ADULT IQOS USER POSTMARKET CROSS-SECTIONAL STUDY IN THE UNITED STATES (PMSS-PMX-01-US)

Study Protocol

Study Title:	Adult IQOS User Postmarket Cross-Sectional Study in the United States
Protocol Number:	PMSS-PMX-01-US
Product Name:	*IQOS*
Sponsor:	Philip Morris Products S.A. Avenue de Rhodanie 50 1007 Lausanne Switzerland
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PRINCIPAL INVESTIGATOR`S SIGNATURE

Study Title:	Adult IQOS User Postmarket Cross-Sectional Study in the United States
Protocol Number:	PMSS-PMX-01-US
Version Number:	1.0
Version Date:	April 22, 2024

As the Principal Investigator, your role on this study is to ensure that the study is conducted according to the study protocol and applicable regulations; for protecting the rights and welfare of the participants.

By signing this protocol, the Principal Investigator agrees that:

- They will act as the Principal Investigator for this study.
- They have read the protocol described above.
- They agree to conduct the study in accordance with the protocol and comply with all applicable laws and regulations.
- They agree to keep the information and documents provided by the Sponsor in strict confidence and to request similar confidentiality from their staff. The information provided by the Sponsor to the Principal Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from participants in the study.

Jessica Seifert, PhD, MPH *Head of Regulatory Postmarket Research*	Please refer to electronic signature
Philip Morris Products S.A., Washington, D.C., USA	

SPONSOR SIGNATURES

Study Title:	Adult IQOS User Postmarket Cross-Sectional Study in the United States
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This Study Protocol was subject to critical review and has been approved by the Sponsor. The following signatories approved this protocol:

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THIRD PARTIES PERSONNEL SIGNATURES

Study Title:	Adult IQOS User Postmarket Cross-Sectional Study in the United States
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The following third-party personnel contributed to writing and approving this protocol:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**		

Administrative Change No.	Date of Administrative Change		

1 SYNOPSIS

Study Sponsor	Philip Morris Products S.A.
Study Title	Adult IQOS User Postmarket Cross-Sectional Study in the United States
Study Identifier	PMSS-PMX-01-US
Planned Study Period	The study will be conducted annually over a period of four years. The expected recruitment duration each year will be approximately 6-8 weeks from first participant in through last participant out.
Study Research Partner	(b) (4)
Study Purpose	The purpose of the Adult IQOS User Postmarket Cross-Sectional Study in the United States (US) is to provide repeated real-world survey data from cross-sections of adult ever established IQOS users and to assess IQOS use and related risk perceptions and associations with other tobacco use behaviors.
Study Objectives	1. Describe the sociodemographic and health-related characteristics of adult ever established IQOS users. 2. Characterize historical and current tobacco use patterns of adult ever established IQOS users. 3. Assess adult ever established IQOS users' health risk perceptions related to IQOS use, cigarette smoking, and complete smoking cessation. 4. Characterize IQOS use and other tobacco use patterns, including product initiation, complete switching from cigarette smoking to IQOS, transitions to (never smokers) and back (former smokers) to cigarette smoking, and quitting behaviors relevant to IQOS use.
Study Design	This study is an online, repeated, 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. Main Survey items were curated 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.
Study Population	Participants will include US adult (≥ 21 years) ever established IQOS users (i.e., have used at least 100 IQOS heated tobacco sticks in lifetime by the time of enrollment). Participants will be assigned to one of two ever established IQOS user study groups: ▪ **Current established IQOS users:** Adult ever established IQOS users who report using IQOS in the past 30 days at time of assessment. ▪ **Former established IQOS users:** Adult ever established IQOS users who report not having used IQOS in the past 30 days at time of assessment.

Inclusion Criteria	Participants must satisfy the following criteria at the time of screening to be eligible for the study: 1. US resident. 2. 21 years of age or older. 3. Voluntarily consent to serve as a participant in the study by electronically acknowledging an Informed Consent Statement (ICS), with approval or exemption determined by a qualified Institutional Review Board (IRB). 4. Acknowledge willingness and ability to comply with all study requirements as listed in the ICS. 5. Meet criteria for inclusion as a current or former established IQOS user (i.e., an individual who has used at least 100 IQOS heated tobacco sticks in lifetime by the time of enrollment).
Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible for the study: 1. Unable to read, speak, or understand English. 2. Is a current or former employee or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member who is a current or former employee of the tobacco or e-cigarette industry. 3. Is a current or former employee or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member who is a current or former employee of the study CRO. 4. Is or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member involved in litigation (e.g., as a named party or class representative) with any company involved in the tobacco or e-cigarette industry.
Study Sample Size	The timing and execution of this study depends on the distribution and consumer uptake of IQOS in the US marketplace. With an expected response rate of 3.0% (based on previous execution of this study by Altria Client Services, N ≥ 30,000 IQOS Customer Loyalty Program (CLP) registrants (the primary sampling frame) will be required to yield the target annual sample of N = 1,000 ever established IQOS users (n ≈ 900, Current Established Users; n ≈ 100 Former Established Users).
Objectives and Outcome Measures	**Objective 1 – Describe sociodemographic and health-related characteristics of adult ever established IQOS users.** ▪ Sociodemographic characteristics – age, race, ethnicity, sex, gender identity, sexual orientation, education, income, employment status, geographic region, marital status, and military/veteran status. ▪ Health-related information – pregnancy status, ever told they had a chronic health condition, ever told they had a mental health condition, and currently receiving treatment for a mental health condition.

	Objective 2 – Characterize historical and current tobacco use patterns of adult ever established IQOS users. a) Historical tobacco or nicotine product (TNP) use: ▪ Use prior to first trying IQOS – ever use, lifetime established use, past 30-day use. ▪ At time of assessment – ever use, lifetime established use. b) Current TNP use at time of assessment: ▪ Past 30-day use. ▪ Number of days used in the past 30 days. ▪ Amount of product used on days used in the past 30 days (IQOS heated tobacco sticks and cigarettes only). ▪ Monthly average amount of product used per day (IQOS heated tobacco sticks, cigarettes, and combined sticks and cigarettes). ▪ Current use of given TNP relative to use in the 30 days prior to first trying IQOS. ▪ IQOS use duration. ▪ Cigarette smoking duration. ▪ Quit IQOS duration. c) IQOS heated tobacco stick flavor(s) use (ever, first, current, most often used). d) Past 30-day exclusive IQOS use, dual (IQOS and one other TNP) use, or poly (IQOS and two or more other TNPs) use. e) IQOS dependence (Fagerström Test for Nicotine Dependence [FTND], Heatherton et al., 1991). f) Use of IQOS not as intended. g) Cigarette smoking status. h) Cigarette dependence (FTND). **Objective 3 – Assess adult ever established IQOS users' health risk perceptions related to IQOS use, cigarette smoking, and complete smoking cessation.** a) Health risk perceptions of IQOS, cigarettes, and smoking cessation (ABOUT™ – Perceived Risk Instrument; Cano et al., 2018). b) 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. **Objective 4 – Characterize IQOS use and other tobacco use patterns, including: product initiation, complete switching to IQOS, transitions to (never smokers) and back (former smokers) to cigarette smoking, and quitting behaviors relevant to IQOS use.** a) 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. ▪ First tried IQOS after not smoking cigarettes for ≥12 months. ▪ First tried IQOS after not using all tobacco products for ≥12 months.

	b) Complete Switching After First Trying IQOS ▪ Cigarettes to IQOS. ▪ All tobacco to IQOS. c) Complete Switching from IQOS to Cigarette Smoking d) Transitions To Cigarette Smoking After First Trying IQOS ▪ Relapse to cigarette smoking. ▪ Re-initiation of cigarette smoking. ▪ Initiation of established cigarette smoking. e) Quitting Behaviors ▪ Current Established Smokers: o Past 12-month quit attempt. o Motivation to Stop Smoking (MTSS). ▪ Ever Established Smokers who completely quit smoking cigarettes after first trying IQOS. ▪ Ever Established TNP Users who completely quit all tobacco products after first trying IQOS. f) Last Tobacco Cessation Treatment Use Outcomes of initiation, complete switching from cigarettes to IQOS, dual use, quitting, and quitting attempts will be stratified by menthol vs. non-menthol IQOS heated tobacco sticks use as well as menthol vs. non-menthol cigarette use (used) when sample size allows.
Data Analysis	This study is descriptive in nature. Categorical outcomes will be summarized using counts and percentages (n, %). Continuous outcomes will be summarized using means (M), standard deviations (SD), medians, first (Q1) and third (Q3) quartiles, minimums (Min), and maximums (Max). Ninety-five percent confidence intervals will also be calculated when applicable. Specific details on intended statistical analyses and statistical software packages are described in the Statistical Analysis Plan (SAP).
Report, Transfer & Archiving	(b) (4) will provide PMP with a study report summarizing all study data and providing the results of all analyses. Study data will be transferred to PMP electronically based on an agreed schedule and format. Data transferred to PMP will not include any participant personal identification information. (b) (4) 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's designated length of time.

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5 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Health Event
CASRO	Council of American Survey Research Organizations
CFR	Code of Federal Regulations
CLP	Customer Loyalty Program
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
E-Cigarette	Electronic cigarette or other electronic vapor product
ESOMAR	European Society for Opinion and Marketing Research
FDA	United States Food and Drug Administration
FDCA	United States Federal Food, Drug and Cosmetic Act
GEP	Good Epidemiological Practice
ICC	International Chamber of Commerce
ICS	Informed Consent Statement
IQOS	IQOS Tobacco Heating System and IQOS heated tobacco sticks
IRB	Institutional Review Board
M	Mean
Max	Maximum value
Min	Minimum value
MRTPA	Modified Risk Tobacco Product Application
(b) (4)	(b) (4)
PMP	Philip Morris Products S.A.

PMSS	Postmarket Surveillance and Studies
PSS	Product Safety Surveillance
Q1	First quartile (25th percentile)
Q3	Third quartile (75th percentile)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SRF	Safety Reporting Form
TNP	Tobacco or Nicotine Product
US	United States

6 DEFINITION 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 tobacco or nicotine product (TNP) user is someone who reports using the TNP in the past 30 days at least once (i.e., current use) and meets the lifetime established criterion for that TNP (i.e., established use). Unless otherwise specified, IQOS refers to IQOS Tobacco Heating System and IQOS heated tobacco sticks in this document.

Complete Switching

Complete switching generally refers to transitioning from *established use* of a given TNP to reporting no past 30-day use of that TNP (i.e., former established use) and *current established* use of a different TNP.

Outcomes related to complete switching in this study include:

1. Complete switching from cigarettes to IQOS after first trying IQOS will be defined as reporting:

   Prior to first trying IQOS:

   - Met the *lifetime established use criterion* for cigarettes (i.e., 100 or more), AND
   - Smoked cigarettes in the 30 days prior to first trying IQOS.

   At time of assessment:

   - Has not smoked cigarettes in the past 30 days, AND
   - Is a current established IQOS user.

2. Complete switching from all tobacco products to IQOS after first trying IQOS will be defined as reporting:

   Prior to first trying IQOS:

   - Met the *lifetime established use criterion* for given TNP, AND
   - Used given TNP in the 30 days prior to first trying IQOS.

   At time of assessment:

   - Has not used any TNP in the past 30 days, AND
   - Is a current established IQOS user.

3. Complete switching from IQOS to cigarettes after initiating tobacco use with IQOS will be defined as reporting:

At time of assessment:

- IQOS as first TNP ever used, AND
- Is a former established IQOS user, AND
- Is a current established smoker.

Consistent Basis

Consistent basis will be defined as reporting "Yes" to "Have you ever used [tobacco 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 Established Smoker

Current established smoker will be defined as reporting:

1. Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more lifetime cigarettes), AND
2. Having smoked cigarettes in the past 30 days at time of assessment.

Current Established Tobacco or Nicotine Product Use

Current established use of a given TNP will be defined as reporting:

1. Having met the *lifetime established use criterion* for the given TNP, AND
2. Having used the given TNP in the past 30 days at time of assessment.

Current Tobacco or Nicotine Product Use

Current TNP use will be defined as reporting having used given TNP in the past 30 days at time of assessment.

Ever Established Tobacco or Nicotine Product Use

Ever established TNP use refers to meeting the *lifetime established use criterion* (see definition below) for a given TNP.

Ever Tobacco or Nicotine Product Use

Ever TNP use will be defined as reporting "Yes" to "Have you ever [used/smoked] [TNP] even one time?"

Former Established Tobacco or Nicotine Product Use

Former established TNP use will be defined as reporting:

1. Having met the *lifetime established use criterion* of the given TNP, AND
2. No past 30-day use of given TNP at time of assessment.

Former Tobacco or Nicotine Product Use

Former TNP use will be defined as reporting:

1. Having ever used a given TNP, even one time, AND
2. Not having used the given TNP in the past 30 days at time of assessment.

Initiation

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

1. "First tobacco product ever tried" defined as the given product endorsed in item, "What was the first product you ever tried even one time?"
2. "First tobacco product ever used on a consistent basis" defined as the given product endorsed in item, "What was the first product you used on a consistent basis?"
3. Initiation of established cigarette smoking after first trying IQOS:

   Prior to first trying IQOS:

   - Never smoked cigarettes, OR
   - Did not met the lifetime established use criterion for cigarettes (i.e., 100 or more).

   At time of assessment:

   - Is an established cigarette smoker.

Lifetime Established Use Criterion

The lifetime established use criterion for each TNP will be defined for:

1. Cigarettes as reporting ever having smoked 100 or more cigarettes.
2. IQOS as reporting ever having used 100 or more IQOS heated tobacco sticks.
3. Cigars (including regular cigars, cigarillos, or little filtered cigars) as reporting ever having smoked 50 or more cigars (including regular cigars, cigarillos, or little filtered cigars).
4. Smokeless tobacco (including chewing tobacco, dip, snuff, or snus pouch) as reporting having ever used smokeless tobacco 20 or more times.
5. Regular pipe as reporting ever having smoked 50 bowls or more.
6. Traditional hookah as reporting ever having smoked tobacco in a hookah on a "*consistent basis.*"
7. Electronic cigarettes (e-cigarettes) and other e-vapor products as reporting ever having used e-cigarettes on a "*consistent basis.*"

8. Oral nicotine pouches as reporting ever having used oral nicotine pouches on a "*consistent basis."*

Quit Duration

Quit duration is the length of time since a former established TNP user last used the given established TNP and will be dichotomized into:

1. **Short-term TNP quitter** will be defined as reporting not having used given established TNP for less than 12 months.
2. **Long-term TNP quitter** will be defined as reporting not having used given established TNP for 12 months or longer.

Quitting Established Tobacco or Nicotine Product Use

Quitting established TNP use will be defined as reporting:

1. Having used a given TNP to the *lifetime established use criterion*, AND
2. Having "completely stopped/quit" using the given TNP.

Quitting All Established Tobacco or Nicotine Product Use

Quitting all established TNP use will be defined as reporting:

1. Having used any TNP to the *lifetime established use criterion*, AND
2. Having "completely stopped/quit" using all TNP ever used.

Re-Initiation of Cigarette Smoking after First Trying IQOS

Re-initiation of cigarette smoking after first trying IQOS will be defined as reporting:

Prior to first trying IQOS:

- Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more), AND
- Not having smoked cigarettes for 12 months or longer, AND

At time of assessment:

- Past 30-day cigarette smoking.

Relapse to Cigarette Smoking after First Trying IQOS

Relapse to cigarette smoking after first trying IQOS will be defined as reporting:

Prior to first trying IQOS:

- Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more), AND
- Not having smoked cigarettes for less than 12 months, AND

At time of assessment:

- Past 30-day cigarette smoking.

Tobacco or Nicotine Products

Tobacco or nicotine products (TNP) include products containing tobacco and/or nicotine. These products may be combustible or non-combustible, depending on intended use.

1. **Combustible Tobacco or Nicotine Products** burn tobacco and produce smoke when consumed/used as intended and include cigarettes, cigars (regular cigars, cigarillos, and little filtered cigars), regular pipes, and traditional hookah (or water pipe).
2. **Non-Combustible Tobacco or Nicotine Products** do not burn tobacco or produce smoke when consumed/used as intended and include heat-not-burn products (e.g., IQOS), smokeless tobacco (dip, snuff, chewing tobacco, and snus pouches), electronic cigarettes (e-cigarettes), and oral nicotine products (excluding nicotine replacement therapy products).

Novel TNP categories may be added to these lists, as well as assessed in this study as they emerge in future US markets.

United States (US) IQOS Customer Loyalty Program (CLP) Database

Once the modified-risk tobacco product is commercialized in the US, adult IQOS consumers will be able to voluntarily register their device with the IQOS CLP. The CLP database will function as the primary sampling frame for this study.

7 BACKGROUND AND INTRODUCTION

7.1 Background

Philip Morris Products S.A. (PMP) submitted a Modified Risk Tobacco Application (MRTPA) to the US Food and Drug Administration (FDA) seeking authorization to market the IQOS Tobacco Heating System and IQOS heated tobacco sticks (formerly commercialized as "Marlboro HeatSticks") as modified risk tobacco products. The IQOS Tobacco Heating System is an electronic device that heats IQOS heated tobacco sticks, generating a nicotine-containing aerosol with significantly fewer harmful and potentially harmful chemicals than the smoke generated by combustible tobacco products. Based on the evidence provided in the MRTPA, the FDA issued two "Modified Risk Granted Orders – Exposure Modification" authorizing PMP to market IQOS with a reduced exposure claim (FDA, 2020; FDA, 2022).

The Orders are conditioned upon the execution of postmarket surveillance and studies (PMSS) in accordance with protocols approved by FDA. This document was prepared as part of the PMSS program for IQOS pursuant to the Orders.

7.2 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" (FDA, 2012). For this reason, PMP[1], plans to conduct certain components of PMSS to assess the effect of the MRTP among US 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, Adult IQOS User Postmarket Cross-Sectional Study in the United States (US) is one such study.

[1] *Note.* Prior to April 2024, Altria Client Services developed and executed the IQOS PMSS program on behalf of PMP. The IQOS PMSS program will be managed and executed by PMP beginning May 2024

8 STUDY OBJECTIVES

8.1 Purpose

The purpose of the Adult IQOS User Postmarket Cross-Sectional Study in the United States is to provide repeated real-world survey data from cross-sections of adult ever established IQOS users and to assess IQOS use and related risk perceptions and associations with other tobacco use behaviors.

8.2 Objectives

The objectives of this study are to:

1. Describe sociodemographic and health-related characteristics of adult ever established IQOS users.
2. Characterize historical and current tobacco use patterns of adult ever established IQOS users.
3. Assess adult ever established IQOS users' health risk perceptions related to IQOS use, cigarette smoking, switching, and complete smoking cessation.
4. Characterize IQOS use and other tobacco use patterns, including product initiation, complete switching from cigarette smoking to IQOS, transitions to (never smokers) and back (former smokers) to cigarette smoking, and quitting behaviors relevant to IQOS use.

9 STUDY DESIGN

9.1 Overview

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

This study intends to recruit adult (≥ 21 years) ever established (i.e., have used 100 or more IQOS heated tobacco sticks in their lifetime) IQOS users in the US. Study invitations with unique links to the Participant Screener will be delivered via email, direct mail, and/or text to adult IQOS purchasers who have registered their device in the IQOS CLP and opted in to receive communications from PMP. Interested individuals who follow the study invitation link will be directed to begin the Participant Screener. Those not terminated at the initial screen will then be directed to review the study Informed Consent Statement (ICS) detailing the study purpose, the voluntary nature of their participation, data privacy and confidentiality guidelines, and contact information for the Institutional Review Board (IRB) and Contract Research Organization (CRO).

After reviewing the ICS and providing consent to participate in the study, potential participants will complete the Participant Screener Survey to determine their eligibility. Eligible participants will then be administered the Main Survey, that will collect detailed study information to assess the study objectives.

9.2 Study Stimuli

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

9.3 Participant Screener and Main Survey

Main Survey items were curated 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 [Population Assessment of Tobacco and Health Study]; Parsons et al., 2014 [National Health Interview Survey]; The Substance Abuse and Mental Health Services Administration, 2017 [National Survey on Drug Use]). Furthermore, cognitive testing of the study instrument was executed by Altria Client Services in early 2020 and survey items were updated when needed.

Survey questions will capture participants' historical (e.g., ever use) and current (e.g., past 30-day use) IQOS and other TNP use. Generally, most questions pertaining to IQOS will be asked at the brand level not at the IQOS heated tobacco stick variety level (e.g., *Bronze* heated tobacco sticks).

Participants' lifetime health risk perceptions will be measured using the ABOUT™ — Perceived Risk instrument (Cano et al., 2018). ABOUT™ is based on an underlying conceptual framework developed from a range of extensive qualitative studies with

different populations (adult current smokers, adult former smokers, and adult never smokers), literature review, and input from expert panels (Cano et al., 2018). The short 9-item scale version will be used in this study. This version contains psychometrically valid measures capable of measuring health risk perceptions for different types of tobacco products and various levels of smoking status. The study survey will also capture participants' exposure harm perceptions related to smokers completely switching to IQOS.

Tobacco dependence for IQOS and cigarettes will be measured using the Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991). FTND has been validated for use across TNP categories other than cigarettes and has demonstrated good psychometric properties for measuring the intensity of physical dependence on nicotine (Mushtaq et al., 2017; Piper et al, 2020; Sharma et al., 2021).

Current established smokers' motivation to quit will be measured based on the Motivation To Stop Smoking (MTSS) scale (Kotz et al. 2013) response selected:

- "I don't want to stop smoking" (1)
- "I think I should stop smoking but don't really want to" (2)
- "I want to stop smoking but haven't thought about when" (3)
- "I REALLY want to stop smoking but I don't know when I will" (4)
- "I want to stop smoking and hope to soon" (5)
- "I REALLY want to stop smoking and intend to in the next 3 months" (6)
- "I REALLY want to stop smoking and intend to in the next month" (7)

Higher MTSS scale scores indicate higher motivation to stop smoking cigarettes.

The survey will also capture participants' sociodemographic characteristics (e.g., age, gender, income), pregnancy status, and tobacco use-related health outcome history (e.g., heart attack, COPD). See Appendix 1: Participant Screener, Informed Consent Statement, Main Survey for all study items.

For enhancement of data validity and data consistency, checklist items will be randomized and skip logic will be incorporated into the questionnaires to reduce participant burden.

9.4 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. Annual study recruitment, from first participant into last participant out, is expected to take approximately 6-8 weeks.

9.5 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.

9.6 Study Strengths and Limitations

This study has several key strengths:

1. This study uses standard measures from national surveillance systems (e.g., Population Assessment of Tobacco and Health Study) that have been validated for use in the study population, reducing the likelihood of reporting bias.
2. This study intends to leverage the IQOS CLP Database as the study sampling frame. The IQOS CLP Database is a voluntary consumer registry expected to enroll > 80% of US adult IQOS consumers (based on IQOS CLP Database enrollment in similar markets), increasing the generalizability of study findings to all US adult ever established IQOS users in US markets where the product is available.
3. The study intends to recruit a large (N = 1,000) sample each year allowing for precise outcome measures in key study groups.
4. The repeated, cross-sectional design allows for rapid, real-world data collection, capturing underlying trends in use behaviors of users as well as in-market changes in IQOS distribution each year.

However, this study is not without limitations:

1. The results of this study may not be generalizable to the broader population of adult IQOS users (i.e., non-established users) or to ever established IQOS users who decide not to participate in research.
2. It is possible that participants may not accurately recall their tobacco product use. However, all tobacco use and perception measures assessed in the study are derived from standard, validated measures, minimizing the likelihood of reporting bias.
3. The cross-sectional nature of the study precludes establishing causality for descriptive transitions characterized in analyses and subsequent reports.

Due to the cross-sectional design, participants may have variable IQOS use histories, including different durations since first establishing IQOS use. This will need to be considered when interpreting the results.

10 STUDY POPULATION

10.1 Participants

Participants will include adult (≥ 21 years) ever established IQOS users (i.e., have used at least 100 IQOS heated tobacco sticks in lifetime by the time of enrollment).

Participants will be assigned to one of two ever established IQOS user study groups:

- **Current established IQOS users:** Adult ever established IQOS users who report using IQOS in the past 30 days at time of assessment.
- **Former established IQOS users:** Adult ever established IQOS users who report not having used IQOS in the past 30 days at time of assessment.

10.2 Inclusion Criteria

Participants must satisfy the following criteria at the time of screening to be eligible for the study:

1. US resident.
2. 21 years of age or older.
3. Voluntarily consent to serve as a participant in the study by electronically acknowledging an Informed Consent Statement (ICS), with approval or exemption determined by a qualified Institutional Review Board (IRB).
4. Acknowledge willingness and ability to comply with all study requirements as listed in the ICS.
5. Meet criteria for inclusion as a current or former established IQOS user (see Section 10.1).

10.3 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible for the study:

1. Unable to read or understand English.
2. Is a current or former employee or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member who is a current or former employee of the tobacco or e-cigarette industry.
3. Is a current or former employee or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member who is a current or former employee of CRO.
4. Is or has a first-degree relative (e.g., parent, spouse, sibling, child) or household member involved in litigation (e.g., as a named party or class representative) with any company involved in the tobacco or e-cigarette industry.

Note. The size and composition of the study sample is contingent on product sales and growth in CLP registration each year. To account for this uncertainty and ensure sufficient representation of IQOS use behavior across waves, no initial restrictions will be placed on repeat participants. However, if the incidence of repeat observations across successive waves is high (e.g., > 5.0%; Agius et al., 2018), an exclusion criterion or cap may be implemented to ensure sample renewal and independence between waves.

11 STUDY PROCEDURES

11.1 Recruitment

Recruitment is expected to launch after IQOS reaches sufficient market saturation in the US to support a sample size capable of generating reliable estimates. It is anticipated that PMP will establish and maintain a CLP and requisite database which will contain age verified adult IQOS purchasers. Based on experience with similar international markets, the CLP is expected to enroll ≥ 80% of all adult IQOS users and is intended as the primary recruitment source for this study.

Commercialization of IQOS in the US is expected to be limited initially to selected US markets (e.g., one or two cities or states), with gradual market expansion to follow. Study sample size will be dependent on IQOS sales and CLP enrollment. To maximize sample size in the first study year, study invitations will likely be sent to all opt-in, adult IQOS purchasers in the CLP. Random sampling from the CLP database will likely be used in subsequent study years, with study invitations sent until a sufficient sample size is reached (see Section 13.1 for more details on target sample size). PMP may decide to close recruitment prior to meeting the target sample size. If the target sample size cannot be met, certain study outcomes may not be estimated with the expected precision (see Section 13.1 for more details on procedures for reporting small ns). The addition of supplemental recruitment channels, such as online commercial or research panels, may be considered in the future.

Study invitations with unique links to the Participant Screener will be emailed to adult IQOS users who have registered with the CLP and have opted-in to receive communications. Study invitations may also be sent via direct mail and/or text. To increase the likelihood of engagement, four survey completion reminders will be sent 3, 6, 9, and 14 days after the initial invitation. The survey reminder cadence may be adjusted based on experiences with participants at the time of recruitment and response rate(s). All adjustments will be documented in study reports.

11.2 Study Implementation and Timeline

A contract research organization (CRO) will conduct this study under the guidance of PMP. (b) (4) is expected to serve as the CRO for this study. Study invites with unique links will be sent by e-mail, direct mail, and/or text to potential participants registered in the IQOS CLP. Interested individuals who follow the study invitation link will be directed to complete the Participant Screener Survey. Participants will be provided instructions to contact (b) (4) should they have any questions about the study or trouble accessing the survey. Individuals who meet the study inclusion criteria (Section 10.2) and none of the exclusion criteria (Section 10.3) will be eligible for the study and be administered the Main Survey. All participants, regardless of recruitment or study invitation method, will complete the same computerized survey instruments online.

All eligible participants who complete the survey will receive a cash or cash equivalent incentive that will be documented in the ICS at an amount that is commensurate with the length and complexity of the survey.

Timing of Study Milestones

The timing of executing this cross-sectional study depends on the distribution and consumer uptake of IQOS in the US marketplace. As of this writing, IQOS is not commercialized in the US. Initial product launches will be limited to select US markets (e.g., one or two cities or states). Future US market expansion is planned to occur, but the pace and breadth of expansion may depend on learnings achieved from the early market launches.

With an expected response rate of 3.0% (based on previous execution of this study by Altria Client Services), a database of ≥ 30,000 contactable IQOS CLP registrants will be required to yield the target annual sample size of 1,000 ever established IQOS users.

We expect study recruitment will yield a higher proportion of current established IQOS users than former users given the novelty of the product in the US (n ≈ 900, Current Established; n ≈ 100, Former Established; see Section 13.1).

Given the target N and requisite target sampling frame, IQOS will likely need to be in multiple marketplaces beyond the initial product launch locations and/or in regional distribution in order to build the database to a level that will support the estimated target N. The study is expected to launch when the CLP database has reached a sufficient size to recruit the target annual number of participants. Table 1 below summarizes the expected timing of study milestones following study launch. Study events from Months 1-6 will be completed each year. Once launched, each annual wave will commence the same time each year. For example, if Year One data collection launches in October 2025, then Year Two data collection will begin in October 2026.

This study launch approach seeks to balance the desire for timely information with the uncertainties of IQOS presence in the marketplace upon which achieving sufficient sample sizes to generate stable and reliable estimates relies.

Table 1: Target Timing of Study Milestones – Adult IQOS User Postmarket Cross-Sectional Study in the U.S.

	Study Month					
Study Milestone	**1**	**2**	**3**	**4**	**5**	**6**
CLP sample extraction	✓					
Send study invitations and reminders (*if needed*)	✓	✓	✓			
Administer Screener |ICS|, Main Survey, and send study incentives	✓	✓	✓			
Data validation and database lock				✓		
Statistical analysis				✓	✓	
Final report						✓

CLP = Customer Loyalty Program; ICS = Informed Consent Statement

11.3 Adverse Health Event Reporting

Because this repeated study is observational by design and is conducted in a postmarket setting, adverse health event (AE) reporting will follow the Sponsor's already long-established post-market Safety Surveillance Procedures for spontaneously reported events (see additional details below).

Contact details for the study team (i.e., CRO/fieldwork vendor) will be provided in the study invitation and the ICS in the event participants have any general questions or concerns.

The study team will be trained on Safety Surveillance Procedures, and when a report of adverse health events is received, an individual Safety Reporting Form (SRF) will be completed, and a unique case number be assigned. All SRFs are pseudonymized and the link between the unique case number on the SRF and the participant study number will be maintained by the fieldwork provider and will not be shared with the Sponsor.

Electronic SRF forms will be sent to Sponsor Safety Surveillance Department within one business day of the first awareness:

Contact details for Sponsor:

E-mail: (b) (4)

Cc: (b) (4)

The minimum information to be collected in the SRF is as follows:

1. Unique case number (this must not be the participant study number), age and sex.
2. Product identification (e.g., product name).
3. Description of the health problem.
4. Date of record (e.g., date of call).

Day 0 is defined as the day of first awareness of an AE by the Sponsor employee or designee (e.g., interviewers or any study staff).

Study staff receiving information on a participant's AE will advise the participant to seek medical or professional help (as required) and advise the participant to stop using any tobacco product, including IQOS.

If during the review of the safety information received Product Safety Surveillance (PSS) Team identifies missing or inconsistent information, follow-up queries will be sent to the fieldwork provider to collect additional information or clarification as required.

A reconciliation process comparing the data reported by the fieldwork provider with the data processed and finalized in the safety database will be performed at the end of the study. PSS team will issue an AE Line Listing with all the AEs received and will send it to the fieldwork provider for reconciliation and confirmation that all AEs were appropriately collected and sent to PSS. The relevant reconciliation documentation will be filed according to Sponsor procedure.

If required, safety reporting to the IRB will be ensured by the study team designee within required timelines. The study team will send the evidence of submission to Sponsor PSS for documentation in the safety database. Submission of relevant safety cases to FDA will be ensured by Sponsor within required timelines.

11.4 Participant Discontinuation

Participants will be informed that their participation is completely voluntary, and that they may choose not to participate or to discontinue their participation at any time for any reason. Further, participants will be informed that they may refuse or discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. The number of adults 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 (i.e., 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 the study by the Sponsor.

11.5 Replacement of Participants

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

11.6 Termination of Study

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

12 DATA MANAGEMENT

12.1 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 or rationale will be provided for each correction.

12.2 Survey Response Database Lock

Following data collection and data quality evaluation each year, the survey response database will be locked, and data will no longer be subject to change.

12.3 Data Transfer of Study Results

Study data transfers will be sent to PMP, or their designee, electronically on a schedule and in a format mutually agreed upon by PMP, or their designee, and (b) (4). Data transferred to PMP will not include any participant personal identification information.

12.4 Data Handling

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

13 STATISTICAL METHODS

13.1 Determination of Sample Size

This study will evaluate some independent outcomes measures for each study group. To ensure an acceptable minimum N to generate reliable estimates, the former established IQOS user study group (an expected minority in study population) was used to generate the study target N.

In a previous version of this study conducted by Altria Client Services, the prevalence of former established IQOS users was approximately 6.0%. To facilitate sample size estimation, an expected prevalence of 10.0% was used. With an expected ever established user ratio of 9:1 current to former users, a total N size of 1,000 is needed to yield 100 former established users.

Table 2 summarizes former established user sample sizes with requisite increasing outcome proportions and 95% Confidence Intervals. Estimates are expected to be less precise for rare events (i.e., low study group prevalence). However, the prevalence of former established users is expected to naturally increase over time (i.e., become less rare) with subsequent increases in estimate precision for this study group.

Table 2: Former Established IQOS User Sample Size and Outcome Proportion 95% Confidence Intervals

N	Outcome Proportion									
	95% Confidence Interval									
	0.05	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.45**	**0.50**
100	.02, .11	.05, .18	.09, .24	.13, .29	.17, .35	.21, .40	.26, .45	.30, .50	.35, .55	.40, .60
150	.02, .10	.06, .16	.10, .22	.14, .27	.18, .33	.23, .38	.27, .43	.32, .48	.37, .53	.42, .58
200	.02, .09	.06, .15	.10, .21	.15, .26	.19, .32	.24, .37	.28, .42	.33, .47	.38, .52	.43, .57
250	.03, .09	.07, .14	.11, .20	.15, .26	.20, .31	.24, .36	.29, .41	.34, .46	.39, .51	.44, .56
300	.03, .08	.07, .14	.11, .20	.16, .25	.20, .30	.25, .36	.30, .41	.34, .46	.39, .51	.44, .56
500	.03, .07	.08, .13	.12, .18	.17, .24	.21, .29	.26, .34	.31, .39	.36, .44	.41, .50	.46, .55

The following standards will be implemented in reporting small study ns:

1. All non-zero counts less than 10 will be suppressed.
2. All rates or proportions derived from suppressed counts will also be suppressed.
3. When possible and appropriate, data will be aggregated to minimize the need for suppression.
4. Estimates with denominators less than 50 or having a relative standard error greater than 30.0% will be reported with a note of low statistical precision.

13.2 Data Analyses

This study is descriptive in nature. Categorical outcomes will be summarized using counts and percentages. Continuous outcomes will be summarized using means, standard deviations (SD), medians, first (Q1) and third quartile (Q3), minimum (Min) and maximum (Max). Ninety-five percent confidence intervals will also be calculated for percentages and means when applicable.

See Appendix 2: Statistical Analysis Plan (SAP) for specific details on intended statistical analyses and statistical software packages.

Deviations from the approved SAP will be reported in an amended SAP and in the study report.

13.3 Outcome Measures

13.3.1 Objective 1 – Describe sociodemographic and health-related characteristics of adult ever established IQOS users.

Participants' sociodemographic characteristics and select health-related information (see below) will be summarized for the overall sample and by study group. Sociodemographic characteristics and pregnancy status will be further summarized for current established IQOS users by menthol IQOS heated tobacco stick use.

Participants' sociodemographic characteristics will include age, sex, gender identity, sexual orientation, race, ethnicity, education, income, employment status, geographic region, marital status, and military/veteran status.

Participant health-related information will include:

- Pregnancy status,
- Ever told they had a chronic health condition(s) or comorbidity by a health care provider,
- Ever told they had a mental health condition by a health care provider, and
- Currently receiving treatment for a mental health condition.

13.3.2 Objective 2 – Characterize historical and current tobacco use patterns of adult ever established IQOS users.

Participants' historical and current tobacco use patterns will be characterized using the following outcome measures and endpoints:

a) Historical TNP use will be summarized as counts and percentages (n, %) for the overall sample and by study group:

   TNP use history prior to first trying IQOS:

   - Ever use of given TNP.
   - Met lifetime established use criterion of given TNP.
   - Used TNP in the 30 days prior to first trying IQOS.

   Historical TNP use at time of assessment:

   - Ever use of given TNP.
   - Met lifetime established use criterion of given TNP.

b) Current TNP use at time of assessment will be described as summary statistics for the overall sample, by study group, and by menthol IQOS heated tobacco use (where applicable):

   - Past 30-day use of given TNP will be described using count (n), and percentage (%).
   - Number of days used given TNP in the past 30 days will be described using Mean (M), Standard Deviation (SD), Median, first and third quartiles (Q1, Q3), Minimum (Min), and Maximum (Max).
   - Amount of product (IQOS heated tobacco sticks and cigarettes) used on days used in the past 30 days will be described using M, SD, Median, Q1, Q3, Min and Max.
   - Monthly average amount of product (IQOS heated tobacco sticks, cigarettes, and combined sticks and cigarettes) used per day described using M, SD, Median, Q1, Q3, Min and Max.
   - Current use (i.e., amount) of given TNP relative to use in the 30 days prior to first trying IQOS categorized as, and described using n (%):
     - Fewer TNP per day.
     - More TNP per day.
     - Same TNP amount per day.

- Use duration for IQOS described using M, SD, Median, Q1, Q3, Min and Max.
- Smoking duration described using M, SD, Median, Q1, Q3, Min and Max.
- Quit IQOS duration (among former established IQOS users):
  - Long-term.
  - Short-term.

c) IQOS heated tobacco sticks flavor(s) ever and currently used will be summarized using counts and percentages (n, %) for the overall sample and by study group (where applicable):
   - Flavor(s) ever tried.
   - First flavor ever tried.
   - Flavor currently using (among current established IQOS users).
   - Flavor currently most often used (among current established IQOS users).
   - Flavor most often used when used IQOS (among former established IQOS users).

d) Past 30-day exclusive, dual, or poly use will be measured using counts and percentages (n, %) for current established IQOS users overall and by current IQOS heated tobacco stick menthol use:
   - Exclusive: IQOS only.
   - Dual: IQOS plus one other tobacco product:
     - IQOS and one combustible tobacco product.
       - IQOS and cigarettes (also stratified by menthol cigarette use).
     - IQOS and one other non-combustible tobacco product.
   - Poly: IQOS plus two or more other tobacco products:
     - IQOS and at least one combustible tobacco product.
       - IQOS, cigarettes, and one or more other tobacco products (overall and stratified by menthol cigarette use).
     - IQOS and two or more other non-combustible products (i.e., participant's reporting poly-tobacco use does not include any combustible tobacco products).

e) IQOS Dependence among current established IQOS users will be summarized using FTND scale score (M, SD, Median, Q1, Q3, Min and Max) for current established

IQOS users overall and by established smoking status (never smoker, current or former).

f) Use of IQOS not as intended will be summarized using counts and percentages (n, %) for the overall sample and by study group:

- Ever lit an IQOS heated tobacco stick like a cigarette.
- Ever used an IQOS heated tobacco stick not with an IQOS device.
- Ever used an IQOS device with a product other than IQOS heated tobacco stick.
- Overall, ever use of IQOS not as intended (i.e., endorsing any of the above three behaviors).

Frequency ("Only once," "Sometimes," "Most of the time," or "All the time") for each endorsed use of IQOS not as intended behavior will also be summarized using counts and percentages (n, %).

g) Cigarette smoking status will be summarized as counts and percentages (n, %) for the overall sample, by study group, and current established IQOS user by menthol IQOS heated tobacco stick use:
   - Never smoker.
   - Current smoker (overall and stratified by current menthol cigarette use).
     - Current established smoker.
   - Former smoker (overall and stratified by former menthol cigarette use).

h) Cigarette Dependence among current established smokers will be summarized using FTND scale score (M, SD, Median, Q1, Q3, Min and Max) for each study group.

13.3.3 Objective 3 – Assess adult ever established IQOS users' health risk perceptions related to IQOS use, cigarette smoking, and complete smoking cessation.

a) Participant health risk perceptions related to IQOS use, cigarette smoking, and complete smoking cessation will be summarized using the ABOUT scale score categories (n, %) for the overall sample, current established IQOS users who are current cigarette smokers, current established IQOS users who are long-term former smokers, and former established IQOS users.

b) In addition to health risk perceptions, participants' perceptions of harmful or potentially harmful chemical (HPHC) exposure ("More," "Same," "Less," "No," or "Don't know") following switching from cigarettes to IQOS will be summarized using counts and percentages (n, %) for the overall sample and by study group.

Understanding of what smokers must do to reduce HPHC exposure based on closed option categories will be captured for participants who perceive that those switching from cigarettes to IQOS would have less exposure to HPHC and will be summarized using counts and percentages (n, %).

13.3.4 Objective 4 – Characterize IQOS use and other tobacco use patterns, including: product initiation, complete switching to IQOS, transitions to (never smokers) and back (former smokers) to cigarette smoking, and quitting behaviors relevant to IQOS use.

a) Product initiation will be summarized using counts and percentages (n, %) for the overall sample, by study group, and study group by menthol IQOS heated tobacco stick use:

- IQOS as first TNP ever tried.
- IQOS as first TNP ever used on a consistent basis.
- First tried IQOS after not smoking for ≥12 months (overall and stratified by former menthol cigarette use).
- First tried IQOS after not using any TNP for ≥12 months.

b) Complete Switching to IQOS will be summarized using counts and percentages (n, %) for current established IQOS users overall and by current menthol IQOS heated tobacco stick use:

- Complete switching from cigarettes to IQOS (overall and stratified by former menthol cigarette use).
- Complete switching from all tobacco products to IQOS.

c) Complete switching from IQOS to cigarette smoking will be summarized using counts and percentages (n, %) for the sample overall and stratified by current menthol cigarette use.

d) Transitions to cigarette smoking after first trying IQOS will be summarized using counts and percentages (n, %) for the overall sample, by study group, and study group by menthol IQOS heated tobacco stick use:

- Relapse to cigarette smoking (overall and stratified by current menthol cigarette use).
- Re-initiation of cigarette smoking (overall and stratified by current menthol cigarette use).
- Initiation of established cigarette smoking (overall and stratified by current menthol cigarette use).

e) Quitting behaviors will be summarized using count and percentage (n, %) for the overall sample, by study group, and study group by menthol IQOS heated tobacco stick use:

- Current Established Smokers:
  - Past 12-month quit attempt.
  - Motivation to Stop Smoking (MTSS) scale response (1-7; with higher scores indicating higher motivation).
- Ever established smokers who completely quit smoking cigarettes after first trying IQOS (overall and stratified by quit duration).
- Ever established TNP users who completely quit all tobacco products after first trying IQOS (overall and stratified by quit duration; former established IQOS users only).

f) Last tobacco cessation treatment use will be summarized using counts and percentages (n, %) by study group, as well as summarized independently for current established IQOS users who completely switched from cigarettes to IQOS and for those who switched from all tobacco to IQOS.

13.4 Additional Data Summaries

Participation. Participation numbers and response rates will be summarized, including:

- *Survey Invitations*: the number of persons screened for eligibility.
- *Eligibility proportion*: the number of persons eligible for enrollment (i.e., persons who meet all inclusion criteria and no exclusion criteria); and
- *Completion proportion*: the number of completed interviews.

13.5 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 follows: 1) verbatim responses that were provided as an "other" response, but fit into one of the pre-listed responses will be "up-coded;" 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., 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."

14 ETHICAL, REGULATORY AND LEGAL CONSIDERATIONS

14.1 Institutional Review Board (IRB)

This study does not involve an 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 (ICS) or determine that the study is exempt.

Before study initiation and if the IRB does not determine that the study is exempt from its review, (b) (4) study staff must have written and dated approval from the IRB for the protocol and 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. PMP 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.

14.2 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; Hoffman et al., 2019), Council of American Survey Research Organization's (CASRO) Code of Standards and Ethics (CASRO, 2016), and the International Chamber of Commerce (ICC) / European Society for Opinion and Marketing Research's (ESOMAR) International Code on Market and Social Research (ICC / ESOMAR, 2016). Freely given informed consent will be obtained from every participant. For further details on informed consent, see Section 14.3. 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).

14.3 Informed Consent Procedures

Study staff will have the final protocol, questionnaires, and ICS prior to running the study. Participants will have as much time as they need to review the ICS and will electronically consent to participate in the study by clicking a box next to the word "Agree" at the end of 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 is provided to participants as soon as practicable). PMP, or CRO on PMP's behalf, 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.

14.4 Confidentiality

The study staff affirms to PMP that information furnished to the study staff by PMP 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 PMP (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.

14.5 Debriefing

This is a naturalistic observational study conducted entirely online. Participants will not be provided any products or interventions. While not required given the nature of the study, a short study debrief will be provided at survey end:

"Thank you for your time to complete this survey.

We would like to emphasize that in conducting this research study, we were not trying to market, sell, or promote any tobacco or nicotine-containing product to you.

Nicotine is addictive. No amount of tobacco or nicotine-containing product use is safe.

For more information on the harms and risks associated with tobacco and nicotine-containing product use visit https://therealcost.betobaccofree.hhs.gov.

It can be very difficult to quit using tobacco or nicotine-containing products altogether, but this fact should not deter those who smoke or use tobacco or nicotine-containing products.

For information on quitting tobacco or nicotine-containing products visit https://smokefree.gov".

15 ADMINISTRATIVE CONSIDERATIONS

This study is sponsored by PMP. (b) (4) will be contracted to conduct the study on behalf of PMP.

Sponsor
Philip Morris Products S.A.
Avenue de Rhodanie 50
1007 Lausanne, Switzerland

Contract Research Organization

(b) (4)

15.1 Protocol Compliance and Amendments

Study procedures will not be changed without the agreement of the Sponsor. Any amendments, new versions, or administrative changes must be approved by the Sponsor. Any sponsor-approved amendments will be documented and will be submitted to the IRB and to the FDA when appropriate. Protocol amendments will be implemented in fieldwork only after IRB approval.

Representatives of PMP will periodically assess data quality and study integrity. This will be accomplished through telephone and e-mail exchanges with (b) (4) which will be carried out on an ongoing basis throughout study planning, execution, and reporting.

15.2 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.

(b) (4) 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.

PMP will maintain documentation relating to the study including an electronic copy of the anonymized dataset according to PMP's internal standard procedures and/or for at least 15 years after the study report has been finalized.

15.3 Study Reports

(b) (4) 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 PMP. (b) (4) will also provide PMP a draft and final study report summarizing all study data and providing the results of all analyses.

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