marital status, pregnancy status, presence of pre-existing medical conditions or co-morbidities, presence of mental illness, LGBTQ status, military personnel/veteran status

- ii. Length of time (i.e., years/months) using IQOS[®] and cigarettes
- iii. Cigarette and IQOS[®] dependence
- iv. Varieties of IQOS[®] ever used, first used, currently use, currently use most often, and previously used most often (among former established IQOS[®] users)
- v. Variety of menthol vs. non-menthol cigarette use

The IQOS[®] LC PACS will characterize the following:

1. Tobacco use behaviors

This module will collect information on the following items:

- i. Percent and count of participants in the IQOS[®] user group at baseline that report before first trying IQOS[®]:
 - Never tobacco use
 - Long term former tobacco use
 - Current smoking
 - Other current tobacco use
- ii. Percent and count of participants in the IQOS[®] user and cigarette smoker groups at each survey that report current use of (i.e., currently using “every day” or “some days”):
 - IQOS[®] only
 - Cigarettes only
 - IQOS[®] plus one other tobacco product: IQOS[®] and cigarettes, IQOS[®] and one other tobacco product, excluding cigarettes
 - IQOS[®] plus two or more other tobacco products: IQOS[®] and two or more other tobacco products, including cigarettes, IQOS[®] and two or more other tobacco products, excluding cigarettes

The current use categories will be stratified by predominant use of menthol or regular HeatSticks[®] and use of a cessation treatment.

- iii. Percent of prior wave IQOS[®] and cigarette dual users from the IQOS[®] user group who at surveys 2, 3, 4, 5, or 6 have either reduced cigarettes per day by at least 50%, increased cigarettes per day by at least 50%, or had the same cigarettes per day (less change than $\pm 50\%$) compared to the prior

wave and baseline accounting for predominant use of menthol or regular HeatSticks[®] and use of a cessation treatment

- iv. Mean cigarettes per day among IQOS[®] and cigarette dual users in the IQOS[®] user group at each follow-up survey, after controlling for cigarettes per day at baseline and accounting for predominant use of menthol or regular HeatSticks[®] and use of a cessation treatment
- v. Number of days of tobacco use in the past 30 days (IQOS[®], cigarettes, and e-vapor): Number of days used in the past 30 days will be reported using mean and standard deviations, median and interquartile range for IQOS[®] and cigarettes – compared within and across study groups – at surveys 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks[®] and cigarettes.
- vi. Amount of tobacco use on days used in the past 30 days (IQOS[®], cigarettes, and e-vapor): Varieties of Marlboro HeatSticks[®] used in the past 30 days and used most often (Marlboro HeatSticks[®], Marlboro Smooth Menthol HeatSticks[®], Marlboro Fresh Menthol HeatSticks[®]). Number of uses per day in the past 30 days reported using median and interquartile range for IQOS[®] and cigarettes – compared within and across study groups – at surveys 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks[®] and cigarettes reported as:
 - Number of HeatSticks[®]/cigarettes per day on days used
 - Number of HeatSticks[®]/cigarettes per day in the past 30 days
- vii. Percent of participants in the IQOS[®] user and cigarette smoker groups who are current established cigarette smokers at each survey, after accounting for predominant use of menthol or regular HeatSticks[®] and cigarettes, and use of a cessation treatment compared within and across study groups – at surveys 1, 2, 3, 4, 5, and 6.

2. Product use transitions

i. Change among Dual users

- Percent and count of prior wave IQOS[®] and cigarette dual users from the IQOS[®] user group who at surveys 2, 3, 4, 5, or 6 are exclusive IQOS[®] users, exclusive smokers, IQOS[®] and smoking dual users, or users of neither

product, irrespective of other tobacco product use and accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment.

ii. *Complete Switching Outcomes*

- Percent of established smokers from the IQOS® user and cigarette smoker groups who, at a future survey, report current established IQOS® use and no cigarette use accounting for predominant use of menthol or regular HeatSticks® and cigarettes, and use of a cessation treatment, including descriptive statistics for switching within and between menthol and non-menthol products.
- Percent of established IQOS® users in the IQOS® user group who, at a future survey, report current established smoking and no IQOS® use accounting for predominant use of menthol or regular HeatSticks® and cigarettes, and use of a cessation treatment.

iii. *Initiation outcomes*

- Percent of participants in the IQOS® user and cigarette smoker groups who report ever use (even one time) at surveys 2, 3, 4, 5, or 6 of a tobacco product never used, even one time, at survey 1 accounting for predominant use of menthol or regular HeatSticks®.
- Percent of participants in the IQOS® user and cigarette smoker groups who report ever established use at surveys 2, 3, 4, 5, or 6 of a tobacco product never used, even one time, at survey 1 accounting for predominant use of menthol or regular HeatSticks®.

iv. *Smoking relapse and re-initiation outcomes*

- Percent of established IQOS® users in the IQOS® user group that report established use of cigarettes but report not currently using cigarettes at survey 1, and at a subsequent survey report resuming current use of cigarettes within 12 months of not smoking accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment.
- Percent of established IQOS® users in the IQOS® user group that report established use of cigarettes but report not currently using cigarettes at survey 1, and at a subsequent survey report resuming current use of cigarettes 12 or more months after not smoking accounting for predominant use of menthol or

regular HeatSticks® and use of a cessation treatment.

v. *Quitting Behaviors*

- Percent and count of the IQOS® user group who were established smokers and smoked in the 30 days before first trying IQOS® and quit smoking at survey 1 accounting for predominant use of menthol or regular HeatSticks® and baseline use of a cessation treatment.
- Percent of established smokers from the IQOS® user and cigarette smoker groups who attempted to quit smoking cigarettes in the past 12 months at survey 1 and at each interval between subsequent surveys, accounting for predominant use of menthol or regular HeatSticks®.
- Percent of participants from the IQOS® user and cigarette smoker groups who report use of a cessation treatment at baseline (more than 12 months ago, over 30 days but less than 12 months, past 30 days, never) and incident use of a cessation treatment at surveys 2, 3, 4, 5, or 6.
- Percent of established smokers from the IQOS® user and cigarette smoker groups who completely quit smoking cigarettes at surveys 2, 3, 4, 5, or 6, accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment.
- Percent of established IQOS® users who completely quit IQOS® at surveys 2, 3, 4, 5, or 6 accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment.
- Percent of participants in the IQOS® user and cigarette smoker groups who completely quit all tobacco products at surveys 2, 3, 4, 5, or 6, accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment.

3. Health related quality of life, signs, symptoms, and disease

The facets of quality of life that will be measured as outcomes in this study include:

- i. Mean physical health T-score in the IQOS® user group relative to the mean physical health T-score in the cigarette smoker group at each follow-up survey, after controlling for the mean physical

health T-score at baseline and years smoked cigarettes.

- ii. Mean mental health T-score in the IQOS[®] user group relative to the mean mental health T-score in the cigarette smoker group at each follow-up survey, after controlling for the mean mental health T-score at baseline and years smoked cigarettes.

The signs and symptoms outcomes will include:

- iii. Mean number of cardiovascular symptoms present in the IQOS[®] user group relative to the mean number of cardiovascular symptoms present in the cigarette smoker group at each follow-up survey, after controlling for cardiovascular symptoms at baseline and years smoked cigarettes.
- iv. Mean number of respiratory symptoms present in the IQOS[®] user group relative to the mean number of respiratory symptoms present in the cigarette smoker group at each follow-up survey, after controlling for respiratory symptoms at baseline and years smoked cigarettes.

4. Risk perceptions of IQOS[®] and cigarettes; perceptions and understanding of IQOS[®] and exposure reduction

- i. Mean, standard deviation, median, and interquartile range of the health risk perceptions (PRI-G) composite score of IQOS[®] and cigarettes among the IQOS[®] user group and the cigarette smoker group – at surveys 1, 4, and 6.
- ii. Percent and count of participants in the IQOS[®] user and cigarette smoker groups' perception that switching completely to IQOS[®] results in reduced harmful or potentially harmful chemical exposure at surveys 2, 3, 4, 5, or 6.
- iii. Percent and count of participants in the IQOS[®] user and cigarette smoker groups' understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure (among participants who perceive that switching completely to IQOS[®] results in reduced harmful or potentially harmful chemical exposure) at surveys 2, 3, 4, 5, or 6.

Data Management

Data Validation and Database Lock

Quality control measures (e.g., assessment of inconsistent responses and clarification probes) will be implemented to provide assurances of data integrity and validity. Digital audit trails will be maintained along with written rationale for any data corrections or changes. When data collection is considered complete, the survey response database will be locked with no further permissible changes.

Data analysis

Only completed surveys will be used for data analysis and reporting; weights may be assigned to account for non-response patterns. Participation proportions consisting of contact-, eligibility-, response-, and completion-proportions will be reported for both studies.

Contact proportion: the number of persons screened for eligibility divided by the total number of persons attempted to be reached for eligibility screening (i.e., the number of invitations sent).

Eligibility proportion: the number of persons eligible for enrollment (i.e., persons who meet all inclusion criteria and no exclusion criteria) divided by the total number of persons screened for eligibility.

Completion proportion: the number of completed interviews divided by the number of attempted interviews (completed plus partial).

Response proportion: the number of completed interviews divided by the number of invitations sent.

Descriptive statistics will be generated for outcomes of both studies, including sample sizes, measures of central tendency, measures of variability, and 95% CI. Additionally, the LC PACS research objectives will be evaluated using a series of generalized linear models (such as GEE log-binomial regression, GEE Poisson regression). Propensity scoring will be used to reduce confounding between groups and will be calculated from demographic characteristics and other variables likely to predict being a cigarette user or an IQOS[®] user.

All estimates with sample sizes less than 50 or exhibiting a relative standard error greater than 30% will be noted for low statistical precision. Estimates with sample sizes less than 20 will be noted for sample size constraints but not reported.

Coding of open-ended data

This will be performed for survey questions where participants can provide other responses that vary from pre-listed answers. Verbatim responses that conform to pre-listed answers but were provided as “other” by respondents will be “upcoded” to reflect agreement with the expected response key. Responses that cannot be upcoded will be categorized by frequency. Responses exceeding the 2-5% threshold will be coded and reported, however, responses below this threshold will be reported as “other”.

Protection of Human Subjects

IRB approval

Both studies gather information on self-reported behavior and perceptions of participants. As neither study involves interventions or stimuli, we consider that the risks posed to participants are minimal. ALCS will obtain IRB approval or exemption in writing before the study is conducted.

Ethical conduct of studies

Study conduct and protocols adhere to guidelines consistent with the following: Belmont report, 21 CFR parts 50 and 56, Good Epidemiological Practice (GEP; IEA, 2007), Code of Standards and Ethics (CASRO, 2016) advocated by the Council of American Study Research Organization (CASRO), and the International Code on Market and Social Research (ESOMAR, 2016) originating from the International Chamber of Commerce/European Society for Opinion and Marketing Research (ESOMAR). Study personnel are qualified, trained, and experienced to always prioritize the health, safety, and well-being of participants. Resources will be made available to answer any participant questions or concerns via email and/or phone.

Informed consent procedures

All study participants must submit electronically signed informed consent statements (ICS). Informed consent is freely given and participation is voluntary.

Confidentiality

All data generated by the two studies will be treated as highly confidential by study staff. Stringent confidentiality measures remain applicable to all participant and study data, subject to the possibility

that rules governing study data access preclude guarantees of absolute confidentiality.

Study protocol compliance and amendments

The IQOS[®] CS PACS and IQOS[®] LC PACS will be conducted in compliance with study protocols. The contract research organization will notify ALCS of any deviations from study protocols within 48 hours and document the same in writing.

If amendments to the study protocols significantly alter the study design or increase the potential risks to participants, the ALCS investigator must revise the ICS, obtain IRB review and approval, and get the revised ICS signed by currently enrolled participants. In case of new enrollees, the revised ICS must be signed prior to study commencement.

Study records

All study data are captured and stored via a secure web-based data collection system and stored in a restricted-access secure database. All study records will be maintained by the contract research organization for at least four years after publication of the final study report or specified length of time designated by the sponsor.

Study reports

The contract research organization will provide enrollment reports, termination reports, completion reports, and withdrawal reports of study participants. Process functioning reports related to questions or concerns regarding survey instrument and administration will be provided to ALCS. The contract research organization will also furnish all interim and final study reports summarizing all study findings and analyzing the results at the designated completion of the studies.

Results

The first annual IQOS[®] CS PACS recruitment was fielded in limited IQOS[®] markets in the US for two months. Data analysis is complete for the first annual IQOS[®] CS PACS survey and the results are expected to be made public. The IQOS[®] LC PACS has not been administered yet. Continued study administration is dependent on distribution and availability of IQOS[®] in the marketplace.

Discussion

In a real-world setting, post-market studies provide evidence of the potential impact of an MRTP order on consumer perception, behavior, and health and enable FDA to review the accuracy of the determinations upon which the MRTP order was based. There exist a plethora of studies deemed “fit for purpose” from both academia and industry examining heated tobacco product (HTP) usage, risk profiles, acceptance, and perceptions in European markets [16][19][21][40][41]. To date, this is one of the first FDA reviewed and approved protocols for industry sponsored PMSS, to examine tobacco use patterns, perceptions, and behavior in IQOS[®] users drawn from US market segments. The cross-sectional IQOS[®] PMSS conducted in the US aims to assess tobacco use patterns in IQOS[®] users, risk perceptions of IQOS[®], and tobacco transition and cessation behaviors related to IQOS[®] over a four-year period. A longitudinal study of IQOS[®] users over time in comparison with cigarette users adds an additional dimension to study findings with its emphasis on transitions and health outcomes. This is one of the first US PMSS to assess cardiovascular and respiratory health outcomes related to tobacco use patterns.

Research on HTPs has shown substantial reductions in HPHC exposure compared to cigarette smoking [40][41][42][43]. A recent study following combustible cigarette users switching to HTP usage over a 12-month period noted significant declines in biomarkers of exposure along with reductions in biomarkers of potential harm relating to cardiovascular disease, suggestive of improved health outcomes over a prolonged period [43]. The findings underscore the potential public health benefits when individuals switch from cigarette smoking to IQOS[®]. The cross-sectional and longitudinal real-world data collected through the IQOS[®] CS and LC PACS will provide evidence of such benefit.

The questionnaires were comprehensively constructed from an array of nationally and internationally administered tobacco surveys permitting the capture of information related to a wide variety of tobacco products, including emerging tobacco products and tobacco use behaviors. The inclusion of health risks along with incorporation of cardiovascular and respiratory outcomes were intended to measure perception of risk of IQOS[®] products in comparison to traditional combustible tobacco products. These postmarket studies help parse user preferences, tobacco

use and transition/quitting patterns, and identify risk perceptions and beliefs regarding tobacco products and/or switching to heated tobacco products [19][21]. The survey design accommodated assessment of behaviors related to both initiation and transitions to provide useful insights into product acceptance, motivation to stop smoking, and impacts on public health outcomes.

The main strength of the PMSS is in its adherence to the key principles for an optimal survey instrument outlined by Cano et al. [44]. These features include: (i) the construction of a survey instrument based on literature review and prior national surveys of import, (ii) comparisons spanning a wide range of tobacco products, (iii) inclusion of different types of product users representing never-, current-, and former-users, (iv) the mining of health risk perceptions of individual and population health significance, (v) purposing of findings to clinical and population health investigations, and (vi) multiple modes of participant recruitment to minimize selection bias [44]. Multiple modes of recruitment such as mail and email were devised to limit the risks of sampling a non-representative population. Based on a rigorous analysis of dropout rates from prior studies [27][28][29][30][31][32][33][34][35][36][37][38], the sampling approach for the IQOS[®] LC PACS was precisely tailored to absorb the effects of survey attrition and still retain robust statistical power.

However, certain limitations constrain our study findings. Limited distribution and/or low consumer uptake can limit ability to generalize findings and/or achieve adequate sample sizes. Further, not all purchasers of IQOS[®] devices may be registered in the company database and there is a small risk of low sampling due to non-participation by registered users. Prior studies on HTP suggest that while exposure to HPHC may be definitively reduced when compared with cigarettes, there is a paucity of longitudinal studies defining the long-term health impacts [42][43]. Since the PMSS data rely largely on self-reported outcomes from participants, associated recall bias and/or selection bias may curtail interpretation and warrant caution with inferences. Participants' self-reported information will not be subject to bio-verification of nicotine status or abstinence. Currently there is little or no consensus on harmonized numerical thresholds for lifetime product usage for emerging novel tobacco segments. There are inherent limitations associated with co-opting the numerical thresholds designated for conventional cigarettes for novel tobacco products [45]. Lastly, some

findings may be limited by survey attrition or insufficient statistical power due to low enrollment.

In summary, post-market assessment of IQOS[®] provides detailed information on tobacco use behaviors, tobacco product transitions, product risk perceptions, and self-reported measures of health and disease-related outcomes that will satisfy regulatory requirements and also have the potential to inform the larger tobacco harm reduction debate. The IQOS[®] CS PACS and IQOS[®] LC PACS protocols have the review and approval of FDA and the methodology can be applied to future post-market surveillance of other modified risk tobacco products.

Author Contributions

Hui Cheng conceptualized and designed the cross-sectional study protocol. Andrea Vansickel and Brendan Noggle conceptualized and designed the longitudinal study protocol. Sucharitha Iyer drafted and edited the study manuscript. Hui Cheng, Brendan Noggle, Sucharitha Iyer, and Andrea Vansickel undertook critical technical review and revision of this article.

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Footnotes

¹ On July 27, 2020, FDA authorized the marketing of the IQOS[®] Tobacco Heating System[®] and Marlboro HeatSticks[®] with the following reduced exposure claim: “AVAILABLE EVIDENCE TO DATE: · The IQOS system heats tobacco but does not burn it. · This significantly reduces the production of harmful and potentially harmful chemicals. · Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.”

² Tobacco product categories under study include cigarettes, cigars (regular cigars, cigarillos, little filtered cigars), regular pipes, water pipes/hookahs, e-vapor products (e-cigarettes, e-hookah, e-cigars, e-pipes, mods, vapes, tanks, pods, cartridges), smokeless tobacco (chewing tobacco, “dip”/snuff, snus pouches),

oral tobacco-derived nicotine products (excluding medicinal nicotine replacement products), and IQOS[®]

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Declarations

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