Appendix C1:
IQOS® Cohort PACS Protocol

Please find on the following pages study protocol for IQOS® Longitudinal Cohort PACS.

IQOS® WITH MARLBORO HEATSTICKS® LONGITUDINAL COHORT

POSTMARKET ADULT CONSUMER STUDY (PACS)

"IQOS® Cohort PACS"

(b) (4)

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PROTOCOL VERSION HISTORY

Version	Version Date	Modification(s)	Reason(s) for Modification(s)
V1.0	8/6/2020	(b) (4)	
V2.0	11/4/2020		In its October 5th letter, FDA determined that these changes are necessary to monitor participants' understanding of the risks of using IQOS at baseline and over time
			To better understand the role menthol plays in behaviors
			Reduce respondent burden
			To provide a granular view of smokers' intention to stop smoking.
			Understand role of menthol HeatSticks in increasing IQOS adoption and complete switching in menthol cigarette smokers
			To understand if cessation therapies are being used alongside tobacco products including IQOS and to assess the overall history of cessation treatment use among IQOS users

		(b) (4)	To account for additional analyses of regular and menthol HeatStick flavors
			To better interpret the public health implications
			To ensure study validity
			To enable the agency to understand whether excluding potentially invalid data and imputing missing data influenced results substantively

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DEFINITIONS OF TERMS

Terms are arranged in alphabetic order. Italicized parts of definitions have their own definition in this section. Users are defined by use behaviors; for example, a current established user is someone who reports current tobacco product use and established use of a tobacco product. Unless otherwise specified, IQOS® refers to IQOS® Tobacco Heating System and Marlboro HeatSticks® in this document.

Cigarette Smoker Group (also referred to as the Reference Group)

The Cigarette Smoker Group, or Reference Group, are adults who report at recruitment (Survey 1 (Time 0)): (1) never using IQOS®, (2) having smoked at least 100 cigarettes in their lifetime, (3) now smoke "every day" or "some days", and (4) having smoked cigarettes in the past 30 days (irrespective of use of any other tobacco product).

Complete Switching

Complete switching generally refers to the event of completely transitioning from *established use* of one tobacco product to now not using that product and *current established use* of another tobacco product. Outcomes related to complete switching in this study include:

- Established smokers who, at a future survey, report current established IQOS® use and no smoking
- Established IQOS® users who, at a future survey, report current established smoking and no IQOS® use

Consistent Basis

Consistent basis refers to "using the product routinely or with some type of regularity. Examples might include using the product every day, a few times every week, only on the weekend."

Current Tobacco Product Use

Current tobacco product use refers to using a given tobacco product "every day" or "some days" now, irrespective of whether or not the lifetime established use criterion was met.

Established Tobacco Product Use

Established tobacco product use refers to having met or exceeded the *lifetime established use criterion* for a given tobacco product.

Ever Tobacco Product Use

Ever use refers to having used a given tobacco product in a person's lifetime, irrespective of whether or not the lifetime established use criterion was met.

Former Tobacco Product Use

Former tobacco product use refers to having *ever used* a given tobacco product and now "not at all" using the product, irrespective of whether or not the lifetime established use criterion was met.

Initiation

Initiation generally refers to the first use of a given tobacco product. Outcomes related to initiation in this study include:

- Ever use (even one time) of a product never used at recruitment
- Ever established use of a product never used at recruitment

IQOS® Consumer Database

The IQOS® Consumer Database is a database of registered IQOS® consumers in the U.S. These consumers may be existing members of ALCS' Adult Tobacco Consumer Database (ATCD) and flagged as an IQOS® consumer as a result of their registration of their IQOS® device or newly entered into the ATCD by virtue of their purchase and registration of their IQOS® device. Thus, collectively, ALCS will develop a database of IQOS® consumers.

IQOS® User Group (also referred to as the Test Group)

The IQOS® user group, or Test Group, are adults who report at recruitment (Survey 1 (Time 0)): (1) now using IQOS® "every day" or "some days", (2) having used IQOS® during the past 30 days, (3) having used IQOS® for a period of 6 months or less (irrespective of use of any other tobacco product), and (4) having used at least 100 Marlboro HeatSticks® in their lifetime.

Lifetime Established Use Criterion

For purposes of this research, the lifetime established use criterion is defined for:

1) cigarettes as ever use of 100 or more cigarettes,
2) IQOS® as ever use of 100 or more Marlboro HeatSticks®,
3) cigars as ever use of 50 or more cigars,
4) dip/snuff, chewing tobacco, and snus as ever use of 20 or more times per product,
5) regular pipe as ever use of 50 bowls or more,

6) all other tobacco products, including e-cigarettes and other e-vapor products, hookah and oral tobacco-derived nicotine products, as ever used on a "*consistent basis*."

Long-Term Former Tobacco Product Use

Long-term former tobacco product use refers to having *ever used* a given tobacco product, now "not at all" using the product, and having not used the product for 12 months or longer.

Quitting a Tobacco Product

Quitting a tobacco product refers to having used a given tobacco product to the *lifetime established use criterion*, now "not at all" using the product, and having "completely stopped/quit" using the product.

Quitting All Tobacco Products

Quitting all tobacco products refers to having used any tobacco product to the *lifetime established use criterion*, now "not at all" using any tobacco product, having "completely stopped/quit" using all tobacco products ever used.

Re-initiation of Cigarette Smoking

Re-initiation of cigarette smoking refers to *current use* of cigarettes and having had smoked at least 100 cigarettes and having not smoked cigarettes for 12 months or longer.

Relapse to Cigarette Smoking

Relapse to cigarette smoking refers to *current use* of cigarettes and having had smoked at least 100 cigarettes and having not smoked cigarettes for less than 12 months.

Tobacco Products

In this study, tobacco products include cigarettes, cigars (regular cigars, cigarillos, little filtered cigars), regular pipes, water pipes/hookahs, e-vapor products (e-cigarettes, e-hookahs, 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®.

SYNOPSIS

Protocol Number: (b) (4)
Abbreviated Protocol Title: IQOS® Cohort PACS
Long Protocol Title: IQOS® with Marlboro HeatSticks® Longitudinal Cohort Postmarket Adult Consumer Study
Study Purpose: The purpose of the IQOS® with Marlboro HeatSticks® (hereinafter IQOS®) Longitudinal Cohort Postmarket Adult Consumer Study (IQOS® Cohort PACS) is to assess tobacco use behaviors and transitions as well as health status and perceptions of adult[1] current established consumers of IQOS® relative to adult established cigarette smokers over time.
Study Objectives: 1. To characterize tobacco product use behaviors (e.g., current use, dual use, number of days and amount used) among adult established IQOS® users and cigarette smokers over time. 2. To characterize transitions (initiation, switching from tobacco/cigarettes to IQOS®, transitioning to/back to cigarettes and quitting) among adult established IQOS® users and cigarette smokers over time. 3. To assess self-reported health-related quality of life, signs and symptoms by product use among adult established IQOS® users and cigarette smokers over time. 4. To assess risk perceptions of IQOS® and cigarettes among adult established IQOS® users and cigarette smokers over time.
Study Design: This prospective, longitudinal cohort study will provide information regarding IQOS® with Marlboro HeatSticks® and other tobacco use behaviors and transitions as well as self-reported health status and perceptions of adult established IQOS® users and cigarette smokers who have never tried IQOS® over a closed 24-month observation period. Potential adult IQOS® user participants will be identified and invited to participate in this IQOS® Cohort PACS during the IQOS® Cross-sectional Postmarket Adult Consumer Study (IQOS® Cross-sectional PACS). The survey data collected during the IQOS® Cross-sectional PACS will transfer to the IQOS® Cohort PACS for those participants who also qualify for and agree to participate in the Cohort Study and will serve as baseline data for those IQOS® users that continue participation. Those who are eligible for the Cohort and agree to participate will be required to complete specific relevant IQOS® Cohort PACS Survey 1 (Time 0) modules[2]

[1] Individuals who meet the study inclusion criteria (Section 4.3) and none of the exclusion criteria (Section 4.4) will qualify for the study.

[2] After completion of the Cross-sectional survey, all eligible Cohort participants will be asked to complete the following survey modules: Quality of Life, Signs and Symptoms, and Diagnoses. See Section 3 for additional details.

after completing the cross-sectional study survey.[3] IQOS® Cohort PACS Survey 2 (Time 3 months), Survey 3 (Time 6 months), Survey 4 (Time 12 months), Survey 5 (Time 18 months), and Survey 6 (Time 24 months) will be administered every 3 months for the first 6 months then every 6 months for the remainder of the study. The study will have a 2-year maximum follow-up period. The study length was selected to enable the ability to detect changes in behaviors and health over time. A 3 and 6-month interval is a sufficient timeframe for measuring changes in tobacco use behaviors (O'Connor et al., 2005; O'Connor et al., 2011; Pulvers et al., 2016; Pulvers et al., 2015; Halpern et al., 2018; Mantey et al., 2017; McKeganey et al., 2018). The initial 3 month follow-up and subsequent 3 month follow-up (6 months post baseline) will provide more opportunity to detect changes in early tobacco use behavior for new IQOS® users. Ability to detect changes in some clinical and self-reported health status was seen in studies with a harm reduction focus within 6 months in one study (Campagna et al., 2016) and within a year or less in other studies (Cibella et al., 2016; Farsalinos et al., 2014; Polosa et al., 2014; Polosa et al., 2016). Thus, we selected a 24-month study period with follow-up at 3 months for the first 6 months then every 6 months thereafter.

The survey will take a modular approach to minimize survey length and time to complete. For example, diagnoses will be asked yearly. The cross-sectional/baseline survey and five cohort follow-up surveys will include measures grouped in the following modules:

- Demographics
- Tobacco Use Behaviors
- Tobacco Dependence
- Quitting Behaviors
- Risk Perceptions
- Perception and Understanding of IQOS® and Exposure Reduction
- Quality of Life, Signs, Symptoms, and Diagnoses

Modules are being administered at particular points in time to meet study objectives. Specifically, tobacco use behaviors, tobacco dependence, quality of life, signs and symptoms, quitting behaviors, and perception and understanding of IQOS® and exposure reduction will be asked at every survey. Risk perceptions and diagnoses will be asked yearly.

Study Groups: Study groups will consist of two groups of qualified adults 21 years of age and older:

- IQOS® Users (Test Group): The IQOS® user group will be comprised 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 6 months or less (irrespective of use of any other tobacco product), and (4) having used at least 100 Marlboro HeatSticks® in their lifetime

[3] Participants will be invited to complete the required modules as mentioned above immediately following completion of the cross-sectional survey. Participants who choose not to complete immediately after may re-enter the survey and complete it within 7 days of completing the cross-sectional survey.

- Cigarette Smokers (Reference Group): The reference group will be comprised of adults who report: (1) never trying IQOS® at time of recruitment, (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)

Sample Recruitment

Recruitment will occur in the United States when the estimated number of established IQOS® users is sufficient to support the study. The sampling approach uses a sampling method that utilizes a mix of recruiting modes: (1) a database of IQOS® users and (2) commercial, online panels for cigarette users from geographies where IQOS® is sold. ALCS, working on behalf of Philip Morris USA, will utilize a database of registered IQOS® consumers in the U.S. These consumers may be existing members of ALCS' Adult Tobacco Consumer Database (ATCD) and flagged as an IQOS® consumer as a result of their registration of their IQOS® device or newly entered into the ATCD by virtue of their purchase and registration of their IQOS® device. Invitations to participate in the IQOS® Cohort PACS will be sent to participants of the annual IQOS® Cross-sectional PACS who meet the criteria for the IQOS® Cohort study groups. The cigarette smoker reference groups will be recruited through commercial, online panels, run by a third party. The third party will administer the survey to individuals who meet recruitment criteria. Participants will be recruited using a non-probability method on a schedule that matches the IQOS® Cross-sectional PACS during the single time that the IQOS® Cohort PACS will recruit participants until sample size requirements are met. Once a potential participant expresses interest in participating in the study and meets initial qualifying criteria, he/she will be provided the Informed Consent Statement, which will include, among other things, a summary of the study, including the study objectives, the voluntary nature of his/her participation, and data privacy/confidentiality guidelines and cash or cash equivalent incentives.

After agreeing to participate in the study, a potential participant will complete the Participant Screener Survey to determine his/her eligibility for the study. As part of the process of determining eligibility, the potential participant's age will be verified to ensure that he/she meets the inclusion criterion of being 21 or older. Those eligible will then be presented with the remaining survey modules, which will collect the detailed study information to meet the study objectives.

Sample Size and Power Considerations

A sample size of (b) (4) participants will be recruited for the IQOS® user group and (b) (4) for the cigarette smoker group. If sample size requirements for the IOQS user group are not met through IQOS® Cross-sectional PACS recruitment, then additional participants will be recruited though an internal database of IQOS® users. The sample size and the study duration were designed to be sufficient to detect differences in quitting cigarette smoking between the IQOS® user and cigarette smoker groups with over 90% power over the 24-month study period and differences in quitting cigarette smoking between IQOS® menthol or regular HeatSticks® varieties compared to the cigarette smoker group with 80% power. Prior relevant longitudinal studies have experienced dropout rates ranging from 12% to 66% (Pacifici et al., 2015; Norton et al., 2014; Dobbie et al., 2015; Choi et al., 2014;

Berg et al., 2014; Caponnetto et al., 2013; Grana et al, 2014; McRobbie et al., 2015; Nides et al., 2014; Polosa et al., 2014). This study's sample size for both groups accounts for a 65% dropout rate and is informed by prior IQOS® cohort studies in other countries.

Outcome Measures:

The outcomes relate to the study objectives and will describe:

1. Tobacco use behavior
   a. Current use
   b. Dual use
   c. Number and amount of IQOS® use and smoking
2. Product use transitions
   a. Switching
   b. Initiation
   c. Relapse and Re-initiation
   d. Quitting
3. Health-related quality of life, signs and symptoms
4. Risk Perception
   a. Risk perceptions of IQOS® and cigarettes
   b. Perception and Understanding of IQOS® and Exposure Reduction

Data Analysis:

The IQOS® Cohort PACS is observational, from which comparisons will be made within and between the IQOS® user and cigarette smoker groups across time. Descriptive analyses will include an assessment of participant demographic characteristics and outcome measures.

Participation proportions including contact proportion, response proportion, eligibility proportion, and completion proportion will be summarized. Descriptive statistics will be reported for all study groups, including summaries of sample sizes, central tendency measures (e.g., means, median), and variability measures (e.g., standard deviation, range). Additionally, 95% confidence intervals will be reported. A series of generalized linear models (e.g., Generalized estimating equations (GEE) log-binomial regression, GEE Poisson regression) will be employed to address research objectives. Estimates with denominator sample sizes less than (b) or having a relative standard error greater than 30% will be reported with a note of low statistical precision. Estimates with denominator sample sizes less than (b) will not be reported with a note of small sample size.

1 INTRODUCTION

1.1 Background

Philip Morris Products S.A. (PMP S.A.) developed the IQOS® Tobacco Heating System and Marlboro HeatSticks® (hereinafter referred to as IQOS®) as novel tobacco and nicotine-containing products with the potential to reduce harm or the risk of tobacco-related disease associated with smoking cigarettes. PMP S.A. submitted Modified Risk Tobacco Product Applications for IQOS® to the U.S. Food and Drug Administration (FDA) seeking authorization to market the products as modified risk tobacco products. On July 7, 2020, FDA issued "Modified Risk Granted Orders – Exposure Modification" authorizing IQOS® to be marketed with a reduced exposure claim. The Orders are conditioned upon agreement to conduct postmarket surveillance and studies (PMSS) in accordance with protocols approved by FDA. This document is prepared as part of the PMSS program for IQOS® pursuant to the Orders.

1.2 Rationale

The Federal Food, Drug and Cosmetic Act (FDCA) directs the FDA to condition an exposure modification order received under FDCA § 911(g)(2) on the MRTP applicants' agreement to conduct PMSS (FDCA §§ 911(g)(2)(C)(ii)). "The outcomes evaluated in postmarket surveillance and studies should focus on the effect of the MRTP on consumer perception, behavior and health under real world conditions of use" (Food and Drug Administration, 2012). For this reason, ALCS[4] on behalf of the applicant, PMP S.A., plans to conduct certain components of PMSS to assess the effect of the MRTP among U.S. consumers. The program will consist of a collection of data over time that supports an assessment of IQOS® in the postmarket setting. The current study, IQOS® with Marlboro HeatSticks® Longitudinal Cohort Postmarket Adult Consumer Study (IQOS® Cohort PACS), is one such study.

2 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of the IQOS® Cohort PACS is to assess tobacco use behaviors and transitions as well as the health status and perceptions of adult established consumers of IQOS® relative to adult established cigarette smokers over time.

[4] Altria Client Services (ALCS) and the parent of PMP S.A., Philip Morris International Management S.A., have entered into a distribution agreement by which ALCS and its affiliates have exclusive rights to distribute and sell IQOS® in the U.S. after FDA authorization. ALCS affiliate PM USA markets IQOS® in the U.S. Therefore, PMSS that involves the study of consumers and consumption in the U.S. will be conducted by ALCS to be submitted as part of PMSS reporting by PMP S.A.

2.2 Objectives

1. To characterize tobacco product use behaviors (e.g., current use, dual use, number of days and amount used) among adult established IQOS® users and cigarette smokers over time.
2. To characterize transitions (initiation, switching from tobacco/cigarettes to IQOS, transitioning to/back to cigarettes and quitting) among adult established IQOS® users and cigarettes smokers over time.
3. To assess self-reported health-related quality of life, signs and symptoms by product use among adult established IQOS® users and cigarette smokers over time.
4. To assess risk perceptions of IQOS® and cigarettes among adult established IQOS users and cigarette smokers over time.

3 STUDY DESIGN

3.1 Overview

This prospective longitudinal cohort study will provide information regarding tobacco use behavior (e.g., current use, dual use, number of days and amount used) and transitions (e.g., complete switching, initiation and quitting), self-reported health status and quality of life and perceptions among adult established users of IQOS® with Marlboro HeatSticks® and a reference group of adult established cigarette smokers over a closed 24-month observation period. Additional measures (e.g., tobacco dependence, health diagnoses) will be collected and may be used to describe participants and be treated as confounding or interacting variables when appropriate.

The IQOS® Cohort PACS will recruit qualified adults from an annual IQOS® Cross-sectional Postmarket Adult Consumer Study (IQOS® Cross-sectional PACS). We intend to conduct the IQOS® Cohort PACS in geographies in concert with the second annual IQOS® Cross-sectional PACS, which we anticipate to be approximately two years after IQOS® is launched into the U.S. marketplace. By this time, we assume IQOS® to be in distribution in diverse geographies and used among a consumer base large enough to facilitate recruitment of participants that meet the study inclusion criteria. Participants in the IQOS® Cross-sectional PACS will be invited to participate in the IQOS® Cohort PACS if they meet criteria for the IQOS® user group. The IQOS® user group will consist of adult established, current, past 30-day users of IQOS®.

After agreeing to participate in the study, the potential participant will complete the Participant Screener Survey to determine his/her eligibility for the study. As part of the process of determining eligibility, the potential participant's age will be verified to ensure that he/she meets the inclusion criteria. Eligible participants will then be presented with the remaining survey modules which will collect the detailed study information to assess the study objectives.

Eligible participants who agree to participate will be asked to complete specific relevant IQOS® Cohort PACS Survey 1 (Time 0) modules[5] after completing the Cross-sectional survey.[6] IQOS® Cohort PACS Survey 2 (Time 3 months), Survey 3 (Time 6 months), Survey 4 (Time 12 months), Survey 5 (Time 18 months), and Survey 6 (Time 24 months) will be administered every 3 months for the first 6 months then every 6 months for the remainder of the study (Figure 1). The study length was selected to enable the ability to detect changes in behaviors and health over time. A 3 and 6-month interval is a sufficient timeframe for measuring changes in tobacco use behaviors (O'Connor et al., 2005; O'Connor et al., 2011; Pulvers et al., 2016; Pulvers et al., 2015; Halpern et al., 2018; Mantey et al., 2017; McKeganey et al., 2018). The initial 3 month follow-up and subsequent 3 month follow-up (6 months post baseline) will provide more opportunity to detect changes in early tobacco use behavior for new IQOS® users. Detecting changes in some clinical and self-reported health status was seen in studies with a harm reduction focus within 6 months in one study (Campagna et al., 2016) and within a year or less in other studies (Cibella et al., 2016; Farsalinos et al., 2014; Polosa, et al., 2014; Polosa et al., 2016). Thus, we selected a 24 month study period with follow-up at 3 months for the first 6 months then every 6 months thereafter.

The survey will take a modular approach to minimize survey length and time to complete. For example, diagnoses will be asked yearly. Checklist items will be randomized. Skip logic will be incorporated into surveys to reduce participant burden. The cross-sectional and five cohort surveys will include measures grouped in the following modules:

- Demographics
- Tobacco Use Behaviors
- Tobacco Dependence
- Quitting Behaviors
- Risk Perceptions
- Perception and Understanding of IQOS® and Exposure Reduction
- Quality of Life, Signs, Symptoms, and Diagnoses

Participants will complete all surveys online and will receive e-mail invitations and reminders to complete each survey. Participants will have a 30-day window in which to complete each follow-up survey and will receive reminders to do so up to/until they complete the survey. Participants will receive compensation for each survey that they complete. If a participant misses a survey, he/she will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule.

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[5] After completion of the Cross-sectional survey, all eligible Cohort participants will be asked to complete the following survey modules: Quality of Life, Signs and Symptoms, and Diagnoses. See Section 3 for additional details.

[6] Participants will be invited to complete the required modules as mentioned above immediately following completion of the cross-sectional survey. Participants who choose not to complete immediately after may re-enter the survey and complete it within 7 days of completing the cross-sectional survey.

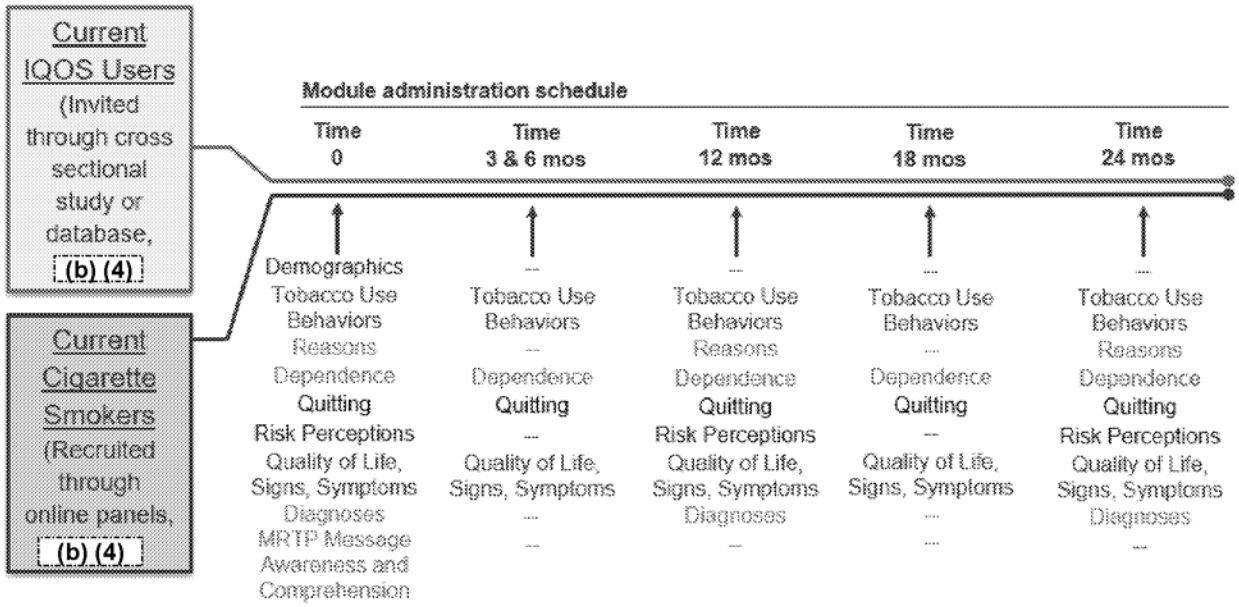

Figure 1: IQOS® Cohort Study Design

3.2 Study Stimuli

There will be no study stimuli other than the survey questions. The survey instruments will include written descriptions of tobacco products, as well as tobacco product images and images of IQOS®, and IQOS® product packaging to facilitate clarity and understanding.

3.3 Study Surveys

The IQOS® Cohort PACS survey items were designed to address the objectives of this study. Wherever feasible, survey items were sourced from national surveys and items used in previous studies (Hyland et al., 2017; Substance Abuse and Mental Health Services Administration, 2017; Parsons et al., 2014). Furthermore, ALCS commissioned cognitive testing of the study instrument in early 2020 and updated survey items based on the findings.

Below, we outline the modules that each survey will capture:

Demographics and Population Characteristics Module

Demographic and population characteristic module items will include:

- Sex
- Age
- Race
- Ethnicity

- Education level
- Income
- Marital Status
- Pre-existing medical conditions or co-morbidities
    - Cardiovascular disease
    - Respiratory disease
    - Cancer
    - Diabetes
- Mental illness
- Pregnancy status (among women 21 to 49 years of age)
- Military or Veteran Status
- Sexual Identity

Tobacco Use Behaviors Module

Tobacco use behaviors will be collected through items used in previous studies. These items were originally sourced through national surveys such as the 2016 National Survey on Drug Use and Health (NSDUH), 2016 National Health Interview Survey (NHIS), and the 2014-2016 Population Assessment of Tobacco and Health (PATH). In this study, the phrase "use IQOS" replaces "smoke a cigarette" in the original items. The tobacco use behaviors module will collect information regarding:

- Types of tobacco ever used (even one time) and currently using
- Current tobacco use status ("every day", "some days", or 'not at all")
- Amount of tobacco used in lifetime by type
- Types of tobacco completely quit
- Number of days of tobacco use in the past 30 days (IQOS®, cigarettes, and e-vapor)
- 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®)
- Type of cigarettes smoked most often among current and former smokers (menthol or non-menthol)

Tobacco Dependence Module

The Heaviness of Smoking Index (HSI, Heatherton, 1989) will be used to measure smoking and IQOS® dependence, respectively, through the use of two tobacco use items: uses per day and time to first use. Cigarette and IQOS® uses per day will be measured as described in the tobacco use module. The time to first use question for smoking will be sourced from the PhenX smoking dependence protocol (Swan et al., 2020). For IQOS®, the phrase "use your first IQOS" replaces "smoke your first cigarette" in the IQOS® time to first use question.

Quitting Behaviors Module

Quitting behaviors will be collected through items used in previous studies. These items were originally sourced from the literature and national surveys. Motivation to stop smoking will be assessed through the Motivation to Stop Scale (Kotz et al., 2013). The quitting behaviors module will capture information regarding:

- Attempts to quit smoking cigarettes
- Motivation to stop smoking cigarettes
- Use of a tobacco cessation treatment[7]

Risk Perceptions Module

Risk perceptions will be collected through the Perceived Risk Instrument for general risk assessment (PRI-G; Cano et al., 2018). The risk perceptions module will include items related to general risks to health. The PRI-G will be used (instead of PRI for personal risk assessment (PRI-P)) in order to be able to measure risk perceptions of cigarette smoking and IQOS use among all participants irrespective of respondent's current use status.

Perception and Understanding of IQOS® and Exposure Reduction

The perception and understanding of IQOS® and exposure reduction module will include:

- Perception of harmful or potentially harmful chemical exposure when switching from cigarettes to IQOS®
- Understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure

Quality of Life, Signs and Symptoms Module

Health-Related Quality of Life (HRQOL) is a multidimensional concept that includes positive and negative aspects of life as well as physical health, and measures of physical, social and

[7] Use of a cessation treatment will be captured as: Never, Past 30 Days, >30 Days -12 Months, >12 Months at baseline and past 30 day and > past 30 day to last assessment at each follow-up survey.

psychological functioning that directly relate to health (World Health Organization, 1998). HRQOL has been shown in literature to be correlated with health outcomes including cardiovascular and respiratory diseases. HRQOL will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS©) Global Health short form. The PROMIS© Global Health was designed to measure patient-reported outcomes related to physical, mental, and overall health using a 10-item bank. The quality of life, signs and symptoms module will include:

- Health-Related Quality of Life
  - Physical health
  - Mental health
- Signs and symptoms
  - Cardiovascular
  - Respiratory

Diagnoses Module

A set of diagnoses were selected that relate to tobacco use and could impact health and tobacco use behaviors (U.S. Department of Health and Human Services, 2014). Survey items were sourced from national surveys (e.g., Behavioral Risk Factor Surveillance System [BRFSS], NHIS, NSDUH). The diagnoses module will include:

- Cardiovascular disease diagnoses
  - Myocardial infarction
  - Stroke
  - Angina
  - Coronary heart disease
  - Congestive heart failure
  - Hyperlipidemia
  - Hypertension
  - Other cardiovascular diseases
- Diabetes diagnosis
- Respiratory disease diagnoses
  - Chronic obstructive pulmonary disorder (COPD)
  - Asthma
  - Chronic bronchitis
  - Emphysema
  - Apnea

  - Other respiratory diseases
- Malignancy diagnoses
- Mental illness
  - Diagnoses
  - Taking medicine or receiving treatment

The longitudinal cohort study will take place over a total duration of two years with six surveys administered every 3 months for the first 6 months then every 6 months for the remainder of the study. The study modules at each study phase, as shown in Figure 1, are as follows:

Survey 1 (Time 0)

- Demographics module
- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Risk perceptions module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module
- Diagnoses module

Survey 2 (Time 3 months)

- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module

Survey 3 (Time 6 months)

- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module

Survey 4 (Time 12 months)

- Tobacco use behaviors module

- Tobacco dependence module
- Quitting behaviors module
- Risk perceptions module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module
- Diagnoses module

Survey 5 (Time 18 months)

- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module

Survey 6 (Time 24 months)

- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Risk perceptions module
- Perception and understanding of IQOS® and exposure reduction module
- Quality of life, signs, and symptoms module
- Diagnoses module

3.4 Study Duration

The IQOS® Cohort PACS will take approximately 27 months to complete (from first participant in, to last participant out). Initial enrollment will occur within a 12-week period and the study will follow the cohort over 24 months.

3.5 Length of Participation

Participants in the IQOS® Cohort PACS will respond to surveys for a 24-month period. Each survey will take approximately 15 – 25 minutes to complete. Completion times will vary depending on tobacco product use, health conditions reported, and number of modules within the survey. Participants that report trying multiple tobacco products, use IQOS®, or have more health conditions are expected to require more time, on average. IQOS® user group participants are expected to require more time than cigarette smoker group participants, on average, because they will be asked additional questions pertaining to Marlboro HeatSticks® varieties.

4 STUDY POPULATION

4.1 Study Groups

Study groups will consist of current established IQOS® users and cigarette smokers. Participants of the IQOS® Cross-sectional PACS will be invited to the IQOS® Cohort PACS if they meet criteria for the IQOS® user group and will consist of qualified adults 21 years of age and older. The cigarette smoker group will be recruited from commercial, online panels and will consist of qualified adults 21 years of age and older. At the time of recruitment, the groups will be defined as:

- IQOS® Users (Test Group): The IQOS® user group will be comprised 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 6 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 be comprised 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)

Participants will be added on a schedule that matches the IQOS® Cross-sectional PACS during the single time that the IQOS® Cohort PACS will recruit participants.

4.2 Sample Size and Power Considerations

A power analysis was conducted to determine the necessary ending sample size. We selected one of the primary outcomes, quitting cigarette smoking that has been well established at the population level in the literature. Specifically, previous research has shown that cigarette smokers quit smoking at a rate of 4.8% while e-vapor users quit smoking at a rate of 8.2% per year (Zhu et al., 2017). Extending these findings to the IQOS® and cigarette study groups with separate analyses of Menthol and Regular HeatStick preference and study time (two years), results from the power analysis on detecting a difference between quit rates (9.6% versus 16.4%) revealed that an ending sample size of (b) (4) per IQOS® HeatStick preference (b) (4) total for the IQOS® group) would be required to detect a difference at a statistical power of 80% and Type I Error of (b) (4) The sample size and the study duration were designed to be sufficient to detect differences in quitting cigarette smoking between the IQOS® user (b) (4)) and cigarette smoker group ((b) (4)) with over 90% power over the 24-month study period. It is assumed that statistical power will be higher for regression models, quit rates are the same over the two years, and that IQOS® use will be related to quitting in the same manner as e-vapor use was in Zhu's study. Prior relevant longitudinal studies have experienced dropout rates ranging from 12% to 66% (Pacifici et al., 2015; Norton et al., 2014; Dobbie et al., 2015; Choi et al., 2014; Berg et al., 2014; Caponnetto et al., 2013; Grana et al., 2014; McRobbie et al., 2015; Nides et al., 2014; Polosa et al., 2014). These studies as well as IQOS® cohort studies in other countries supported the present study's sample size requirement. Sample sizes for both groups were increased by 65% and and rounded to account for attrition over the 24-month study period. The power analysis was conducted for a two-sided Pearson Chi-square Test for Proportion Difference (SAS Institute Inc.). If sample size requirements for the IOQS®

user group are not met through IQOS® Cross-sectional PACS recruitment, then additional participants will be recruited though an internal database of IQOS® users.

4.3 Inclusion Criteria

Participants must satisfy the following criteria at the time of screening to be enrolled into the study:

(b) (4)

4.4 Exclusion Criteria

A participant who meets any of the following exclusion criteria will be disqualified from the study:

(b) (4)

5 STUDY PROCEDURES

5.1 Recruitment

Recruitment will occur in the United States when the estimated number of established IQOS® users is sufficient to support the study. The sampling approach uses a sampling method that utilizes a mix of recruiting modes: (1) a database of IQOS® users and (2) commercial, online panels for cigarette users from geographies where IQOS® is sold.

ALCS, working on behalf of Philip Morris USA, will utilize a database of registered IQOS® consumers in the U.S. for recruitment into this study. These consumers may be existing members of ALCS' Adult Tobacco Consumer Database (ATCD) and flagged as an IQOS® consumer as a result of their registration of their IQOS® device or newly entered into the ATCD by virtue of their purchase and registration of their IQOS® device. The database includes the age and inferred sex of consumers and will indicate whether a consumer has purchased more than one IQOS® device. Based on experience from other countries with similar IQOS® consumer databases, it is assumed that IQOS® consumers listed in the IQOS® database will comprise **(b) (4)**

Commercial online panels, run by a third party, will be used as a recruitment source for cigarette users. The third party will administer the survey to individuals who meet recruitment criteria. Compared to the IQOS® Consumer Database, the online panels can provide a broad sample because of the breadth of consumers included in the panels.

Invitations to participate in the IQOS® Cohort PACS will be administered at the end of the annual IQOS® Cross-sectional PACS to participants who meet criteria for the IQOS® cohort study groups. Participants will be recruited using a non-probability method on a schedule that matches the IQOS® Cross-sectional PACS during the single time that the IQOS® Cohort PACS will recruit participants. If IQOS® Cohort PACS IQOS® user group sample targets cannot be met through the IQOS® Cross-sectional PACS, additional participants will be recruited from the IQOS® Consumer Database. Consumers may be invited through e-mail and direct mail communications. In order to better maximize participation, potential participants may be contacted multiple times via multiple channels when possible (e.g., emails, text messages, and mailings).

Participants for IQOS® user and cigarette smoker groups must have completed an Informed Consent Statement. All qualified participants who complete the survey will receive cash or cash equivalent incentives that will be documented in the Informed Consent Statement at an amount that is commensurate with the length and complexity of the study to promote retention throughout the two-year study period.

Recruiting potential cigarette user participants from multiple online consumer panel companies increases the likelihood of achieving a more diverse sample and completing screening requirements in a timely manner. For these and other reasons, the main contract research organization (CRO) evaluates and selects the online consumer panel companies based on several quality criteria. Those criteria include having established a history of compliance within industry codes and standards and processes for registering panelists (double opt-in), validating member information (via external databases), periodic updating of panel member information, appropriate sample deployment (e.g., randomization, batching), and identifying straight-liners, speeders and other fraudulent data (e.g., bot traffic).

Online survey panel companies use a variety of methods to recruit members to minimize the inherent bias that could result from using one or a few recruiting sources. These methods can include face-to-face, telephone, online, social media, classified newspaper advertisements, and referral programs. Those who agree to join the panel are periodically sent e-mail invitations to complete surveys. Panelists may or may not decide to opt in to a survey. They also may discontinue participation at any point, for any reason.

5.2 Study Implementation and Timeline

An external market research firm will coordinate recruitment of the study sample, ensure correct survey programming and accuracy and integrity of data collection. The vendor will serve as the CRO. In addition, the CRO will be responsible for re-contacting participants at each study time point. The CRO will make every effort to ensure participant protocol compliance and participant retention by providing compensation in a timely manner, contacting participants in a timely and efficient manner to meet data collection timelines, and ensuring survey program performance and accessibility at each study time point.

Estimated Study Timeline

The timing of execution of the cohort study depends on the distribution and consumer uptake of IQOS® in the marketplace. Currently, IQOS® is in very limited distribution in the United States. IQOS® was first launched into a single market, Atlanta, GA, in September 2019; a second market, Richmond, VA, in November 2019; and a third market, Charlotte, NC, in July 2020. Future expansion is planned to occur, but the pace and breadth of expansion may depend on learning achieved from the early market launches.

To plan timing of the cohort study initiation, we focused on the recruiting that will be needed to achieve the minimal sample size (**(b) (4)**) for the IQOS® user group. Assuming a response rate of 5%, we will need to reach about 42,000 consumers with contactable information from our database to yield a final sample of **(b) (4)**

As described in this protocol, five follow-up surveys will be administered (3, 6, 12, 18 and 24 months) and the entire study will take a maximum of approximately 27 months to complete (from first participant in, to last participant out). Initial enrollment will occur within a 12-week period with follow-up surveys over the next 24 months. Participants will have a 30-day window in which to complete each follow-up survey.

Thus, we base our estimated timelines with the assumption that 42,000 contactable IQOS® consumers will be available in the IQOS® Consumer Database. We assume that IQOS® will need to be in multiple marketplaces and/or in regional distribution in order to build the database to a level that will support the current study. The timeline below presumes that the number of consumers in the database will be sufficient to recruit the final number of participants for this study.

Table 1: Estimated Timeline for IQOS® Cohort Study Implementation

Milestone	Date
Initiation of baseline data collection (survey invitations sent)	September 1, 2022
Completion of baseline data collection (survey closes)	December 1, 2022
Initiation of 3-month follow-up data collection	December 1, 2022
Completion of 3-month follow-up data collection	January 1, 2023
Initiation of 6-month follow-up data collection	March 1, 2023
Completion of 6-month follow-up data collection	April 1, 2023
Initiation of 12-month follow-up data collection	September 1, 2023
Completion of 12-month follow-up data collection	October 1, 2023
Completion of 12-month interim report	January 1, 2024
Initiation of 18-month follow-up data collection	March 1, 2024
Completion of 18-month follow-up data collection	April 1, 2024
Initiation of 24-month follow-up data collection	September 1, 2024
Completion of 24-month follow-up data collection	October 1, 2024
Completion of analyses	January 1, 2025
Completion of final report	April 1, 2025

With these estimates, we seek to balance the desire for timely information with the uncertainties of IQOS® presence in the marketplace upon which achieving sufficient sample sizes relies. Should the timing of this study be accelerated or delayed, we will notify FDA in accordance with the market order.

5.3 Adverse Experiences

As this study is observational and conducted on a consumer population using marketed products, it will be conducted in compliance with Good Epidemiological Practice (GEP). Adverse experience reporting will follow ALCS' established consumer research procedure for spontaneously reported adverse experiences.

5.4 Participant Discontinuation

Adult participants will be informed that their participation is completely voluntary, and they may choose not to participate or discontinue their participation at any time for any reason. They will also be informed that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled. Further, participants will be informed that they may discontinue participation at any time without penalty or loss of benefits to which the

participant is otherwise entitled. The number of qualified participants who consent to participate and then prematurely withdraw from the study for any reason will be recorded. Premature discontinuation of participation can happen for any of the following reasons:

1. Withdrawal of informed consent (participant's decision to withdraw at any time for any reason);
2. Failure to comply with study procedures or other protocol requirements;
3. Termination of an individual's participation by the Study Staff, Primary CRO or the Sponsor; or
4. Termination of the study by the Sponsor.

5.5 Replacement of Participants

Adult participants who discontinue a survey before completion will be allowed to re-enter and complete it during their allotted survey completion time. Participants who fail to return and complete the survey will not be replaced. If a participant misses a survey, he/she will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule. Only completed surveys will be used for analysis and reporting. Missing data or surveys will not be imputed and results will be analyzed using available complete data.

A comprehensive analysis of attrition and its possible consequences for introducing bias in the results will be carried out. At each time point, those who complete the survey versus those who do not will be compared on the basis of demographics (age, race, education, income) and study group (IQOS versus cigarette smokers). A logistic regression will be performed with survey completion as the dependent variable; the demographics and study group variables will be the independent variables. A significant omnibus chi-squared test and any significant estimates for the individual variables would indicate potential bias for that wave. If the model and any estimates are significant, post-stratification weights will be created based on iterative proportional fitting to make the respective wave's sample more similar to the baseline sample. Weighting efficiencies will then be examined and, if less than 90%, descriptive statistics based on the weighted data will be provided in the appendix. This analysis will be repeated separately at each time point.

To address the potential bias due to attrition in the GEE models, the weighted GEE estimator originally proposed by Robins, Rotnitzky, and Zhao (1995) will be performed.[8] This approach uses logistic regression to estimate the probability that a subject's survey is missing at a given wave and reweights the data based on the inverse of these probabilities. Results from the weighted and unweighted models will be compared. The unweighted results will be presented, but any changes in inference due to the weighting will be clearly noted in the report.

[8] Implemented in SAS's proc gee with the missmodel statement or in the R package wgeesel (Xu et al., 2019).

5.6 Termination of Study

The Sponsor reserves the right to discontinue this study at any time. The study may terminate early if sample attrition reaches a level where conclusions cannot be drawn.

6 OUTCOME MEASURES

6.1 Tobacco use behavior

Tobacco use outcomes include:

- 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
- 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
- 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 ±50%) compared to the prior wave and baseline accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment
- 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
- 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 Survey 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks® and cigarettes

- Number of uses per day on days used in the past 30 days reported using median and interquartile range for IQOS® and cigarettes – compared within and across study groups - at Survey 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks® and cigarettes
- 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[9] compared within and across study groups - at Survey 1, 2, 3, 4, 5, and 6

6.2 Product use transitions

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

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
- 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

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®

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

[9] This measure includes smoker group members who have since quit.

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

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

6.3 Health-related quality of life, signs and symptoms

The health-related outcomes include quality of life, signs and symptoms. The facets of quality of life[10] that will be measured as outcomes in this study include:

[10]The QOL outcomes will be measured using the PROMIS© Global Health 10 and scored using the PROMIS© scoring manual. Please see health module section for details.

- 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.
- 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:

- 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.
- 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.

6.4 Risk perceptions of IQOS® and cigarettes, and perception and understanding of IQOS® and exposure reduction

- 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 Survey 1, 4 and 6
- 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
- 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

7 DATA MANAGEMENT

7.1 Data Validation

Various checks will be performed to ensure the accuracy, integrity, and validity of the data. These include quality checking the survey instrument program logic before and after study launch to ensure that the data are collected as specified in the study protocol. Participants with inaccurate data due to an error in the survey program logic may be removed from the data set prior to database lock.

Any corrections made to the data set will be thoroughly documented and an explanation/rationale will be provided for each correction. A secure computer-generated digital audit trail must be maintained such that the date and time of correction, the individual making the correction, and the explanation must be captured within the database.

7.2 Database Lock

On completion of the study, after the data have been collected and data validation is complete, the data will no longer be subject to change.

7.3 Data Transfer of Study Results

Study data will be sent to ALCS, or its designee, electronically after each survey wave and in a format mutually agreed upon by ALCS or its designee. Data transferred to ALCS will not include any participant personal identification information (PII).

7.4 Data Handling

All data collected during the study are declared property of ALCS, irrespective of the location of the data and any vendor contributing to the study.

8 DATA ANALYSIS

8.1 Outcome Measures Analyses

The data analysis will consist of the following steps:

(1) Participation proportions will be reported overall and by age and sex:

- 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); and
- Response proportion: the number of completed interviews divided by the number of invitations sent.

(2) Descriptive statistics will be calculated for all demographic characteristics at baseline and study outcomes for each time period specified by study group where appropriate (e.g., use history, current tobacco use, days used and units used, risk perception, including means, medians, standard deviations, and interquartile range for continuous variables (e.g. age) and proportions and frequencies for categorical variables (e.g., sex).

(3) A series of GEE models (e.g., GEE log-binomial regression, GEE Poisson regression) will be employed to address study objectives with comparisons between groups or over time (e.g., tobacco use, transitions, health-related quality of life, signs and symptoms). Some outcomes are only relevant to certain tobacco subpopulations. The populations under analysis will be described in the SAP. For example, an analysis of IQOS® use will be reported among current IQOS® users.

Propensity scoring, described in the statistical analysis plan, 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.

The tenability of all assumptions will be evaluated. In the event assumptions are not met, more appropriate statistical models will be utilized. All statistical tests will be conducted at a Type I Error Rate of (b) (4) Corrections for the potential inflation of Type I Error will not be made due to the potential inflation of Type II error (Perneger, 1998). When testing is employed, significant *p*-values will be reported with high precision (to the 4th decimal place) to allow reviewers to evaluate significance after applying a Bonferroni correction, if desired. Estimates with denominator sample sizes less than (b) or having a relative standard error greater than 30% will be reported with a note of low statistical precision. Estimates with denominator sample sizes less than (b) will not be reported with a note of small sample size. Additional technical details regarding the analytic strategy (e.g., research questions, equations) will be provided in the statistical analysis plan.

8.2 Coding of Open-Ended Data

Certain survey questions may allow participants to provide an answer other than what is pre-listed in the response set (e.g., signs and symptoms). These verbatim responses will be reviewed, evaluated and coded as follows: 1) verbatim responses that were provided as an "other" response, but fit into one of the pre-listed responses will be "up-coded" (e.g., response is typed in as an "other" response but it is provided in the pre-list); 2) responses provided that cannot be "up-coded" will be categorized, and frequency of these responses will be evaluated. Responses with a frequency beyond a certain threshold (e.g., 2-5%) will then be assigned a code, and the coded response will be analyzed and reported as part of the response set for that question. Responses with frequencies below the threshold will be reported as "other."

9 PROTECTION OF HUMAN SUBJECTS

9.1 Institutional Review Board (IRB)

This study does not involve intervention. Therefore, the risks presented to the participants are minimal. Nevertheless, study conduct will follow the principles set forth by the Belmont Report and, where applicable, guidelines established under 21 CFR § 50 and 56. A qualified IRB will review and approve the study protocol and ICF/ICS or determine that the study is exempt from IRB review.

Before study initiation and if the IRB does not determine that the study is exempt from its review, study staff must have written and dated approval from the IRB for the protocol and ICF/ICS. The IRB approval should be obtained in writing, clearly identifying the study, the documents reviewed, and the date of the review.

As applicable and if the IRB does not determine that the study is exempt from its review, amendments to the above stated documents must also be submitted and receive approval or exemption from the IRB prior to implementation. ALCS will obtain written IRB approval or exempt determination clearly identifying the study, the documents reviewed, and the date of the review prior to study conduct.

9.2 Ethics

This study will be conducted in compliance with the study protocol and, where applicable, in accordance with the Guidelines for Good Epidemiological Practice (GEP) (IEA, 2007), Council of American Survey Research Organization's (CASRO) Code of Standards and Ethics (CASRO, 2016), and the International Chamber of Commerce/European Society for Opinion and Marketing Research's (ESOMAR) International Code on Market and Social Research (ESOMAR, 2016).

Freely given informed consent will be obtained from every participant.

The rights, safety and well-being of the participants are the most important considerations. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

9.3 Informed Consent Procedures

Study staff will have the final protocol, final programmed survey instruments, including the final informed consent statement (ICS) prior to running the study. Adult participants will digitally sign the ICS.

The principal investigator will revise the informed consent if any important new information becomes available that may impact a participants' willingness to continue participation in the study or is otherwise relevant to participants' consent (and will ensure that information provided to participants as soon as practicable). ALCS will communicate changes to the informed consent to the IRB and obtain IRB approval or a determination that the study is exempt from IRB review, as applicable. Participants will have the ability to call/email study staff with any study-related questions.

9.4 Confidentiality

The study staff (CRO) affirms to ALCS that information furnished to the study staff by ALCS will be maintained in confidence. Data generated by this study will be considered highly confidential by the study staff.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with applicable legal or regulatory requirement(s), if any. The study staff agree that ALCS (or Sponsor representative), IRB, or Regulatory Agency representatives may review and/or copy study documents in order to verify data. By acknowledging the ICS, the participant agrees to this possibility. Thus, this means that absolute confidentiality cannot be guaranteed.

9.5 Debriefing (If applicable)

Participant debriefing does not apply to the current study. The current study gathers self-reported information about behavior and perceptions. No intervention is involved.

10 ADMINISTRATIVE

10.1 Protocol Compliance and Amendments

The study shall be conducted as described in this protocol. Contractors must notify ALCS of any necessary revision to this protocol, and ALCS or a designee must prepare such revisions. The study staff shall not implement any revision to the protocol without communication with ALCS and/or, if applicable, the IRB. Study staff shall document any significant protocol deviation and notify ALCS within 48 hours.

If an Amendment substantially alters the study design or increases the potential risk to the Participant: (1) the consent statement must be revised and, if applicable, submitted to the IRB(s) for review and approval; (2) the revised statement must be used to obtain consent from participants currently enrolled in the study if they are affected by the Amendment; and (3) the new statement must be used to obtain consent from new participants prior to enrollment.

Representatives of ALCS will periodically assess data quality and study integrity. This is accomplished through telephone and e-mail exchanges, which are carried out on an ongoing basis throughout study planning, execution and reporting.

10.2 Study Records

All data will be captured via a secure data collection system. All data will be captured in real time through a web-enabled portal, and all responses will be time and date stamped. Any corrections made to the data set will be thoroughly documented and an explanation/rationale will be provided for each correction. A secure computer-generated digital audit trail must be maintained such that the date and time of correction, the individual making the correction, and the explanation must be captured within the database. All electronic records will be stored in a secure database with restricted access only to individuals requiring it.

The CRO maintains all study-related records, including recruitment and screening information and study data, for the term of the contract under which the study was conducted and for at least four years after the issuance of the final study report, or Sponsor designated length of time.

10.3 Study Reports

The CRO will (1) provide enrollment reports (which includes the number of individuals who qualified for participation, the number of individuals whose participation was terminated (including reason for termination), the number of individuals who withdrew from the study, and the number of individuals who completed the study) and (2) process functioning reports (which outlines any questions or concerns related to the functioning of the study and/or questionnaire instruments) at a frequency agreed upon with ALCS.

The CRO will also provide ALCS interim and final study reports summarizing all study data and providing the results of all analyses.

11 SPONSOR

Altria Client Services LLC

601 E. Jackson Street

Richmond, VA 23219

12 LIST OF ABBREVIATIONS

Acronym	Word or Phrase
ALCS	Altria Client Services LLC
ATCD	Adult Tobacco Consumer Database
CASRO	Council of American Survey Research Organizations
CFR	Code of Federal Regulations
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
ER	Emergency room
ESOMAR	European Society for Opinion and Marketing Research
FDA	Food and Drug Administration
FDCA	United States Food, Drug and Cosmetic Act
GEE	Generalized estimating equation
GEP	Good Epidemiological Practice
HRQOL	Health-Related Quality of Life
ICS	Informed Consent Statement
IRB	Institutional Review Board
MRTP	Modified Risk Tobacco Product
NHIS	National Health Interview Survey
NSDUH	National Survey on Drug Use and Health
PACS	Postmarket Adult Consumer Study
PATH	Population Assessment of Tobacco and Health
PII	Personal identification information
PMP S.A.	Philip Morris Products S.A.
PMSS	Postmarket Surveillance and Studies

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