POSTMARKET ADULT IQOS CONSUMER COHORT STUDY (US ADULT COH) IN THE UNITED STATES (PMSS-COH-01-US)

Study Protocol

Study Title:	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Protocol Number:	PMSS-COH-01-US
Product Name:	*IQOS*
Sponsor:	Philip Morris Products S.A. Avenue de Rhodanie 50 1007 Lausanne Switzerland
Version Number:	1.0
Amendment Number:	NA
Version Date :	May 13, 2024
Authors:	Jessica Seifert, Philip Morris Products S.A. Emery Ngamasana, Philip Morris Products S.A.

PRINCIPAL INVESTIGATOR`S SIGNATURE

Study Title:	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Study Identifier:	PMSS-COH-01-US
Version Number:	1.0
Version Date:	May 13, 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.

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:	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Study Identifier:	PMSS-COH-01-US
Version Number:	1.0
Version Date:	May 13, 2024

This Study Protocol was subject to critical review and has been approved by the Sponsor. The following signatories approved this protocol:

Authors:

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

Emery Ngamasana, MSc *Manager Regulatory Consumer Research*	Please refer to electronic signature
Philip Morris Products S.A., Washington, D.C., USA	

Approvers

Pierpaolo Magnani, PhD *Global Head of Regulatory Insights*	Please refer to electronic signature
Philip Morris Products S.A., Lausanne, Switzerland	

THIRD PARTIES PERSONNEL SIGNATURES

Study Title:	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Study Identifier:	PMSS-COH-01-US
Version Number:	1.0
Version Date:	May 13, 2024

The following third-party personnel contributed to writing and approving this protocol:

Authors

NA

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	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Study Identifier	PMSS-COH-01-US
Planned Study Period	The study will launch approximately two years following product launch in the United States to ensure a sufficient sample. The longitudinal cohort will be followed for 24 months.
Study Research Partner	To be contracted.
Study Purpose	The purpose of the Postmarket Adult IQOS Consumer Cohort Study in the US is to provide real-world data evaluating longitudinal tobacco or nicotine product (TNP) use behaviors and transitions, as well as health-related risk perceptions and outcomes among adult current established IQOS users relative to adult current established smokers.
Study Objectives	To conduct the following among US adult current established IQOS users and current established smokers over time: 1. Characterize TNP use behaviors (e.g., past 30-day use, dual product use). 2. Describe behavioral transitions, including: product use initiation, complete switching from cigarettes or other TNP to IQOS, transitioning to (never smokers) or back to cigarettes (former smokers) to cigarettes, and quitting. 3. Assess self-reported health-related quality of life, signs and symptoms by product use. 4. Assess relative risk perceptions related to IQOS and cigarettes. 5. Assess perception of nicotine harmfulness in IQOS and cigarettes.
Study Design	This prospective longitudinal study will follow a cohort of US adult (≥21 years) current established IQOS users and current established smokers over a 24-month observational period. One baseline survey and five follow-up surveys (month 3, 6, 12, 18, & 24) will be administered to eligible participants via online surveys. Study surveys will take a modular approach to minimize survey length and time to complete. The baseline survey and five follow-up surveys will include measures grouped in the following modules: ▪ Sociodemographic characteristics – baseline only ▪ TNP use behaviors – baseline and all follow ups ▪ Quitting behaviors – baseline and all follow ups ▪ Risk perceptions – baseline and follow up months 12 & 24 ▪ Perceived exposure to harmful or potentially harmful constituents – baseline and all follow ups ▪ Product dependence – baseline and all follow ups ▪ Conditions and diagnoses – baseline and follow up months 12 & 24

	▪ Quality of Life – baseline and all follow ups • Signs and Symptoms – baseline and all follow ups
Study Population	Participants will belong to one of two study groups: Current established IQOS users will be defined as adult IQOS users who report at baseline: 1) Having met the lifetime established use criterion for IQOS heated tobacco sticks (i.e., 100 or more lifetime sticks), AND 2) Having used IQOS in the past 30 days at baseline, AND 3) Having used IQOS for six or fewer months (regardless of other TNP use). Current established smokers will be defined as adult cigarette smokers who report at baseline: 1) Having met the lifetime established use criterion for cigarettes (i.e., 100 or more), AND 2) Having smoked cigarettes in the past 30 days at baseline (regardless of other TNP use), AND 3) Have never tried IQOS.
Inclusion Criteria	Participants must satisfy the following criteria at the time of screening to be eligible for the study: 1. US resident 21 years of age and older. 2. Voluntarily consent to serve as a participant in the study by digitally signing an Informed Consent Statement (ICS) approved or given an exempt determination by a qualified Institutional Review Board (IRB). 3. Acknowledge willingness and ability to comply with all study requirements. 4. Meet criteria for inclusion in study groups (see Section 10.1).
Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in 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 a market research or other company involved in the conduct of the research. 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	Sample Recruitment Recruitment will occur in the United States when the estimated number of established IQOS users is sufficient to support the study. This study will leverage two recruitment sources: 1) US Customer Loyalty Program (CLP) database to recruit current established IQOS users and 2)

	commercial, online panels to recruit current established smokers from geographies where IQOS is sold. Current established IQOS users will be recruited from PMP's repeated, online, cross-sectional study (US Adult PMX Study). Study invitations for the US Adult PMX Study will be sent to adult IQOS purchasers who have registered their device in the CLP and opted in to receive communications from PMP. Study invitations for this study will be administered at the end of the US Adult PMX Study to individuals who meet the current established IQOS user cohort study group criteria. If the current established IQOS user group sample targets cannot be met through the US Adult PMX, then additional participants will be recruited from the CLP database. Current established smokers will be recruited from multiple online consumer panel companies to increase the likelihood of achieving a diverse sample and completing screening in a timely manner. Online survey panel companies use a variety of methods to recruit members, including by not limited to face-to-face, social media, classified newspaper advertisements, and referral programs. Panelists will be sent email invitation to participant in this study. <u>Sample Size and Power Considerations</u> A sample size of $n = 2{,}100$ participants will be recruited for the current established IQOS user group and $n = 2{,}100$ for the current established smoker group. The sample size and the study duration were designed to be sufficient to detect differences in quitting cigarette smoking between the study groups while accounting for differences in quitting between menthol and non-menthol IQOS heated tobacco stick use, potential loss of power with propensity score weighting, and lost to follow up.
Objectives and Outcome Measures	**Objective 1 – Characterize tobacco or nicotine product (TNP) use behaviors.** a) At baseline, participants' TNP use before first trying IQOS, specifically: ▪ Having never used any TNP ▪ Long-term former established tobacco use ▪ Current established smoking ▪ Other current established TNP use b) Past 30-day exclusive, dual, or poly use at follow-up months 3,6,12,18, and 24: ▪ Exclusive: IQOS only. ▪ Exclusive: Cigarettes only. ▪ Dual: IQOS plus one other TNP: ▪ IQOS and one combustible TNP. ▪ IQOS and cigarettes. ▪ IQOS and one other non-combustible TNP. ▪ Poly: IQOS plus two or more other TNP: ▪ IQOS and at least one combustible TNP. ▪ IQOS, cigarettes, and one or more other TNP. ▪ IQOS and two or more other non-combustible TNP (i.e., participants reporting poly-tobacco use does not include any combustible TNP). c) Mean number of days used IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24. d) Mean number of days smoked cigarettes at baseline and follow-up months 3, 6, 12, 18, and 24.

	e) Mean number of IQOS heated tobacco sticks used per day at baseline (Current established IQOS users only) and at follow-up months 3, 6, 12, 18, and 24. f) Mean number of cigarettes smoked per day at baseline and at follow-up months 3, 6, 12, 18, and 24 months (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only). g) Mean number of IQOS heated tobacco sticks used and cigarettes smoked per day at baseline and follow-up months 3, 6, 12, 18, and 24 months (Current established IQOS users reporting dual IQOS and cigarette use at baseline and Current established smokers reporting dual IQOS and cigarette use at follow ups). h) Percent change in cigarettes smoked per day from baseline for follow-up months 3, 6, 12 ,18, and 24 (Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only): a. Reduced cigarettes smoked per day by ≥50% b. Increased cigarettes smoked per day by ≥50% c. Maintained cigarettes smoker per day (i.e., change < ±50%) i) Prevalence of current established smoking at baseline and at follow-up months 3, 6, 12, 18, and 24. j) Mean score of the FTND for IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24. k) Mean score of the FTND for cigarettes at baseline (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette use at baseline) and follow-up months 3, 6, 12, 18, and 24. **Objective 2 – Describe behavioral transitions, including: product use initiation, completely switching from cigarettes to other TNP or to IQOS, transitioning to (never smokers) or back (former smokers) to cigarettes, and quitting.** a) Product initiation: ▪ Ever use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24. ▪ Established use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24. b) Complete switching to IQOS (i.e., baseline current established smokers from either study group reporting current established IQOS use and no past 30-day smoking at follow up) at follow-up months 3, 6, 12, 18, and 24. c) Complete switching from IQOS to cigarette smoking (i.e., current established IQOS users reporting current established smoking and no past 30-day IQOS use at follow up) at follow-up months 3, 6, 12, 18, and 24. d) Follow up behavioral transitions among current established IQOS users who report dual IQOS and cigarette use at baseline for follow-up months 3, 6, 12, 18, and 24: ▪ Exclusive IQOS use ▪ Exclusive cigarette smoking ▪ Dual IQOS and cigarette use ▪ No past 30-day IQOS use or cigarette smoking (regardless of other TNP use). e) Transition to cigarette smoking at follow-up months 3, 6, 12, 18, and 24 months:

	▪ Relapse to cigarette smoking among baseline current established IQOS users who report short-term former established smoking at baseline. ▪ Re-initiation of cigarette smoking among baseline current established IQOS users who report long-term former established smoking at baseline. f) Quitting behaviors: ▪ Quit smoking after first trying IOQS – Baseline current established IQOS users who report former established smoking at baseline who smoked in the 30-days prior to first trying IQOS. ▪ Quit attempts in the past 12 months – Baseline current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers who attempted a quit attempt in the 12 months prior to baseline. ▪ Use of cessation treatment at baseline and follow-up months 3, 6, 12, 18, and 24. ▪ Completely quit smoking cigarettes at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers). ▪ Completely quit IQOS use at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users). ▪ Complete quit all TNP at follow-up months 3, 6, 12, 18, and 24. **Objective 3 – Assess self-reported health-related quality of life, signs, and symptoms by product use.** a) Mean physical health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24. b) Mean mental health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24. c) Change in mean physical health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS. d) Change in mean mental health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS. e) Difference in mean physical health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24. f) Difference in mean mental health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24. g) Mean number of cardiovascular symptoms at baseline and follow-up months 3, 6, 12, 18, and 24. h) Mean number of respiratory symptoms at baseline and follow-up months 3, 6, 12, 18, and 24. i) Change in mean number of cardiovascular symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS. j) Change in mean number of respiratory symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS. k) Difference in mean number of cardiovascular symptoms between study groups at follow-up months 3, 6, 12, 18, and 24.

	l) Difference in mean number of respiratory symptoms between study groups at follow-up months 3, 6, 12, 18, and 24. **Objective 4 – Assess risk perceptions related to IQOS and cigarettes.** a) Percent and count (n, %) of participants in each category of the ABOUT™ scale assessing risk perception related to IQOS use, cigarette smoking, and complete smoking cessation at baseline and follow-up months 12 and 24. b) Percent distribution of perceived harmful or potentially harmful chemical (HPHC) exposure following switching from cigarettes to IQOS ("More", "Same", "Less", "No", or "Don't know") at follow-up months 3, 6, 12, 18, and 24. c) Percent distribution of the understanding of what smokers must do to reduce HPHC exposure among participants who perceive reduced ("Less") HPHC exposure following switching from cigarettes to IQOS at follow-up months 3, 6, 12, 18, and 24.
Data Analysis	The US Adult COH is observational, from which comparisons will be made within and between the baseline current established IQOS user and baseline current established smoker groups across time. Descriptive analyses will include an assessment of participant sociodemographic characteristics and outcome measures. Participation proportions including contact proportion, response proportion, eligibility proportion, and completion proportion will be summarized. Descriptive statistics will be reported for all study groups, including summaries of sample sizes, central tendency measures (e.g., means, median), and variability measures (e.g., standard deviation, range). Additionally, 95% confidence intervals will be reported. A series of generalized linear models (e.g., Generalized estimating equations (GEE) log-binomial regression, GEE Poisson regression) will be employed to address research objectives. Specific details on intended statistical analyses and statistical software packages are described in the Statistical Analysis Plan (SAP).

2 TABLE OF CONTENTS

3 LIST OF TABLES

4 LIST OF APPENDICES

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 nicotine vapor product
ESOMAR	European Society for Opinion and Marketing Research
FDA	United States Food and Drug Administration
FDCA	United States Food, Drug and Cosmetic Act
FTND	Fagerström Test of Nicotine Dependence
GEE	Generalized estimating equation
GEP	Good Epidemiological Practice
HPHC	Harmful or potentially harmful constituents
HRQOL	Health-Related Quality of Life
ICC	International Chamber of Commerce
ICS	Informed Consent Statement
IQOS	IQOS Heating System and IQOS heated tobacco sticks
IRB	Institutional Review Board
M	Mean
Max	Maximum value
Min	Minimum value

MRTP	Modified Risk Tobacco Product
MTSS	Motivation To Stop Smoking
PATH	Population Assessment of Tobacco and Health
PMP S.A.	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
SRF	Safety Reporting Form
TNP	Tobacco or Nicotine Product
US	United States
US Adult PMX	Adult IQOS User Postmarket Cross-sectional Study in the United States
US Adult COH	Postmarket Adult IQOS Consumer Cohort Study in the 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 current tobacco product use (i.e., past 30-day use) and meets the lifetime criterion for that TNP (i.e., established use). Unless otherwise specified, IQOS refers to IQOS 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 and *current established* use of a different TNP at follow-up. Outcomes related to complete switching in this study include:

1. **Complete switching from cigarettes to IQOS** – Baseline current established smokers who, at a future follow-up survey, report current established IQOS use and no past 30-day smoking.
2. **Complete switching from IQOS to cigarettes** – Baseline current established IQOS users who, at a future survey, report current established smoking and no past 30-day IQOS use.

Consistent Basis
Consistent basis refers to 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 IQOS User
Participants will be assigned to the Current Established IQOS User study group if they report the following at Baseline:

1. Having met the *lifetime use criterion* for IQOS (i.e., 100 or more lifetime IQOS heated tobacco sticks),
2. Having used IQOS for a period of 6 months or less (regardless of any other TNP use), AND
3. Having used IQOS during the past 30 days.

Current Established Smoker
Participants will be assigned to the Current Established Smoker study group if they report the following at Baseline:

1. Having never used IQOS, not even once,
2. Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more lifetime cigarettes), AND
3. Having smoked cigarettes in the past 30 days (irrespective of use of any other tobacco product).

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 a given TNP in the past 30 days at time of assessment – irrespective of whether the lifetime established use criterion was met.

Ever Established Tobacco or Nicotine Product Use
Ever established TNP use refers to meeting the *lifetime established use criterion* (see definitions below) for a given TNP.

Ever Tobacco or Nicotine Product Use
Ever TNP use refers to reporting "Yes" to "Have you ever [used / smoked] [TNP] even one time?" – irrespective of whether the lifetime established use criterion was met.

Former Established Tobacco or Nicotine Product Use
Former established TNP use will be defined as reporting:

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

Former Tobacco or Nicotine Product Use
Former TNP use refers to reporting:

1. Having *ever used* a given TNP, AND,
2. Not having used the given TNP in the past 30 days.

Irrespective of whether the lifetime established use criterion was met.

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

- Ever use (even one time) of a TNP never used at baseline, OR
- Ever established use of a TNP never used at baseline.

Lifetime Established Use Criterion

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

1. Cigarettes: as reporting having ever smoked 100 or more cigarettes.
2. IQOS: as reporting having ever used 100 or more heated tobacco sticks.
3. Cigars (including regular cigars, cigarillos, or little filtered cigars): as reporting having ever used 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 per product.
5. Regular pipe: as reporting having ever smoked 50 bowls or more.
6. Traditional hookah: as reporting having ever smoked tobacco in a hookah on a "*consistent basis."*
7. Electronic cigarettes (e-cigarettes) and other e-vapor products: as reporting having ever vaped e-cigarettes on a *"consistent basis."*
8. Oral nicotine pouches: as reporting having ever 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:

> **Short-term TNP quitter** will be defined as reporting not having used given established TNP for less than 12 months.
>
> **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 refers to 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 refers to 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
Re-initiation of cigarette smoking refers to reporting at time of assessment:

1. Having not smoked cigarettes for 12 months or longer,
2. Having met the *lifetime established use criterion* for cigarettes, AND
3. Past 30-day cigarette smoking.

Relapse to Cigarette Smoking

Relapse to cigarette smoking refers to reporting:

1. Having not smoked cigarettes for less than 12 months,
2. Having met the *lifetime established use criterion* for cigarettes, AND
3. Past 30-day cigarette smoking.

Tobacco or Nicotine Products

Tobacco or nicotine products 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 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 US IQOS Customer Loyalty Program (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 Heating System and IQOS tobacco sticks (formerly "Marlboro HeatSticks") as modified risk tobacco products. The IQOS 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 (Food and Drug Administration [FDA], 2020).

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.

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, Postmarket Adult IQOS Consumer Cohort Study in the US (US Adult COH), is one such study.

[1] *Note.* Prior to April 2024, Altria Client Services LLC 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 Postmarket Adult IQOS Consumer Cohort Study in the US (US Adult COH) is to provide real-world data evaluating longitudinal tobacco or nicotine product (TNP) use behaviors and transitions, as well as health-related risk perceptions and outcomes among adult current established IQOS users relative to adult current established smokers.

8.2 Objectives

The objectives of this study are to conduct the following among US adult current established IQOS users and current established smokers over time:

1. Characterize tobacco or nicotine product (TNP) use behaviors (e.g., past 30-day use, dual product use).
2. Describe behavioral transitions, including product use initiation, complete switching from cigarettes or other TNP to IQOS, transitioning to (never smokers) or back (former smokers) to cigarettes, and quitting.
3. Assess self-reported health-related quality of life, signs, and symptoms by product use.
4. Assess relative risk perceptions related to IQOS and cigarettes.
5. Assess perception of nicotine harmfulness in IQOS and cigarettes.

9 STUDY DESIGN

9.1 Overview

This prospective longitudinal study will follow a cohort of US adult (≥21 years) current established IQOS users (i.e., meets IQOS lifetime use criterion and reports past 30-day IQOS use at Baseline) and current established smokers (i.e., meets cigarette lifetime use criterion and reports past 30-day smoking, and never used IQOS at Baseline) over a 24-month observational period.

This study intends to recruit adult current established IQOS users from the annual Adult IQOS Use Postmarket Cross-sectional Study (US Adult PMX; see PMSS-PMX-01-US for more details). We intend to conduct US Adult COH in geographies in concert with the second annual US Adult PMX, which we anticipate being approximately two years after IQOS is launched into the US marketplace. By this time, we assume IQOS to be in distribution in diverse geographies and used among a consumer base large enough to facilitate recruitment of participants that meet the study inclusion criteria. Participants in the US Adult PMX will be invited to participate in the US Adult COH if they meet criteria for the current established IQOS user study group. Current established smokers will be recruited via online panels.

After agreeing to participate in the study, potential participants will complete the Participant Screener Survey (Appendix 1) to determine their eligibility for the study. Age verification is a prerequisite for registration in the US IQOS Customer Loyalty Program (CLP) – the sampling frame for US Adult PMX – so eligible current established IQOS users recruited for this study via the US Adult PMX will not require additional age verification. Current established IQOS users not recruited via the US Adult PMX and current established smokers will be age verified during screening.

Eligible participants who agree to participate will be asked to complete the baseline survey (Appendix 1)[2]. Participants will have 7 days to complete the baseline survey. Follow up surveys (Appendix 2) will be administered at months 3, 6, 12, 18, and 24. The study length was selected to enable the ability to detect changes in behaviors and health over time. A 3- and 6-month interval is a sufficient timeframe for measuring changes in tobacco use behaviors (Mantey et al., 2017; McKeganey et al., 2018; O'Connor et al., 2005; O'Connor et al., 2012; Pulvers et al., 2018; Pulvers et al., 2015). The initial 3-month follow-up and subsequent 3-month follow-up (6 months post-baseline) will provide more opportunity to detect changes in early tobacco use behavior for new IQOS users. Detecting changes in some clinical and self-reported health status was seen in studies with a harm reduction focus within 6 months in one study (Campagna et al., 2016) and within a year or less in other studies (Cibella et al., 2016; Farsalinos et al., 2014; Polosa et al., 2014; Polosa et al., 2016). Thus, we selected a 24-month study period with follow-up at 3 months for the first 6 months then every 6 months thereafter.

The survey will take a modular approach to minimize survey length and time to complete. For example, diagnoses will be asked yearly. Checklist items will be randomized. Skip logic will

[2] After completion of the US Adult PMX main survey, all eligible current established IQOS user cohort participants will be asked to complete the following survey modules: Quality of Life, Signs and Symptoms, and Diagnoses. See Section 9.3 for additional details.

be incorporated into surveys to reduce participant burden. The baseline and five follow-up surveys will include measures grouped in the following modules:

- Sociodemographic and health-related characteristics.
- Tobacco or nicotine product (TNP) use behaviors.
- Quitting behaviors.
- Risk perceptions.
- Perception and understanding of IQOS and harmful or potentially harmful constituent (HPHC) exposure reduction.
- Product dependence (IQOS and cigarettes).
- Conditions and diagnoses.
- Health-related quality of life (HRQOL).
- Signs and symptoms.

Participants will complete all surveys online and will receive e-mail invitations and reminders to complete each survey. Participants will have a 14-day window to complete each follow-up survey and will receive reminders to do so up to/until they complete the survey. Participants will receive compensation for each survey that they complete. If a participant misses a survey, they will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule. Participants who complete all six study surveys (baseline through month 24) will be eligible for a small bonus incentive.

9.2 Study Stimuli

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

9.3 Study Surveys

Survey items were selected to address the objectives of this study. Wherever feasible, survey items capturing TNP use 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, 2014) [National Health Interview Survey]; (Substance Abuse and Mental Health Services Administration [SAMHSA], 2017) [National Survey on Drug Use and Health]). Furthermore, Altria Client Services LLC commissioned cognitive testing of the study instrument in early 2020 and updated survey items based on the findings.

9.3.1 Survey Module Overview

9.3.1.1 *Sociodemographic and Health-Related Characteristics Module*

The baseline survey will capture participants' sociodemographic and health-related characteristics, including:

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

9.3.1.2 Tobacco or Nicotine Product Use Behaviors Module

Survey items will capture participants historical (e.g., ever use) and current (e.g., past 30-day use) IQOS and other TNP use, including:

- Ever use of a given TNP (even one time).
- Lifetime use of a given TNP.
- Past 30-day use of a given TNP.
- Number of days of used a given TNP in the past 30 days.
- Amount of product used on days used in the past 30 days (IQOS, cigarettes, and e-cigarettes).
- IQOS heated tobacco stick flavor(s) ever used, currently using, and used most often used.
- Menthol use (current and former smokers only)
- Types of TNP completely quit.

9.3.1.3 Quitting Behaviors Module

Current Established Smokers' will be asked to provide the number of previous quit attempts they have made at time of assessment. Their motivation to stop smoking will be measured using the Motivation To Stop Smoking (MTSS) scale (Kotz et al., 2013). MTSS responses include the following seven items:

- "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 score on the MTSS scale indicate higher motivation to stop smoking cigarettes.

Use of tobacco cessation treatment will be captured for all participants as: Never; past 30 days; >30 days to 12 months; > 12 months at baseline; and past 30 days and > past 30 days at last assessment for each follow-up survey.

9.3.1.4 Risk Perceptions Module

At baseline, 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 for the assessment of health risk perceptions for different types of tobacco products and various levels of smoking status. In addition, given the prevailing misconceptions about the role of nicotine in relation to cancer and other tobacco-related diseases, the study also outsourced two questions from the PATH adult study on the perception of perception of harmfulness of nicotine in cigarettes compared to nicotine in IQOS (Westat, 2023).

9.3.1.5 IQOS and HPHC Exposure Reduction Module

Participants' perception and understanding of IQOS and exposure reduction will also be assessed, specifically:

- 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.

9.3.1.6 Product Dependence Module

Tobacco dependence for IQOS and cigarettes will be measured using the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1989). 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 & Beebe, 2017; Piper et al., 2020; Sharma et al., 2021).

9.3.1.7 Cardiovascular Diseases, Diabetes, Respiratory Diseases, Malignancy, and Mental Health Diagnoses Module

A set of diagnoses were selected that relate to TNP use and could impact health and tobacco use behaviors (U.S. Department of Health and Human Services [DHHS], 2020). Survey items were sourced from national surveys (e.g., Behavioral Risk Factor Surveillance System, National Health Information Survey, National Survey on Drug Use and Health), and include the following diagnoses:

- Cardiovascular disease diagnoses
  - Myocardial infarction
  - Stroke
  - Angina
  - Coronary heart disease
  - Congestive heart failure
  - Hyperlipidemia
  - Hypertension
  - Other cardiovascular diseases
- Diabetes diagnosis
- Respiratory disease diagnoses
  - Chronic obstructive pulmonary disorder (COPD)
  - Asthma
  - Chronic bronchitis
  - Emphysema
  - Apnea
  - Other respiratory diseases
- Malignancy diagnoses
- Mental illness
  - Diagnoses
  - Taking medicine or receiving treatment

9.3.1.8 Health-Related Quality of Life, Signs, and Symptoms Modules

Health-Related Quality of Life (HRQOL) is a multidimensional concept that includes positive and negative aspects of life as well as physical health, and measures of physical, social, and psychological functioning that directly relate to health (World Health Organization [WHO], 1998). HRQOL has been shown in literature to be correlated with health outcomes including cardiovascular and respiratory diseases. HRQOL will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS©) Global Health short form. The PROMIS© Global Health was designed to measure patient-reported outcomes related to physical, mental, and overall health using a 10-item bank. The HRQOL, signs, and symptoms module will include:

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

9.3.2 Baseline and Follow-up Survey Modules

The longitudinal cohort study will take place over a total duration of two years with six follow-up surveys administered at months 3, 6, 12, 18, and 24. The study modules at each study phase are summarized in Table 1.

Table 1. Survey Module Administration Schedule for Baseline and All Follow Up Survey Months (3, 6, 12, 18, and 24)

Survey Module	Baseline	Follow Up Month				
		3	6	12	18	24
Sociodemographic	✓					
TNP Use Behaviors	✓	✓	✓	✓	✓	✓
Quitting Behaviors	✓	✓	✓	✓	✓	✓
Risk Perceptions	✓			✓		✓
Perceived Exposure to HPHCs	✓	✓	✓	✓	✓	✓
Product Dependence	✓	✓	✓	✓	✓	✓
Conditions & Diagnoses	✓			✓		✓
Quality of Life	✓	✓	✓	✓	✓	✓
Signs & Symptoms	✓	✓	✓	✓	✓	✓

TNP = Tobacco or nicotine product; HPHC = Harmful or potentially harmful constituents
Note. Check marks indicate inclusion of survey module in survey.

9.4 Study Duration

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

9.5 Length of Participation

Participants will respond to surveys for a 24-month period. Each survey will take approximately 15 – 25 minutes to complete. Completion times will vary depending on tobacco product use, health conditions reported, and number of modules within the survey. Participants that report trying multiple tobacco products, use IQOS, or have more health conditions are expected to require more time, on average. Current established IQOS user study group participants are expected to require more time than current established smoker study group participants, on average, because they will be asked additional questions pertaining to IQOS heated tobacco stick flavor(s) used.

9.6 Study Strengths and Limitations

The longitudinal nature of this study confers several advantages including, but not limited to the ability to follow participants, thereby enabling researchers to establish a sequence of events (e.g., use behaviors), identify changes over time, and minimize issues of recall biases (Caruana et al., 2015).

US Adult COH will follow two groups of individuals, categorized based on their baseline IQOS use and cigarette smoking status. The design offers the opportunity to extend observation of the two groups beyond a single moment in time. The study is therefore able to establish the order of product initiation, and capture transitions between tobacco use statuses in real time, which should eliminate issues of recall biases that may arise in cross-sectional or retrospective studies. Also, the repeated nature of observations in US Adult COH also offers an opportunity to minimize the impact of differences between individual, while accounting for within individual changes. For instance, it is less likely that over the course of US Adult COH individual intrinsic characteristics will play a role in behavior change.

Like in any other study, US Adult COH have comes with some limitations. The first and unequivocal limitation is the potential for attrition, with the prospect of losing participants over the course of the study, which may create incomplete data. However, this study will encourage participant retention by sending multiple reminders across different channels (e.g., text, email), allow participant continuation following a missed follow up survey, and providing an incentive for each survey at time of completion as well as an additional incentive for completing all study surveys (baseline through month 24).

Any potential insights (e.g., transitions, complete cessation, etc.) from repeated measures can take time to be detected. There is a chance that some endpoints may be right censored (i.e., not observed at the time of study closure). However, the follow-up duration has been chosen to minimize such instances. There is potential for inaccuracy in conclusion if the proposed statistical techniques fail to account for the intra-individual correlation of measures (Caruana et al., 2015). The proposed statistical analyses (linear mixed effect models) are chosen to account for within-individual correlation.

10 STUDY POPULATION

10.1 Study Groups

Participants will include adult (≥ 21 years) current established IQOS users recruited from the US Adult PMX study and current established smokers recruited from commercial, online panels. Participants for both study groups will be recruited simultaneously.

Current established IQOS users will be defined as adult IQOS users who report at baseline:

1. Having met the *lifetime established use criterion* for IQOS heated tobacco sticks (i.e., 100 or more lifetime sticks), AND
2. Having used IQOS in the past 30 days at baseline, AND
3. Having used IQOS for six or fewer months (regardless of other tobacco or nicotine product [TNP] use).

Current established smokers will be defined as adult cigarette smokers who report at baseline:

1. Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more), AND

2. Having smoked cigarettes in the past 30 days at baseline (regardless of other TNP use), AND
3. Have never tried IQOS.

10.2 Inclusion Criteria

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

1. U.S. resident 21 years of age and older.
2. Voluntarily consent to serve as a participant in the study by digitally signing an Informed Consent Statement (ICS) approved or given an exempt determination by a qualified Institutional Review Board (IRB).
3. Acknowledge willingness and ability to comply with all study requirements as listed in the ICS.
4. Meet criteria for inclusion in one of the two study groups (see Section 10.1).

10.3 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in 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 a market research or other company involved in the conduct of the research.
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.

10.4 Sample Size and Power Considerations

A power analysis was conducted to determine the necessary ending sample size. We selected one of the primary outcomes, quitting cigarette smoking, because it has received substantial attention both among regulators and in the scientific community (DHHS, 2020; Swan et al., 2020). A recent comprehensive study by (Kasza et al., 2024), leveraged the large sample from the Population Assessment of Tobacco and Health (PATH) adults to compare cigarette smoking quit rates between baseline (wave 5) dual users of cigarettes and e-cigarettes against exclusive smokers using the most recent waves of data collection: 2018/19 for wave 5 to 2021 for wave 6.

Specifically, Kasza et al. (2024) found that over the two years (using wave 5 as the baseline), exclusive cigarette smokers quit smoking at a cumulative rate of 21% while those combining cigarettes with e-cigarettes quit smoking at a cumulative rate of 29.7%. Given these estimates and the exponential nature of the distribution of quit rates (Getsios et al., 2013), instantaneous smoking quit rates were obtained using the natural log of the above survival rates for two years follow-up:

- In the cigarette group, given that 79.0% (i.e., 1-0.21) continued to smoke after two years follow-up, the instantaneous quit rate can be obtained as:

$$\frac{-\ln(0.79)}{2} = 0.1179.$$

- In the e-cigarette group, given that 70.3% (i.e., 1-0.297) continued to smoke after two years follow-up, the instantaneous quit rate can be obtained as:

$$\frac{-\ln(0.703)}{2} = 0.1762.$$

- Given these instantaneous quit rates, the hazard ratio of cigarette smoking can be obtained as:

$$\frac{Instantaneous\ Quit\ Rate\ in\ Test\ Group}{Instantaneous\ Quit\ Rate\ in\ Control\ Group} = \frac{0.1762}{0.1179} = 1.4950$$

At these prevailing rates, and extending these findings to the IQOS and cigarette study groups for the same study time (two years), results from the power analysis using a *logrank* test (with Schoenfeld method) for comparison of two survival functions revealed that 260 events (~ overall number of subjects who quit smoking) and an initial sample size of 1,026 participants (n=513 per study group) would be required to detect a difference (e.g., bi-annual hazard ratio of 1.4950) with a statistical power of 90% and Type I Error of α=0.05. That power analysis was conducted for a two-sided *logrank* test, with Schoenfeld method for determining the number of events and power using Stata 18 (StataCorp LLC). If sample size requirements for the current established IOQS user group are not met through US Adult PMX recruitment, then additional participants will be recruited though an internal database of IQOS users.

However, prior relevant longitudinal studies have experienced dropout rates ranging from 12% to 66% (Berg et al., 2014; Caponnetto et al., 2013; Choi & Forster, 2014; Dobbie et al., 2015; Grana et al., 2014; McRobbie et al., 2015; Nides et al., 2014; Norton et al., 2014; Pacifici et al., 2015; Polosa et al., 2014). Given the likelihood of dropout, we allowed the sample to be inflated to account for a potential dropout rate of 50% (instantaneous rate of drop out: $\frac{-\ln(0.50)}{2} = 0.3466$), thereby yielding a sample size of 1,570, rounded at 1,600 participants (n=800 per study group) with an expected count of 260 participants reporting the event of interest (i.e., cigarette cessation).

Considering the potential loss of power with propensity score weighting, and the plan to present stratified analyses comparing menthol versus non-menthol IQOS users in the IQOS group, we allowed an additional sample inflation of 30%:

- In the current established IQOS group: [800 * 1.30] * 2 ≈ 2,100 (multiplying by two for menthol and non-menthol stratification).

- In the current established smoker group: [800 * 1.30]*2 ≈ 2,100.
- Hence a total baseline line sample of 4,200 respondents.

11 STUDY PROCEDURES

11.1 Recruitment

Recruitment is expected to launch when the number of established IQOS users is sufficient to support the study. This study will leverage two recruitment sources: 1) US Customer Loyalty Program (CLP) database to recruit current established IQOS users and 2) commercial, online panels to recruit current established smokers from geographies where IQOS is sold.

11.1.1 Recruiting Current Established IQOS Users – US Customer Loyalty Program

It is anticipated that PMP will establish and maintain a US 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.

US Adult PMX Study Recruitment

This study intends to recruit adult (≥ 21 years) current established IQOS users who were invited and eligible to participate in the US Adult PMX Study (PMSS-PMX-01-US), PMP's repeated, online, cross-sectional survey.

Study invitations for the US Adult PMX study will be delivered via email, direct mail, and/or text to adult IQOS purchasers who have registered their device in the 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 US Adult PMX 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).

US Adult COH

Study invitations for the US Adult COH will be administered at the end of the US Adult PMX main survey to individuals who meet the current established IQOS user study group criteria. Participants will be recruited using a non-probability method on a schedule that matches the US Adult PMX during the single time that the US Adult COH will recruit participants. If the current established IQOS user group sample targets cannot be met through the US Adult PMX, additional participants will be recruited from the CLP database. To better maximize participation, potential participants may be contacted multiple times via multiple channels when possible (e.g., emails, text messages, and mailings).

11.1.2 Recruiting Current Established Smokers – Online panels

Current established smokers will be recruited from multiple online consumer panel companies to increase the likelihood of achieving a more diverse sample and completing screening requirements in a timely manner. For these and other reasons, the main contract

research organization (CRO) will evaluate and select the online consumer panel companies based on several quality criteria, including having established a history of compliance with industry codes and standards and processes for:

- Registering panelists,
- Validating member information via external databases,
- Periodic updating of panel member information,
- Appropriate sample deployment (e.g., batching), and
- Identifying straightliners, speeders, and other fraudulent data (e.g., bot traffic).

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

11.2 Study Implementation and Timeline

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

Estimated Study Timeline

The timing of execution of the cohort study depends on the distribution and consumer uptake of IQOS in the marketplace. 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 learning achieved from the early market launches.

To plan timing of the cohort study initiation, we focused on the recruiting that will be needed to achieve the minimal sample size (n=2,100) for the current established IQOS user group. Assuming a response rate of 5%, we will need to reach about 42,000 consumers with contactable information from our database to yield the target study group sample of 2,100.

Five follow-up surveys will be administered (3, 6, 12, 18 and 24 months) and the entire study will take a maximum of approximately 27 months to complete (from first participant in, to last participant out). Initial enrollment will occur within a 12-week period with follow-up surveys over the next 24 months. Participants will have a 14-day window in which to complete each follow-up survey.

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. Table 2 summarizes the estimated timing of study milestones.

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 2: Estimated Timing of Study Milestones - Postmarket Adult Consumer Cohort Study in the US

	Study Month						
	0	**3**	**6**	**12**	**18**	**24**	**27**
Study Milestone							
CLP reaches 42,000 registrants	✓						
CLP sample extraction	✓						
Send study invitations	✓						
Send study reminders (*if needed*)	✓						
Participant Screener |ICS	✓						
Baseline survey	✓						
Month 3 follow-up survey		✓					
Month 6 follow-up survey			✓				
Month 12 follow-up survey				✓			
Month 18 follow-up survey					✓		
Month 24 follow-up survey						✓	
Data validation						✓	✓
Database lock						✓	✓
Main/sensitivity analyses						✓	✓
Final report						✓	✓

CLP = Customer Loyalty Program; ICS = Informed Consent Statement

11.3 Adverse Health Event Reporting

Because this 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. AE reporting, documentation, or assessment will not be part of the repeated cross-sectional study conduct or study report (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 they may choose not to participate or discontinue their participation at any time for any reason. They will also 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 eligible participants who consent to participate and then prematurely withdraw from the study for any reason will be recorded. Premature discontinuation of participation can happen for any of the following reasons:

1. Withdrawal of informed consent (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

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

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

To address the potential bias due to attrition in the GEE models, the weighted GEE estimator originally proposed by Robins et al. (1995) will be performed.[3] This approach uses logistic regression to estimate the probability that a subject's survey is missing at a given wave and reweights the data based on the inverse of these probabilities. Results from the weighted and unweighted models will be compared. The unweighted results will be presented, but any changes in inference due to the weighting will be clearly noted in the report.

11.6 Termination of Study

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

[3] Implemented in SAS's (SAS version 9.4, SAS Institute Inc., Cary, North Carolina) proc gee with the missmodel option or in the R package wgeesel (Xu et al., 2019).

12 OUTCOME MEASURES

12.1 Objective 1 – Characterize tobacco or nicotine product (TNP) use behaviors.

The following outcome measures will be used to characterize participants' TNP use behaviors:

l) At baseline, participants' TNP use before first trying IQOS, specifically:
- Having never used any TNP
- Long-term former established tobacco use
- Current established smoking
- Other current established TNP use

m) Past 30-day exclusive, dual, or poly use at follow-up months 3,6,12,18, and 24:
- Exclusive: IQOS only.
- Exclusive: Cigarettes only.
- Dual: IQOS plus one other TNP:
  - IQOS and one combustible TNP.
    - IQOS and cigarettes.
  - IQOS and one other non-combustible TNP.
- Poly: IQOS plus two or more other TNP:
  - IQOS and at least one combustible TNP.
    - IQOS, cigarettes, and one or more other TNP.
  - IQOS and two or more other non-combustible TNP (i.e., participants reporting poly-tobacco use does not include any combustible TNP).

n) Mean number of days used IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24.

o) Mean number of days smoked cigarettes at baseline and follow-up months 3, 6, 12, 18, and 24.

p) Mean number of IQOS heated tobacco sticks used per day at baseline (Current established IQOS users only) and at follow-up months 3, 6, 12, 18, and 24.

q) Mean number of cigarettes smoked per day at baseline and at follow-up months 3, 6, 12, 18, and 24 months (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only).

r) Mean number of IQOS heated tobacco sticks used and cigarettes smoked per day at baseline and follow-up months 3, 6, 12, 18, and 24 months (Current established IQOS users reporting dual IQOS and cigarette use at baseline and Current established smokers reporting dual IQOS and cigarette use at follow ups).

s) Percent change in cigarettes smoked per day from baseline for follow-up months 3, 6, 12 ,18, and 24 (Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only):
   a. Reduced cigarettes smoked per day by ≥50%

b. Increased cigarettes smoked per day by ≥50%
c. Maintained cigarettes smoker per day (i.e., change < ±50%)

t) Prevalence of current established smoking at baseline and at follow-up months 3, 6, 12, 18, and 24.

u) Mean score of the FTND for IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24.

v) Mean score of the FTND for cigarettes at baseline (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette use at baseline) and follow-up months 3, 6, 12, 18, and 24.

12.2 Objective 2 – Describe behavioral transitions, including: product use initiation, completely switching from cigarettes to other TNP or to IQOS, transitioning to (never smokers) or back (former smokers) to cigarettes, and quitting.

The following outcome measures will be used to describe participants' IQOS and other TNP use behavioral transitions:

g) Product initiation:
- Ever use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24.
- Established use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24.

h) Complete switching to IQOS (i.e., baseline current established smokers from either study group reporting current established IQOS use and no past 30-day smoking at follow up) at follow-up months 3, 6, 12, 18, and 24.

i) Complete switching from IQOS to cigarette smoking (i.e., current established IQOS users reporting current established smoking and no past 30-day IQOS use at follow up) at follow-up months 3, 6, 12, 18, and 24.

j) Follow up behavioral transitions among current established IQOS users who report dual IQOS and cigarette use at baseline for follow-up months 3, 6, 12, 18, and 24:
- Exclusive IQOS use
- Exclusive cigarette smoking
- Dual IQOS and cigarette use
- No past 30-day IQOS use or cigarette smoking (regardless of other TNP use).

k) Transition to cigarette smoking at follow-up months 3, 6, 12, 18, and 24 months:
- Relapse to cigarette smoking among baseline current established IQOS users who report short-term former established smoking at baseline.

- Re-initiation of cigarette smoking among baseline current established IQOS users who report long-term former established smoking at baseline.

l) Quitting behaviors:
   - Quit smoking after first trying IOQS – Baseline current established IQOS users who report former established smoking at baseline who smoked in the 30-days prior to first trying IQOS.
   - Quit attempts in the past 12 months – Baseline current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers who attempted a quit attempt in the 12 months prior to baseline.
   - Use of cessation treatment at baseline and follow-up months 3, 6, 12, 18, and 24.
   - Completely quit smoking cigarettes at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers).
   - Completely quit IQOS use at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users).
   - Complete quit all TNP at follow-up months 3, 6, 12, 18, and 24.

12.3 Objective 3 – Assess self-reported health-related quality of life, signs, and symptoms by product use.

The health-related outcomes include HRQOL, signs, and symptoms. The facets of quality of life[4] that will be measured as outcomes in this study include:

m) Mean physical health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24.

n) Mean mental health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24.

o) Change in mean physical health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

p) Change in mean mental health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

q) Difference in mean physical health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24.

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

r) Difference in mean mental health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24.

s) Mean number of cardiovascular symptoms at baseline and follow-up months 3, 6, 12, 18, and 24.

t) Mean number of respiratory symptoms at baseline and follow-up months 3, 6, 12, 18, and 24.

u) Change in mean number of cardiovascular symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

v) Change in mean number of respiratory symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

w) Difference in mean number of cardiovascular symptoms between study groups at follow-up months 3, 6, 12, 18, and 24.

x) Difference in mean number of respiratory symptoms between study groups at follow-up months 3, 6, 12, 18, and 24.

12.4 Objective 4 – Assess risk perceptions related to IQOS and cigarettes.

The following outcome measures will be used to assess participants' risk perceptions related to IQOS and cigarettes:

d) Percent and count (n, %) of participants in each category of the ABOUT™ scale assessing risk perception related to IQOS use, cigarette smoking, and complete smoking cessation at baseline and follow-up months 12 and 24.

e) Percent distribution of perceived harmful or potentially harmful chemical (HPHC) exposure following switching from cigarettes to IQOS ("More", "Same", "Less", "No", or "Don't know") at follow-up months 3, 6, 12, 18, and 24.

f) Percent distribution of the understanding of what smokers must do to reduce HPHC exposure among participants who perceive reduced ("Less") HPHC exposure following switching from cigarettes to IQOS at follow-up months 3, 6, 12, 18, and 24.

13 DATA MANAGEMENT

13.1 Data Validation

Various checks will be performed to ensure the accuracy, integrity, and validity of the data. These include quality checking the survey instrument program logic before and after study launch to ensure that the data are collected as specified in the study protocol. Participants with

inaccurate data due to an error in the survey program logic may be removed from the data set prior to database lock.

Any corrections made to the data set will be thoroughly documented and an explanation/rationale will be provided for each correction.

13.2 Database Lock

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

13.3 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 the CRO. Data transferred to PMP will be completely anonymized and will not include any participant personal identification information.

13.4 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.

14 DATA ANALYSIS

14.1 Outcome Measures Analyses

Below is a summary of planned analyses for study summaries and outcome measures. For more details see Appendix 3: Statistical Analysis Plan.

(1) Recruitment and participation disposition will be summarized overall and by age and sex:

- *Screen 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 baseline surveys divided by the number of attempted baseline surveys (completed plus partial); and
- *Response proportion:* the number of completed interviews divided by the number of invitations sent.

(2) Descriptive statistics will be calculated for all demographic characteristics at baseline and study outcomes for each period stratified by study group where appropriate. Continuous outcomes (e.g., age) will be summarized using means, standard deviations, 95% Confidence

Intervals (CI), medians, first and third quartiles (Q1 and Q3, respectively). Categorical outcomes (e.g., ever use) will be summarized using counts, percentages, and 95% CIs.

(3) Propensity score weighting, described in the SAP, will be used to reduce confounding between groups and will be calculated from demographic characteristics and other variables likely to predict being a cigarette user or an IQOS user. This will ensure that both groups are similar in their baseline characteristics, except on IQOS use baseline status (i.e., ignorability assumption). Standardized mean differences will be used to assess balance after propensity weighting (Greifer, 2023).

(4) A series of GEE models (e.g., GEE log-binomial regression, GEE Poisson regression) will be used on the matched data to address study objectives with comparisons between groups or over time (e.g., tobacco use, transitions, health-related quality of life, and signs and symptoms). Some outcomes are only relevant to certain tobacco subpopulations. The populations under analysis will be described in the SAP.

All statistical tests will be conducted at a Type I Error Rate of α=0.05. Corrections for the potential inflation of Type I Error will not be made due to the potential inflation of Type II error (Perneger, 1998). When testing is employed, significant *p*-values will be reported with high precision (i.e., to the 4th decimal place) to allow reviewers to evaluate significance after applying a Bonferroni correction, if desired.

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

1. All non-zero counts less than 10 will be suppressed and will include a note of small sample size.
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.

Additional technical details regarding the analytic strategy (e.g., research questions, equations) will be provided in the SAP.

14.2 Coding of Open-Ended Data

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

15 ETHICAL, REGULATORY AND LEGAL CONSIDERATIONS

15.1 Institutional Review Board (IRB)

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

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

As applicable and if the IRB does not determine that the study is exempt from its review, amendments to the above stated documents must also be submitted and receive approval or exemption from the IRB prior to implementation. 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.

15.2 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) (Hoffmann et al., 2019), Council of American Survey Research Organization's 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 15.3. 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).

15.3 Informed Consent Procedures

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

The principal investigator will revise the informed consent if any important new information becomes available that may impact a participants' willingness to continue participation in the study or is otherwise relevant to participants' consent (and will ensure that information provided to participants as soon as practicable). 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.

15.4 Confidentiality

The study staff (CRO) will affirm 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.

15.5 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.

16 ADMINISTRATIVE CONSIDERATIONS

This study is sponsored by PMP. A CRO 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 Organizations
Note. CRO details to be added following vendor selection.
[CRO]

[CRO Address]

16.1 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. Study staff shall document any significant protocol deviation and notify PMP within 48 hours.

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

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

16.2 Study Records

All data will be captured via a secure data collection system. All data will be captured in real time through a web-enabled portal, and all responses will be time and date stamped. Any corrections made to the data set will be thoroughly documented and an explanation/rationale will be provided for each correction. All electronic records will be stored in a secure database with restricted access only to individuals requiring it.

The CRO 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.

16.3 Study Reports

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

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

17 REFERENCES

Berg, C. J., Barr, D. B., Stratton, E., Escoffery, C., & Kegler, M. (2014). Attitudes toward E-Cigarettes, Reasons for Initiating E-Cigarette Use, and Changes in Smoking Behavior after Initiation: A Pilot Longitudinal Study of Regular Cigarette Smokers. *Open J Prev Med*, *4*(10), 789-800. https://doi.org/10.4236/ojpm.2014.410089

Campagna, D., Cibella, F., Caponnetto, P., Amaradio, M. D., Caruso, M., Morjaria, J. B., Malerba, M., & Polosa, R. (2016). Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *Eur J Clin Invest*, *46*(8), 698-706. https://doi.org/10.1111/eci.12651

Cano, S., Chrea, C., Salzberger, T., Alfieri, T., Emilien, G., Mainy, N., Ramazzotti, A., Lüdicke, F., & Weitkunat, R. (2018). Development and validation of a new instrument to measure perceived risks associated with the use of tobacco and nicotine-containing products. *Health Qual Life Outcomes*, *16*(1), 192. https://doi.org/10.1186/s12955-018-0997-5

Caponnetto, P., Auditore, R., Russo, C., Cappello, G. C., & Polosa, R. (2013). Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health*, *10*(2), 446-461. https://doi.org/10.3390/ijerph10020446

Caruana, E. J., Roman, M., Hernández-Sánchez, J., & Solli, P. (2015). Longitudinal studies. *J Thorac Dis*, *7*(11), E537-540. https://doi.org/10.3978/j.issn.2072-1439.2015.10.63

CASRO. (2016). Code of Standards & Ethics. In.

Choi, K., & Forster, J. L. (2014). Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. *Am J Prev Med*, *46*(2), 175-178. https://doi.org/10.1016/j.amepre.2013.10.007

Cibella, F., Campagna, D., Caponnetto, P., Amaradio, M. D., Caruso, M., Russo, C., Cockcroft, D. W., & Polosa, R. (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)*, *130*(21), 1929-1937. https://doi.org/10.1042/cs20160268

DHHS. (2020). Chapter 4: The health benefits of smoking cessation. In U. S. P. H. S. O. o. t. S. G. N. C. f. C. D. P. a. H. P. U. O. o. S. a. Health. & W. (DC): (Eds.), *Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. https://www.ncbi.nlm.nih.gov/books/NBK555590/

Dobbie, F., Hiscock, R., Leonardi-Bee, J., Murray, S., Shahab, L., Aveyard, P., Coleman, T., McEwen, A., McRobbie, H., Purves, R., & Bauld, L. (2015). Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS): a prospective cohort study. *Health Technol Assess*, *19*(95), 1-156. https://doi.org/10.3310/hta19950

Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. (2014). Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*, *11*(4), 4356-4373. https://doi.org/10.3390/ijerph110404356

Food and Drug Administration [FDA]. (2012). *Guidance for Industry: Modified Risk Tobacco Product Applications* https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UC M297751.pdf

Food and Drug Administration [FDA]. (2020). *Modified Risk Granted Orders – Exposure Modification* https://www.fda.gov/media/139797/download?attachment

Getsios, D., Marton, J. P., Revankar, N., Ward, A. J., Willke, R. J., Rublee, D., Ishak, K. J., & Xenakis, J. G. (2013). Smoking cessation treatment and outcomes patterns simulation: a new framework for evaluating the potential health and economic impact of smoking cessation interventions. *Pharmacoeconomics*, *31*(9), 767-780. https://doi.org/10.1007/s40273-013-0070-5

Grana, R. A., Popova, L., & Ling, P. M. (2014). A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Intern Med*, *174*(5), 812-813. https://doi.org/10.1001/jamainternmed.2014.187

Greifer, N. (2023). *Assessing balance*. Retrieved 3/11/2024 from https://cran.r-project.org/web/packages/MatchIt/vignettes/assessing-balance.html

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., Rickert, W., & Robinson, J. (1989). Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict*, *84*(7), 791-799. https://doi.org/10.1111/j.1360-0443.1989.tb03059.x

Hoffmann, W., Latza, U., Baumeister, S. E., Brünger, M., Buttmann-Schweiger, N., Hardt, J., Hoffmann, V., Karch, A., Richter, A., Schmidt, C. O., Schmidtmann, I., Swart, E., & van den Berg, N. (2019). Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. *Eur J Epidemiol*, *34*(3), 301-317. https://doi.org/10.1007/s10654-019-00500-x

Hyland, A., Ambrose, B. K., Conway, K. P., Borek, N., Lambert, E., Carusi, C., Taylor, K., Crosse, S., Fong, G. T., Cummings, K. M., Abrams, D., Pierce, J. P., Sargent, J., Messer, K., Bansal-Travers, M., Niaura, R., Vallone, D., Hammond, D., Hilmi, N., . . . Compton, W. M. (2017). Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tob Control*, *26*(4), 371-378. https://doi.org/10.1136/tobaccocontrol-2016-052934

ICC/ESOMAR. (2016). *ICC / ESOMAR International Code on Market, Opinion and Social Research and Data Analytics*. https://iccwbo.org/wp-content/uploads/sites/3/2016/12/ICC-ESOMAR-International-Code-on-Market-Opinion-Social-Research-and-Data-Analytics.pdf

Kasza, K. A., Tang, Z., Seo, Y. S., Benson, A. F., Creamer, M. R., Edwards, K. C., Everard, C., Chang, J. T., Cheng, Y. C., Das, B., Oniyide, O., Tashakkori, N. A., Weidner, A. S., Xiao, H., Stanton, C., Kimmel, H. L., Compton, W., & Hyland, A. (2024). Divergence in Cigarette Discontinuation Rates by Use of Electronic Nicotine Delivery Systems (ENDS): Longitudinal Findings From the United States PATH Study Waves 1-6. *Nicotine Tob Res*. https://doi.org/10.1093/ntr/ntae027

Kotz, D., Brown, J., & West, R. (2013). Predictive validity of the Motivation To Stop Scale (MTSS): a single-item measure of motivation to stop smoking. *Drug Alcohol Depend*, *128*(1-2), 15-19. https://doi.org/10.1016/j.drugalcdep.2012.07.012

Mantey, D. S., Cooper, M. R., Loukas, A., & Perry, C. L. (2017). E-cigarette Use and Cigarette Smoking Cessation among Texas College Students. *Am J Health Behav*, *41*(6), 750-759. https://doi.org/10.5993/ajhb.41.6.9

McKeganey, N., Miler, J. A., & Haseen, F. (2018). The Value of Providing Smokers with Free E-Cigarettes: Smoking Reduction and Cessation Associated with the Three-Month Provision to Smokers of a Refillable Tank-Style E-Cigarette. *Int J Environ Res Public Health*, *15*(9). https://doi.org/10.3390/ijerph15091914

McRobbie, H., Phillips, A., Goniewicz, M. L., Smith, K. M., Knight-West, O., Przulj, D., & Hajek, P. (2015). Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. *Cancer Prev Res (Phila)*, *8*(9), 873-878. https://doi.org/10.1158/1940-6207.Capr-15-0058

Mushtaq, N., & Beebe, L. A. (2017). Psychometric Properties of Fagerström Test for Nicotine Dependence for Smokeless Tobacco Users (FTND-ST). *Nicotine Tob Res*, *19*(9), 1095-1101. https://doi.org/10.1093/ntr/ntx076

Nides, M. A., Leischow, S. J., Bhatter, M., & Simmons, M. (2014). Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav*, *38*(2), 265-274. https://doi.org/10.5993/ajhb.38.2.12

Norton, K. J., June, K. M., & O'Connor, R. J. (2014). Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. *Tob Induc Dis*, *12*(1), 17. https://doi.org/10.1186/1617-9625-12-17

O'Connor, R. J., Hyland, A., Giovino, G. A., Fong, G. T., & Cummings, K. M. (2005). Smoker awareness of and beliefs about supposedly less-harmful tobacco products. *Am J Prev Med*, *29*(2), 85-90. https://doi.org/10.1016/j.amepre.2005.04.013

O'Connor, R. J., Norton, K. J., Bansal-Travers, M., Mahoney, M. C., Cummings, K. M., & Borland, R. (2011). US smokers' reactions to a brief trial of oral nicotine products. *Harm Reduct J*, *8*, 1. https://doi.org/10.1186/1477-7517-8-1

Pacifici, R., Pichini, S., Graziano, S., Pellegrini, M., Massaro, G., & Beatrice, F. (2015). Successful Nicotine Intake in Medical Assisted Use of E-Cigarettes: A Pilot Study. *Int J Environ Res Public Health*, *12*(7), 7638-7646. https://doi.org/10.3390/ijerph120707638

Parsons, V. L. (2014). *Design and estimation for the national health interview survey, 2006-2015*. US Department of Health and Human Services, Centers for Disease Control and ….

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *Bmj*, *316*(7139), 1236-1238. https://doi.org/10.1136/bmj.316.7139.1236

Piper, M. E., Baker, T. B., Benowitz, N. L., Smith, S. S., & Jorenby, D. E. (2020). E-cigarette Dependence Measures in Dual Users: Reliability and Relations With Dependence Criteria and E-cigarette Cessation. *Nicotine Tob Res*, *22*(5), 756-763. https://doi.org/10.1093/ntr/ntz040

Polosa, R., Caponnetto, P., Maglia, M., Morjaria, J. B., & Russo, C. (2014). Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health*, *14*, 1159. https://doi.org/10.1186/1471-2458-14-1159

Polosa, R., Morjaria, J. B., Caponnetto, P., Caruso, M., Campagna, D., Amaradio, M. D., Ciampi, G., Russo, C., & Fisichella, A. (2016). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov Med*, *21*(114), 99-108.

Pulvers, K., Emami, A. S., Nollen, N. L., Romero, D. R., Strong, D. R., Benowitz, N. L., & Ahluwalia, J. S. (2018). Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes. *Nicotine Tob Res*, *20*(2), 206-214. https://doi.org/10.1093/ntr/ntw333

Pulvers, K., Hayes, R. B., Scheuermann, T. S., Romero, D. R., Emami, A. S., Resnicow, K., Olendzki, E., Person, S. D., & Ahluwalia, J. S. (2015). Tobacco Use, Quitting Behavior, and Health Characteristics Among Current Electronic Cigarette Users in a National Tri-Ethnic Adult Stable Smoker Sample. *Nicotine Tob Res*, *17*(9), 1085-1095. https://doi.org/10.1093/ntr/ntu241

Robins, J. M., Rotnitzky, A., & Zhao, L. P. (1995). Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *Journal of the American statistical Association*, *90*(429), 106-121.

Sharma, M. K., Suman, L. N., Srivastava, K., Suma, N., & Vishwakarma, A. (2021). Psychometric properties of Fagerstrom Test of Nicotine Dependence: A systematic review. *Ind Psychiatry J*, *30*(2), 207-216. https://doi.org/10.4103/ipj.ipj_51_21

Substance Abuse and Mental Health Services Administration [SAMHSA]. (2017). *National Survey on Drug Use and Health* (National Survey on Drug Use and Health, Issue. https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health

Swan, G. E., Hendershot, T. P., Hamilton, C. M., van Bemmel, D. M., & Wanke, K. L. (2020). The PhenX Toolkit: measures for tobacco regulatory research. In (Vol. 29, pp. s1-s4): BMJ Publishing Group Ltd.

U.S. Department of Health and Human Services [DHHS]. (2020). Chapter 4: The health benefits of smoking cessation. In U. S. P. H. S. O. o. t. S. G. N. C. f. C. D. P. a. H. P. U. O. o. S. a. Health. & W. (DC): (Eds.), *Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. https://www.ncbi.nlm.nih.gov/books/NBK555590/

Westat. (2023, 12/06/2021). *Final Adult Interview: Wave 7 (January 2022 - December 2022)*. Retrieved 12/06/2023 from https://www.icpsr.umich.edu/files/NAHDAP/pathstudy/Final%20PATH%20Wave%207%20English%20Adult%20Questionnaire.pdf

World Health Organization [WHO]. (1998). The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med*(46), 1569-1585.

Xu, C., Li, Z., Xue, Y., Zhang, L., & Wang, M. (2019). An R package for model fitting, model selection and the simulation for longitudinal data with dropout missingness. *Commun Stat Simul Comput*, *48*(9), 2812-2829. https://doi.org/10.1080/03610918.2018.1468457