Appendix B1:
IQOS® Cross-Sectional PACS Protocol

Please find on the following pages study protocol for IQOS® Cross-Sectional PACS.

Confidentiality Statement

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IQOS® WITH MARLBORO HEATSTICKS® CROSS-SECTIONAL POSTMARKET ADULT CONSUMER STUDY (PACS)

"IQOS® Cross-sectional PACS"

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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.
			Reduce respondent burden
			To better understand the role menthol plays in behaviors.
			To provide a granular view of smokers' intention to stop smoking.
			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

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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.

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:

- Complete switching from all tobacco products to IQOS® after first trying IQOS®,
- Complete switching from cigarettes to IQOS® after first trying IQOS®, and
- Complete switching from IQOS® to cigarettes after initiating tobacco use with IQOS®.

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.

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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:

- First tobacco product ever tried,
- First tobacco product ever used on a consistent basis.

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's 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.

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 pouches as ever use of 20 or more times per product,
5) regular pipe as ever use of 50 bowls or more, and
6) all other tobacco products, including e-cigarettes and other e-vapor products, hookah, 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.

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Long-Term Former Use of All Tobacco Products

Long-term former use of all tobacco products refers to having *ever used* a tobacco product(s), now "not at all" using any tobacco products, and having not used **all** tobacco products 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, and having "completely stopped/quit" using all tobacco products ever used.

Re-Initiation of Cigarette Smoking after First Trying IQOS®

Re-Initiation of Cigarette Smoking after First Trying IQOS® refers to *current use* of cigarettes and having had smoked at least 100 cigarettes and having had not smoked cigarettes for 12 months or longer prior to first trying IQOS®.

Relapse to Cigarette Smoking after First Trying IQOS®

Relapse to Cigarette Smoking after First Trying IQOS® refers to *current use* of cigarettes and having had smoked at least 100 cigarettes and having had not smoked cigarettes for less than 12 months prior to first trying IQOS®.

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-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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SYNOPSIS

Protocol Number: (b) (4)
Abbreviated Protocol Title: IQOS® Cross-sectional PACS
Long Protocol Title: IQOS® with Marlboro HeatSticks® Cross-sectional Postmarket Adult Consumer Study
Study Purpose: The purpose of the IQOS® with Marlboro HeatSticks® Cross-sectional Postmarket Adult Consumer Study (IQOS® Cross-sectional PACS) is to provide survey data from qualified[1] adult ever established IQOS® users to assess use and perceptions of IQOS® products and associations with other tobacco use behaviors.
Study Objectives: Among adult ever established IQOS® users, 1. To characterize adult ever established IQOS® users and their tobacco use patterns; 2. To characterize risk perceptions of IQOS®; 3. To describe initiation, complete switching from cigarette smoking to IQOS®, transitions to/back to cigarette smoking, and quitting behaviors relevant to IQOS® use.
Study Design: The design of the study is an online, cross-sectional survey administered annually over the course of four years. Two computerized data collection instruments will be used – a Participant Screener and Main Survey. During the first execution of the IQOS® Cross-Sectional PACS, invitations to participate will be sent to adult tobacco consumers enrolled in the IQOS® Consumer Database. In subsequent executions of the study, adult tobacco consumers may also be recruited from commercial, online panels.[2] All participants, regardless of recruiting source, will complete the same computerized surveys online. 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 a summary of the study, including the study objectives, the voluntary nature of his/her participation, and data privacy/confidentiality guidelines.

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

[2] Commercial online panels, run by a third party, will be used as a registration source. The third party will administer the survey to individuals who meet recruitment criteria.

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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 years of age or older. Those eligible will then be presented with the Main Survey, which will collect the detailed study information to meet the study objectives.

Survey questions have been designed to characterize tobacco use patterns, risk perceptions, use of IQOS® not as intended, and behaviors associated with IQOS®. Most questions will assess outcomes at the brand level (i.e., IQOS® with Marlboro HeatSticks® or, simply, "IQOS®"), not at the individual IQOS® Marlboro HeatSticks® variety level (i.e., Marlboro HeatSticks®, Marlboro Smooth Menthol HeatSticks®, Marlboro Fresh Menthol HeatSticks®). To help characterize use of individual IQOS® Marlboro HeatSticks® varieties, the survey will also include certain questions specific to individual IQOS® Marlboro HeatSticks® varieties, such as individual variety/varieties ever tried, first tried, used during the past 30 days, and used most often. This information will be provided descriptively, and estimates for certain outcomes will be stratified by menthol vs. non-menthol (regular) HeatSticks use.

Checklist items will be randomized. Skip logic will be incorporated into surveys to reduce participant burden.

Participants:

Participants will include adult ever established IQOS® users who are 21 years of age or older.

Ever established IQOS® users will be defined as:

- Ever established IQOS® users: A participant who has used at least 100 Marlboro HeatSticks® in his/her lifetime.
  - 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 now using IQOS® "not at all".

A sufficient sample size was calculated to ensure adequate precision of the estimates (e.g., means, proportions). Assuming the minority of ever established IQOS® users will be former established IQOS® users, a sample size of **(b) (4)** will be needed for former established IQOS® users to achieve a sufficiently narrow confidence interval (NCSS Statistical software, 2017) for the estimates. The current established IQOS® user group will be allowed to fill naturally until the sample size for the former established IQOS® user group achieves

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(b) (4) with a conservative minimum of (b) (4) participants recruited for the current established IQOS® user group.[3]

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) (b) (4) The first annual execution of the IQOS® Cross-sectional Postmarket Adult Consumer study (PACS) will likely entail sending invitations to all members of the IQOS® Consumer Database to achieve the target sample size for former established IQOS® users. Development of random sample frames from the IQOS® database for subsequent annual executions is expected.

The study will begin when it is estimated that the target sample for current established IQOS® users can be met. A 5% response rate will be assumed when making this determination.

Outcome Measures

Use Patterns

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

Risk Perception of IQOS®

- Risk perceptions of IQOS® and cigarettes
- 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

[3] Recruitment is expected to yield a higher number of current established IQOS users than former established IQOS users. The number of current IQOS users enrolled in the study is expected to exceed (b) while filling naturally.

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Initiation of tobacco with IQOS®

- IQOS® as the first tobacco product ever tried
- IQOS® as the first tobacco product ever used on a consistent basis

Initiation of IQOS® as long-term former smokers and long-term former tobacco users

- First trial of IQOS® after not smoking cigarettes for 12 months or longer
- First trial of IQOS® after not using all tobacco products for 12 months or longer

Complete Switching from Cigarettes Smoking/All Tobacco to IQOS®

- Complete switching from cigarettes to IQOS® after first trying IQOS®
- Complete switching from all tobacco products to IQOS® after first trying IQOS®

Transitions To/Back To Cigarette Smoking

- 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®*)
- 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®)*
- Initiation of established cigarette smoking after first trying IQOS® *(among those who never smoked cigarettes prior to first trying IQOS®)*
- Complete switching from IQOS® to cigarette smoking after initiating tobacco use with IQOS® *(among those who never used tobacco prior to first trying IQOS®)*

Quitting Behaviors

- Past 12-month cigarette smoking quit attempt
- Motivation to stop smoking cigarettes
- Quitting cigarettes after first trying IQOS®
- Quitting cigarettes for 12 months or longer after first trying IQOS®
- Quitting all tobacco products after first trying IQOS®
- Quitting all tobacco products for 12 months or longer after first trying IQOS®
- Use of tobacco cessation treatments
- Quitting IQOS®

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- Quitting IQOS® for 12 months or longer

Outcomes of initiation, complete switching from cigarettes to IQOS®, dual use, and quitting and quitting attempts will be stratified by menthol vs. non-menthol HeatSticks use as well as menthol vs. non-menthol cigarette use (used) when sample size allows.

The following will be included to characterize study participants:

- Demographic, background and health-related information
  - Sex
  - Age
  - Race
  - Ethnicity
  - Education
  - Income
  - Marital status
  - Pregnancy status
  - Presence of pre-existing medical conditions or co-morbidities
  - Presence of mental illness
  - LGBTQ status
  - Military personnel/veteran status
- Length of time (i.e., years/months) using IQOS® and cigarettes
- Cigarette and IQOS® dependence
- Varieties of IQOS® ever used, first used, currently use, currently use most often, and previously used most often (among former established IQOS® users)
- Variety of menthol vs. non-menthol cigarettes use

Data Analysis:

Data will be analyzed and summarized while addressing each of the research questions. Descriptive statistics will be reported for all research objectives, including sample sizes, central tendency measures (e.g., means, medians), and variability measures (e.g., standard deviation, range). Additionally, 95% confidence intervals will be reported.

Weights may be applied at each wave based on the IQOS® Consumer Database demographic distribution to account for non-response patterns. Demographics of the sample of IQOS® users at each study wave will be reported. Participation proportions, including contact proportion, response proportion, eligibility proportion, and completion proportion will be summarized.

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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® Cross-sectional Postmarket Adult Consumer Study (IQOS® Cross-sectional PACS), is one such study.

2 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of the IQOS® Cross-sectional PACS is to provide survey data from qualified adult ever established IQOS® users to assess use and perceptions of the products and associations with other tobacco use behaviors.

[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.

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2.2 Objectives

The study objectives are among adult ever established IQOS® users and are as follows:

1. To characterize adult ever established IQOS® users and their tobacco use patterns;
2. To characterize risk perceptions of IQOS®;
3. To describe initiation, complete switching from cigarette smoking to IQOS®, transitions to/back to cigarette smoking, and quitting behaviors relevant to IQOS® use.

3 STUDY DESIGN

3.1 Overview

The design of the study is an online, cross-sectional survey administered annually over the course of four years. Two computerized data collection instruments will be used – a Participant Screener and Main Survey.

During the first execution of the IQOS® Cross-sectional PACS, invitations to participate will be sent to adult tobacco consumers enrolled in the IQOS® Consumer Database. In subsequent executions of the study, adult tobacco consumers may also be recruited from commercial, online panels. All participants, regardless of recruiting mode, will complete the same computerized surveys online. 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 includes a summary of the study, the aim of the study, the voluntary nature of his/her participation, and data privacy/confidentiality guidelines.

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 "Main Survey," which will collect the detailed study information to assess the study objectives.

Survey questions were designed to characterize patterns of tobacco use, risk perceptions, use of IQOS® not as intended, and behaviors associated with IQOS®. Most questions assess outcomes at the brand level (i.e., IQOS® with Marlboro HeatSticks®), not at the individual Marlboro HeatSticks® variety level (i.e., Marlboro HeatSticks®, Marlboro Smooth Menthol HeatSticks®, Marlboro Fresh Menthol HeatSticks®). However, to help characterize use of individual IQOS® varieties, the survey also includes certain questions specific to individual Marlboro HeatSticks® varieties, such as individual Marlboro HeatSticks® variety/varieties ever used, currently used, and currently used most often. This information will be provided descriptively, and estimates for certain outcomes will be stratified by menthol vs. non-menthol (regular) HeatSticks use.

Checklist items will be randomized. Skip logic will be incorporated into surveys to reduce participant burden.

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3.2 Study Stimuli

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

3.3 Survey Questions

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

3.4 Study Frequency and Duration

The study will be conducted annually over a period of four years to account for the anticipated growth in IQOS® distribution and the consumer population over time. The expected duration of the study, from first participant in through last participant out, will be approximately 12 weeks for each annual execution of the study.

3.5 Survey Length

Completion time for the Participant Screener and Main Survey together is estimated to be approximately 20 minutes. The completion time will vary depending on how many different tobacco products the participant reports having ever used.

4 STUDY POPULATION

4.1 Participants

Participants will include ever established IQOS® users who are qualified adults 21 years of age or older. Many outcome measures of interest (e.g., risk perceptions of IQOS®) are applicable to all ever established IQOS® users recruited into the study. However, some outcome measures (e.g., number of days used IQOS® in the past 30 days) are only applicable to current established IQOS® users, while others (e.g., quitting all tobacco products after first trying IQOS®) can only be assessed among former established IQOS® users. As a result, ever established IQOS® users will include participants who have ever used at least 100 Marlboro HeatSticks® and will consist of current and former established IQOS® users.

Ever established IQOS® users will be defined as

- Adults who have ever used at least 100 Marlboro HeatSticks®. Ever established IQOS® users include the following two groups:
    - **Current established IQOS® users:** Adult ever established IQOS® users who now use IQOS® "every day" or "some days".

- **Former established IQOS® users**: Adult ever established IQOS® users who now use IQOS® "not at all."

4.2 Power Analysis and Sample Size Considerations

A sufficient sample size was calculated to ensure adequate precision of the estimates (e.g., means, proportions[5]). Because certain outcome measures are designed for former established IQOS® users and others for current established users, we apply the sample size calculation to the former established IQOS® user group (assuming it is the minority of ever established IQOS® users). The current established IQOS® user group will be allowed to fill naturally until the sample size for the former established IQOS® user group achieves (b) (4) with a conservative minimum of (b) (4) participants recruited for the current established IQOS® user group.[6] Based on our calculation described below, a sample size of (b) (4) will be needed for former established IQOS® users to achieve a sufficiently narrow confidence interval (NCSS Statistical software, 2017) for the estimates. As an example, assuming an expected proportion of an outcome measure is 0.5 (for example, if the proportion of IQOS® users who state the reason for use is to quit cigarette smoking is 0.5), a sample size of (b) (4) (b) (4) (Fleiss et al., 2003; Newcombe, 1998). If a sample size of *n*= (b) cannot be achieved for former established IQOS® users, the confidence interval associated with the actual sample size recruited will be reported. Of note, assuming an expected proportion of 0.5, when the sample size drops to (b) (4) (b) (4) (Figure 1) (Fleiss et al., 2003; Newcombe, 1998), which is still practically acceptable. As a result, (b) (4) will be considered the smallest sample size required for the former established IQOS® user group. Based on these calculations, we expect a total of ~1000 participants to be interviewed for each wave to yield at least (b) former established IQOS® users. (A maximum ratio of current to former users of 9:1 would provide a minimum of (b) (4) former established IQOS® users.) The following table (Table 1) shows 95% confidence intervals for various proportions and sample sizes. We expect the estimates to be less precise for rare events (i.e., low proportions). 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.

Research (Piovesana et al., 2016) has found that a sample size of (b) is required to produce sample means and standard deviations with reasonable precision. Therefore, the estimated minimum sample size of (b) (4) for the former established IQOS® user group is also appropriate for the continuous outcome measures of this study.

The study will begin when it is estimated that the minimum sample size for established IQOS® users can be met. A 5% response rate will be assumed when making this determination.

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[5] The term "proportions" used here is interchangeable with the term "percentages" used in "Section 6. Outcome Measures," as percentages are proportions multiplied by 100.

[6] Recruitment is expected to yield a higher number of current established IQOS users than former established IQOS users. The number of current established IQOS users enrolled in the study is expected to exceed (b) (4) while filling naturally.

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Table 1: 95% Confidence Intervals at Various Proportion Points

n	Proportion
	(b) (4)
	(b) (4)

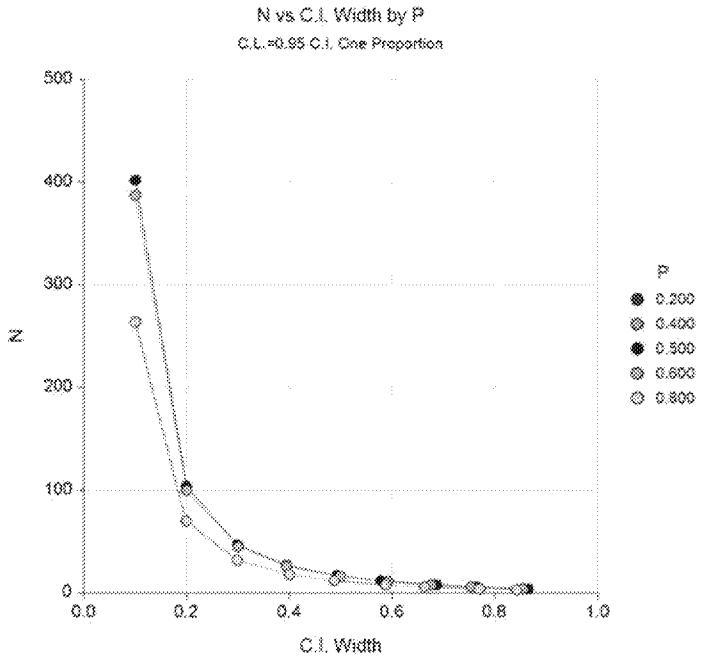

Figure 1: Estimated Sample Sizes for Various Confidence Interval Widths by Expected Proportions

An evaluation of whether the participant population is different than those within the IQOS® Consumer Database will be performed to determine if it is prudent to use model-based methods such as weighting to account for this effect.

4.3 Inclusion Criteria

The Participant Screener asks questions regarding demographics and IQOS® use, as well as questions pertaining to other inclusion/exclusion criteria. Participants must satisfy the following criteria at the time of screening to qualify for the study:

(b)(4)

(b) (4)

4.4 Exclusion Criteria

Participants who meet any of the following exclusion criteria will not qualify for the study:

(b) (4)

5 STUDY PROCEDURES

5.1 Recruitment

Recruitment will occur in the United States when the estimated number of ever established IQOS® users is sufficient to support the study. Participants must have completed the informed consent to be eligible for study participation. All qualified participants who complete the survey will receive a cash or cash equivalent incentive that will be documented in the informed consent at an amount that is commensurate with length and complexity of the survey.

It is anticipated that Philip Morris USA (PM USA), the company that has been granted license from PMP S.A. to distribute, market and sell IQOS® in the U.S. will maintain a database of consumers who purchase the 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) This IQOS® Consumer Database will be utilized to recruit IQOS® established users.

The first annual execution of the IQOS® Cross-sectional study will likely entail sending invitations to all members of the IQOS® Consumer Database to achieve the target sample size for the former established IQOS® users. In subsequent executions of the study, adult tobacco

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consumers may also be recruited from commercial online panels, and probability-based sampling methods (e.g., simple random sampling or stratified sampling) are expected in order to enhance the representativeness of the sample (for example, adult tobacco consumers would be targeted at random by the panel companies if this information is available). Consumers may be invited through e-mail and direct mail communications.

In order to better maximize participation among the IQOS® Consumer Database, participants may be contacted multiple times via multiple channels when possible (e.g., emails, text messages, and mailings). An example of communications for maximizing participant engagement with the survey is depicted in Figure 2:

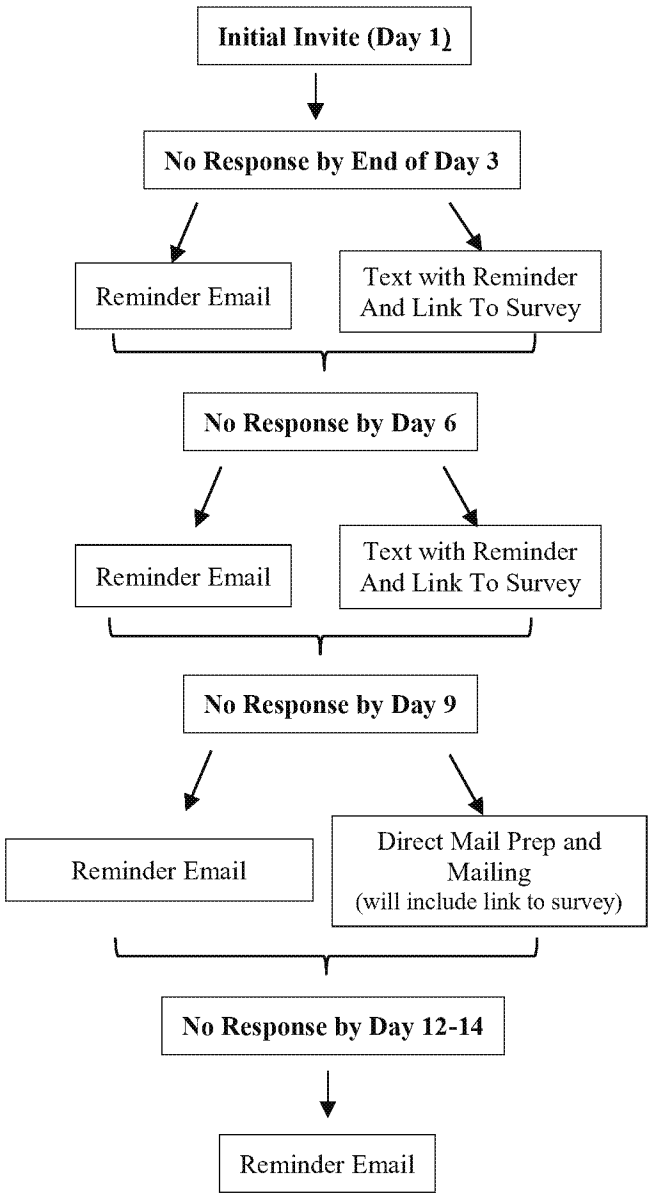

Figure 2: Example of Proposed Timing of Participant Communications

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In this example, waves of invitations (with approximately 2000 invitations per wave) will be conducted in a sequential manner with no initiation of a new wave until the sample within the prior wave has been deemed unproductive (i.e., no incremental increase in response rate). All selected participants will be contacted following the same procedure as described above, including all potential participants in the final wave. The procedure will continue until the target sample size has been achieved. The timing/types of communications may be adjusted based on experiences with consumers at the time of recruitment and the response rate in the initial wave(s). Any adjustments will be documented in the final report.

If the study cannot recruit a sufficient number of qualified adult ever established IQOS® users (i.e., at least (b) former established IQOS® users, as outlined in Section 4.2) within the expected 12 weeks of study recruitment, ALCS may decide to close recruiting without achieving the target sample size. If the target sample size cannot be met, certain outcome measures (e.g., those specific to former established IQOS® users) may not be measured with the expected precision.

5.2 Study Implementation and Timeline

An external market research firm (vendor) will be contracted to conduct this study under the guidance of ALCS. The vendor will serve as the main contract research organization (CRO). It is anticipated that PM USA or ALCS (through the CRO) will send study invites by e-mail and direct mail to potential participants registered in the IQOS® Consumer Database during the first execution of the IQOS® Cross-sectional PACS. In subsequent executions of the study, study invites will be sent to potential participants enrolled in commercial, online panels during as well. Study invites will include a link to access the survey or, in the case of direct mail, a web address and survey code for individuals to access the survey. Individuals will be provided instructions to contact the CRO should they have any questions about the study or trouble accessing the survey. Individuals who meet the study inclusion criteria (Section 4.3) and none of the exclusion criteria (Section 4.4) will qualify for the main study and be administered the main survey. All participants, regardless of recruiting mode, will complete the same computerized survey instruments online.

Estimated Study Timeline

The timing of execution of the cross-sectional 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.

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To plan timing for the cross-sectional study, we focused on the recruiting that will be needed to achieve the minimal sample size ((b) (4)) for each user group. We assume that our recruiting methods will yield more current established users than former users. As described in this protocol, we expect that 1,000 participants will be needed to achieve a sample of *n*= (b) former established users. In this scenario, the desired sample size of (b) for the current users will be comfortably met. Assuming a response level of 5%, we will need to reach 20,000 consumers with contactable information from our database to yield a final sample of approximately (b) (4)

Thus, we base our estimated timelines with the assumption that 20,000 contactable IQOS® consumers will be available in the IQOS® database. We assume that IQOS® will need to be in multiple marketplaces beyond the current locations 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 on the database will be sufficient to recruit the final number of participants for this study.

Table 2: Estimated timeline for the first execution of the IQOS® Cross-sectional Study

Milestone	Estimated Date
Initiation of data collection (survey invitations sent)	September 1, 2021
Completion of data collection (survey closes)	December 1, 2021
Completion of Analyses	February 1, 2022
Completion of Final Report	April 1, 2022

The timeline presented above will be repeated for the three subsequent annual executions, i.e., data collection for Wave 2 will initiate on or about September 1, 2022, Wave 3 will initiate on or about September 1, 2023, and Wave 4 will initiate on or about September 1, 2024.

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 Experience Reporting

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

Participants will be informed that their participation is completely voluntary, and they may choose not to participate or to 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

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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 adult ever established IQOS® users who consent to participate and then prematurely discontinue the survey before completion 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; or
3. Termination of an individual's participation by the prime CRO.
4. Termination of the study by the sponsor.

5.5 Replacement of Participants

Given the cross-sectional nature of the study design, replacement of participants is not applicable.

5.6 Termination of Study

The Sponsor reserves the right to discontinue this study at any time.

6 OUTCOME MEASURES

Objective 1 - Use Patterns

What percentages of ever established IQOS® users report ever tried, use to lifetime criterion and current use of each tobacco product at the time of study assessment and retrospectively prior to first trying IQOS?

- *Types of tobacco products ever tried, used to lifetime criterion, and currently using*

  Percentages and counts of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report:

  - Ever trying a tobacco product
  - Meeting the lifetime criteria for use of a tobacco product (numeric criterion or consistent basis, as applicable)
  - Current use of tobacco product
- *Types of tobacco products ever tried, used to lifetime criterion, and were currently using prior to first trying IQOS®*

  Percentages and counts of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report:

  - Ever trying a tobacco product prior to first trying IQOS®
  - Meeting the lifetime criteria for use of a tobacco product (numeric criterion or consistent basis, as applicable) prior to first trying IQOS®
  - Current use of tobacco product prior to first trying IQOS®

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What percentages of current established IQOS users use IQOS exclusively or dual/poly use with cigarettes and /or other tobacco products?

- *Exclusive and dual/poly tobacco use with IQOS®*

  Percentages and counts of current established IQOS® users reporting current use of (i.e., currently using "every day" or "some days"):

  - IQOS® 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

Estimates will be generated for menthol and non-menthol HeatStick users. Among dual users of IQOS® and cigarettes, estimates will be further stratified by menthol and non-menthol cigarette use.

How often and how much do current established IQOS® users use IQOS®? How often and how much do ever established IQOS® users smoke cigarettes?

- *Number of days of use of IQOS® and cigarettes in past 30 days*
  - Number of days of use will be reported in categories using percentages, in addition to means (standard deviations) and medians (interquartile range, IQR) for number of days used IQOS® in the past 30 days (among current established IQOS® users)
  - Number of days of use will be reported in categories using percentages, in addition to means (standard deviations) and medians (interquartile range, IQR) for number of days used cigarettes in the past 30 days by current and former established IQOS® users (among individuals who are currently using cigarettes "every day" or "some days")

Outcomes for IQOS® use will be stratified by menthol vs. non-menthol HeatStick preference.

- *Amount of Marlboro HeatSticks® and cigarettes in past 30 days*
  - Medians and IQR for number of Marlboro HeatSticks® used on days used in past 30 days (among current established IQOS® users)
  - Medians and IQR for number of cigarettes smoked on days used in past 30 days (among individuals currently smoking cigarettes "every day" or "some days")

Outcomes for IQOS® use will be stratified by menthol vs. non-menthol HeatStick preference.

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How does current tobacco product consumption compare to consumption before trying IQOS®?

- *Amount of tobacco product use before trying IQOS® relative to current tobacco product use*
    - Percentages and counts of current established tobacco product users reporting that they used more, less, or the same amount of each tobacco product per day during the 30 days before they first tried IQOS® compared to the amount currently used per day

What percentage of ever established IQOS® users report ever use of IQOS® not as intended?

- *Description of IQOS® use not as intended among ever established IQOS® users, current established IQOS® users, and former established IQOS® users*
    - Percentage and count citing ever use of a Marlboro HeatStick® without using the IQOS® device
    - Percentage and count of how used Marlboro HeatStick® without using the IQOS® device
    - Percentages and count reporting that they ever used a Marlboro HeatStick® without using the IQOS® device only once, sometimes, most of the time, or all the time (for each way it was used without the device)
    - Percentage and count citing ever use of the IQOS® device with a product other than a Marlboro HeatStick®
    - Percentages and count reporting that they ever used the IQOS® device with a product other than a Marlboro HeatStick® only once, sometimes, most of the time, or all the time
    - Ever use of IQOS® not as intended (i.e., any of above)

Objective 2 –Risk Perceptions of IQOS®

To assess participants' risk perceptions of IQOS®, the following outcomes will be assessed.

What are ever established IQOS® users' risk perceptions of IQOS® and cigarettes?

Risk perceptions will be collected through the Perceived Risk Instrument for general risk assessment (PRI-G; Cano et al., 2018)[7]. Items were constructed based on a literature review, focus groups and expert opinion, and scales were developed and assessed through two U.S.-based web surveys. The resulting 18-item scale contains psychometrically valid measures

[7] We chose to use PRI-G 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.

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capable of measuring health risk perceptions for different types of tobacco products and various levels of smoking status. The risk perceptions module will include items assessing the perception of health risk to the average users of IQOS/cigarette in general.

- Range (min/max), mean, standard deviation, median, and interquartile range of the PRI-G Health risk composite score of IQOS® and cigarettes among *all ever established IQOS® users, current established IQOS® users who are current smokers, current established IQOS® users who are long-term former smokers, and former established IQOS® users.*

What are ever established IQOS® users' perceptions of harmful or potentially harmful chemical exposure from IQOS® and related behavioral change?

- *Perception of harmful or potentially harmful chemical exposure when switching completely from cigarettes to IQOS®*
  - Percentages and counts of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who perceive the level of change in exposure when switching completely from cigarettes to IQOS® (among all participants).
- *Understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure*
  - Percentages and counts of current established IQOS® users who respond to each behavioral response item (among participants who identified 'less exposure' when switching completely from cigarettes to IQOS®).

Objective 3 – Initiation, Complete Switching to IQOS®, Transitions To/Back To Cigarette Smoking, and Quitting Behaviors Relevant to IQOS® Use

Initiation of Tobacco Use with IQOS®

What percentage of ever established IQOS® users initiated tobacco use with IQOS®?

We will adopt two measures of initiation based on measures described in the related scientific literature. These measures pertain to 1) any use of a tobacco product (The Substance Abuse and Mental Health Services Administration, 2017), as represented by the first tobacco product ever used, and 2) the first regular use of a tobacco product (Freedman et al., 2012), as represented by the first tobacco product ever used on a consistent basis.

- Percentage and count of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report IQOS® as the first tobacco product that they ever tried vs. cigarettes or another one of the listed tobacco products (*i.e., first tobacco product ever tried*).
- Percentage and count of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report IQOS® as the first tobacco

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product that they ever used on a consistent basis vs. cigarettes or another one of the listed tobacco products. (*i.e., first tobacco product ever used on a consistent basis*).

Initiation of IQOS® as long-term former smokers and long-term former tobacco users

What percentage of ever established IQOS® users first tried IQOS® after not smoking cigarettes for 12 months or longer?

- Percentage and count of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report that they have smoked at least 100 cigarettes and had not smoked cigarettes for 12 months or longer prior to first trying IQOS® (i.e., "First trial of IQOS® after not smoking cigarettes for 12 months or longer").

What percentage of ever established IQOS® users first tried IQOS® after not using any tobacco products for 12 months or longer?

- Percentage and count of ever established IQOS® users, current established IQOS® users, and former established IQOS® users who report that they have used one or more tobacco products to the lifetime criteria and had not used any tobacco products for 12 months or longer prior to first trying IQOS® (i.e., *"First trial of IQOS® after not using all tobacco products for 12 months or longer").*

Complete Switching from Cigarette Smoking/All Tobacco to IQOS®

What percentage of current established IQOS® users switched from cigarettes to IQOS®?

- Percentage and count of current IQOS® established users who report that they have smoked at least 100 cigarettes, were smoking cigarettes during the 30 days before first trying IQOS® and became former smokers after first trying IQOS® (i.e., *"Complete switching from cigarettes to IQOS® after first trying IQOS®"*), regardless of other tobacco product use.

What percentage of current established IQOS® users switched from all tobacco products to IQOS®?

- Percentage and count of current IQOS® established users who report that they have used at least one tobacco product to lifetime criterion, were using at least one tobacco product during the 30 days before first trying IQOS®, and became former users of all other tobacco products after first trying IQOS® (i.e., "*Complete switching from all tobacco products to IQOS® after first trying IQOS®"*).

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Transitions to/Back to Cigarette Smoking

Relapse to Cigarette Smoking after First Trying IQOS®
What percentage of ever established IQOS® users relapse to cigarette smoking after trying IQOS®?

- Percentage and count of ever established IQOS® users who have smoked at least 100 cigarettes and had not smoked for less than 12 months prior to first using IQOS® and are currently smoking cigarettes "every day" or "some days" (i.e., "*Relapse to cigarette smoking after first trying IQOS®*").

Re-initiation of Cigarette Smoking after First Trying IQOS®
What percentage of ever established IQOS® users re-initiate cigarette smoking after trying IQOS®?

- Percentage and count of ever established IQOS® users who report that have smoked at least 100 cigarettes and had not smoked for 12 months or longer prior to first trying IQOS® and are currently smoking cigarettes "every day" or "some days" (i.e., "*Re-initiation of cigarette smoking after first trying IQOS®*").

Initiation of Established Cigarette Smoking after First Trying IQOS®

What percentage of ever established IQOS® users never smoked cigarettes before first using IQOS® and became an established smoker after using IQOS®?

- Percentage and count of ever established IQOS® users who report that they had never smoked prior to first using IQOS® and have smoked at least 100 cigarettes prior to the assessment. (i.e., "*initiation of cigarette smoking after first trying* IQOS®").

Complete Switching from IQOS to Cigarette Smoking

What percentage of ever established IQOS® users initiated tobacco use with IQOS® and switched from IQOS® to established smoking?

- Percentage and count of ever established IQOS® users who report that IQOS® was the first tobacco product ever tried, "not at all" use IQOS®, and now smoke cigarettes "every day" or "some days", and have smoked at least 100 cigarettes (i.e., *"Complete switching from IQOS® to cigarettes after initiating tobacco use with IQOS®"*).

Objective 3 – Quitting Behaviors

To further describe the participants regarding quitting, several quitting-related measures will be assessed:

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Quit Attempts and Trying to Quit Cigarette Smoking

What percentage of current established cigarette smokers plan to quit or have attempted to quit?

- *Past 12-month quit attempts:*
    - Percentage and count of current *established* cigarette smokers who report that they stopped smoking cigarettes for more than one day in the past 12 months because they were trying to quit smoking among current and former established IQOS® users.
- *Motivation to stop smoking cigarettes:*
    - Percentage and count of current *established* cigarette smokers to each response option in the Motivation to Stop Scale among current and former established IQOS® users.

    Motivation to stop smoking will be assessed through the Motivation to Stop Scale (Kotz et al. 2013).

Quitting Cigarette Smoking After First Trying IQOS®

What percentage of current established IQOS® users quit smoking after first trying IQOS®?

- Percentage and count of ever established cigarette smokers who quit smoking cigarettes among current established IQOS® users.
- Percentage and count of ever established cigarette smokers who quit smoking cigarettes for 12 months or longer among current established IQOS® users.

What percentage of former established IQOS® users quit smoking after first trying IQOS®?

- Percentage and count of ever established cigarette smokers who quit smoking cigarettes among former established IQOS® users.
- Percentage and count of ever established cigarette smokers who quit smoking cigarettes for 12 months or longer among former established IQOS® users.

Quitting All Tobacco After First Trying IQOS®

What percentage of former established IQOS® users quit all tobacco products after first trying IQOS®?

- Percentage and count of former established IQOS® users who report quitting all tobacco products after first trying IQOS® (i.e., Quitting all tobacco products after first trying IQOS®).
- Percentage and count of former established IQOS® users who report quitting all tobacco products for 12 months or longer after first trying IQOS® (i.e., Quitting all tobacco products for 12 months or longer after first trying IQOS®).

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Tobacco Cessation Treatment Use History among Ever Established IQOS® Users

Tobacco cessation treatment use

Among current and former IQOS® established users:

- Percentage and count of ever use but not past 12 months of tobacco cessation treatments.
- Percentage and count of past 12 month but not current use of tobacco cessation treatments.
- Percentage and count of current use of tobacco cessation treatments.

Tobacco cessation treatment use among current established IQOS® users who switched from cigarettes to IQOS®?

Among current IQOS® established users who report that they have smoked at least 100 cigarettes, were smoking cigarettes during the 30 days before first trying IQOS® and became former smokers after first trying IQOS® (i.e., "*Complete switching from cigarettes to IQOS® after first trying IQOS®*"), regardless of other tobacco product use:

- Percentage and count of ever use but not past 12 months of tobacco cessation treatments.
- Percentage and count of past 12 month but not current use of tobacco cessation treatments.
- Percentage and count of current use of tobacco cessation treatments.

Tobacco cessation treatment use among current established IQOS® users switched from all tobacco products to IQOS®?

Among current IQOS® established users who report that they have used at least one tobacco product to lifetime criterion, were using at least one tobacco product during the 30 days before first trying IQOS®, and became former users of all other tobacco products after first trying IQOS® (i.e., "*Complete switching from all tobacco products to IQOS® after first trying IQOS®*"):

- Percentage and count of ever use but not past 12 months of tobacco cessation treatments.
- Percentage and count of past 12 month but not current use of tobacco cessation treatments.
- Percentage and count of current use of tobacco cessation treatments.

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Quitting IQOS®

What percentage of ever established IQOS® users quit IQOS®/quit IQOS® for 12 months or longer?

- Percentage and count of ever established IQOS® users who report that they quit IQOS® (i.e., *"Quitting IQOS®")*.
- Percentage and count of ever established IQOS® users who report that they quit IQOS® for 12 months or longer (i.e., *"Quitting IQOS® for 12 months or longer")*.

Estimates for outcomes under objective 3 will be provided for menthol (including smooth menthol and fresh menthol) vs. non-menthol (regular) HeatStick users as well as menthol vs. non-menthol cigarette users when applicable and when sample size allows.

The following will be included to characterize study participants:

- Demographic, background, and health-related information
  - Sex
  - Age
  - Race
  - Ethnicity
  - Education
  - Income
  - Marital status
  - Pregnancy status
  - Presence of pre-existing medical condition(s) or co-morbidities
  - Presence of mental illness
  - LGBTQ status
  - Military personnel/veteran status
  - Length of time using IQOS® and cigarettes
    - Means (standard deviations) and medians (IQR) and for length of time current established IQOS® users report using IQOS® and current established cigarette smokers report smoking cigarettes, as applicable
  - Cigarette and IQOS® dependence
    - Medians (IQR) and counts and percentages of Heaviness of Smoking Index (HSI) score categories for HSI among current established smokers and corresponding statistics for IQOS® among current established IQOS® users
  - Varieties of Marlboro HeatStick® (i.e., Marlboro HeatSticks®, Marlboro Smooth Menthol HeatSticks®, Marlboro Fresh Menthol HeatSticks®) ever used, first used, currently use, currently use most often, and previously used most often (among former established IQOS® users)
    - Percentages and counts of individual Marlboro HeatStick® variety/varieties ever tried
    - Percentages and counts of first Marlboro HeatStick® variety ever tried

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- Percentages and counts of individual Marlboro HeatStick® variety/varieties currently being used (among current established IQOS® users)
- Percentages and counts of individual Marlboro HeatStick® variety/varieties currently being used most often (among current established IQOS® users)
- Percentages and counts of individual Marlboro HeatStick® variety/varieties previously used most often (among former established IQOS® users)

- Varieties of menthol vs. non-menthol cigarette used
  - Percentages and counts of menthol vs. non-menthol cigarette currently using most often among ever established cigarette smokers
  - Percentages and counts of menthol vs. non-menthol cigarette formerly using most often among former established cigarette smokers

7 DATA MANAGEMENT

7.1 Data Validation

Survey logic will be incorporated into the survey instrument to preclude inconsistent responses to separate measures. Clarification probes and redirects may be incorporated, as needed. 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.

Any corrections made to the data set will be thoroughly documented and an explanation/rationale will be provided for each correction. A 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 survey response database, where response data will be stored.

7.2 Survey Response Database Lock

On completion of the study, after data collection has been deemed complete, the survey response database will be locked, and data will no longer be subject to change.

7.3 Data Transfer of Study Results

Study data transfers will be sent to ALCS, or their designee, electronically on a schedule and in a format mutually agreed upon by ALCS, or their designee, and the vendor responsible for the analysis of these study data. Data transferred to ALCS will not include any participant personal identification information.

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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

Weights may be applied at each wave based on the IQOS® Consumer Database demographic distribution (e.g., sex and age) to account for non-response patterns.

Details of statistical analyses and the statistical software packages to be used will be provided in the statistical analysis plan and study report. Deviations from the approved statistical analysis plan will be reported in an amended statistical analysis plan and in the final study report, if applicable.

8.1 Outcome Measures Analyses

The study outcomes are described in Section 6. Descriptive statistics will be calculated, including medians and quartiles for continuous or count variables (e.g., amount of tobacco use), as well as percentages and counts for categorical variables (e.g., yes/no ever used a tobacco product). Ninety-five percent (95%) confidence intervals will also be calculated when applicable. Note that the outcomes are calculated from survey questions. For further information regarding the survey questions, please refer to the Survey Instruments.

8.2 Additional Data Summaries

Participation. Participation proportions will be summarized, including:

- *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.

8.3 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. These verbatim responses will be reviewed, evaluated and coded as

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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., reason for use 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 participant will be minimal. Nevertheless, study conduct will follow the principles set forth by the Belmont Report and, where applicable, guidelines established under 21 CFR Parts 50 and 56. A qualified IRB will review and approve the study protocol and Informed Consent Statement 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, vendor study staff must have written and dated approval from the IRB for the protocol and Informed Consent Statement. 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. For further details on informed consent, see Section 9.3. 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, questionnaires, and Informed Consent Statement prior to running the study. Participants will electronically consent to participate in the study by clicking a box next to the word "Agree" at the end of the Informed Consent Statement.

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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 is 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. Study staff should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. Study staff will document this communication. Participants will have the ability to call/email study staff with any study related questions.

9.4 Confidentiality

The study staff 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 Informed Consent Statement, the participant agrees to this possibility. Thus, this means that absolute confidentiality cannot be guaranteed.

9.5 Debriefing

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

Protocol (b) (4) is sponsored by ALCS. A vendor (Prime CRO) will be contracted to conduct the study on behalf of ALCS.

10.1 Protocol Compliance and Amendments

The study shall be conducted as described in this approved protocol. The vendor must notify ALCS of any necessary revisions 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 informed 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

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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 will be accomplished through telephone and e-mail exchanges with the vendor (prime CRO), which will be carried out on an ongoing basis throughout study planning, execution and reporting.

10.2 Study Records

Participants will be identified in any reports by study participant identification numbers only (not full participant names).

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. All electronic records will be stored in a secure survey response database with access restricted only to those individuals requiring it.

The vendor will maintain 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 vendor will provide 1) a report (including, but not limited to, the number of people invited to the study, the number of individuals who qualified for participation, the number of individuals whose participation was terminated by reason for termination, the number of people 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 survey instruments) at a frequency agreed upon with ALCS. The vendor will also provide ALCS a draft and final study report 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 CONTRACT RESEARCH ORGANIZATIONS

To be determined

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13 LIST OF ABBREVIATIONS

Acronym	Word or Phrase
ALCS	Altria Client Services
ATCD	Adult Tobacco Consumer Database
CASRO	Council of American Survey Research Organizations
CFR	Code of Federal Regulations
CRO	Contract Research Organization
ESOMAR	European Society for Opinion and Marketing Research
FDA	Food and Drug Administration
FDCA	United States Food, Drug and Cosmetic Act
GEP	Good Epidemiological Practice
IQR	Interquartile Range
IRB	Institutional Review Board
MRTP	Modified Risk Tobacco Product
PACS	Postmarket Adult Consumer Study
PMSS	Postmarket Surveillance and Studies
SAP	Statistical Analysis Plan
PMP S.A.	Philip Morris Products S.A.

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