Appendix C4:
IQOS® Cohort PACS SAP

Please find on the following pages statistical analysis plan for IQOS® Longitudinal Cohort PACS.

STATISTICAL ANALYSIS PLAN

Altria Client Services

Protocol Number: (b) (4)

Protocol Name: IQOS® with Marlboro HeatSticks® Longitudinal Cohort Postmarket Adult Consumer Study (PACS)

November 4, 2020

Signatures

CRO Survey Statistician: _____

Principal Investigator: _____

(b) (6)

Regulatory Science

Altria Client Services LLC

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

DEFINITIONS OF TERMS

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

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

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

Complete Switching

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

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

Consistent Basis

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

Current Tobacco Product Use

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

Established Tobacco Product Use

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

Ever Tobacco Product Use

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

Former Tobacco Product Use

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

Initiation

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

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

IQOS® Consumer Database

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

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

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

Lifetime Established Use Criterion

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

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

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

Long-Term Former Tobacco Product Use

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

Quitting a Tobacco Product

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

Quitting All Tobacco Products

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

Re-initiation of Cigarette Smoking

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

Relapse to Cigarette Smoking

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

Tobacco Products

In this study, tobacco products include cigarettes, cigars (regular cigars, cigarillos, little filtered cigars), regular pipes, water pipes/hookahs, e-vapor products (e-cigarettes, e-hookah, e-cigars, e-pipes, mods, vapes, tanks, pods, cartridges), smokeless tobacco (chewing tobacco, "dip"/snuff, snus pouches), oral tobacco-derived nicotine products (excluding medicinal nicotine replacement products), and IQOS®.

1 INTRODUCTION

1.1 Background

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

1.2 Rationale

The Federal Food, Drug and Cosmetic Act (FDCA) directs the FDA to condition an exposure modification order received under FDCA § 911(g)(2) on the MRTP applicants' agreement to conduct PMSS (FDCA §§ 911(g)(2)(C)(ii)). "The outcomes evaluated in postmarket surveillance and studies should focus on the effect of the MRTP on consumer perception, behavior and health under real world conditions of use" (Food and Drug Administration, 2012). For this reason, ALCS[1] on behalf of the applicant, PMP S.A., plans to conduct certain components of PMSS to assess the effect of the MRTP among U.S. consumers. The program will consist of a collection of data over time that supports an assessment of IQOS® in the postmarket setting. The current study, IQOS® with Marlboro HeatSticks® Longitudinal Cohort Postmarket Adult Consumer Study (IQOS® Cohort PACS), is one such study.

1.3 Study Purpose

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

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

1.4 Study Objectives

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

2 STUDY DESIGN, DEVELOPMENT AND METHODS

2.1 Overview

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

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

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

Eligible participants who agree to participate will be asked to complete specific relevant IQOS® Cohort PACS survey 1 (Time 0) modules[2] after completing the Cross-sectional survey[3]. IQOS® Cohort PACS survey 2 (Time 3 months), survey 3 (Time 6 months), survey 4 (Time 12 months), survey 5 (Time 18 months), and survey 6 (Time 24 months) will be administered every 3 months for the first 6 months then every 6 months for the remainder of the study (Figure 1). The study length was selected to enable the ability to detect changes in behaviors and health over time. A 3 and 6-month interval is a sufficient timeframe for measuring changes in tobacco use behaviors (Halpern et al., 2018; Mantey et al., 2017; McKeganey et al., 2018; O'Connor et al., 2005; O'Connor et al., 2011; Pulvers et al., 2016; 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 be incorporated into surveys to reduce participant burden. The cross sectional/baseline survey and five cohort follow-up surveys will include measures grouped in the following modules:

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

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

---

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

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

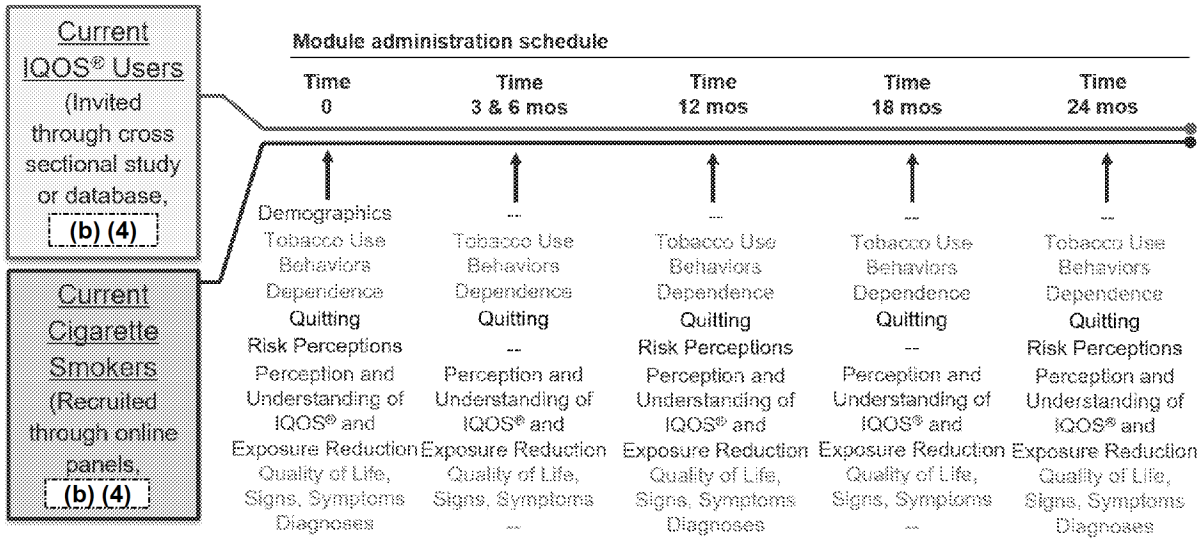

Figure 1: IQOS® Cohort Study Design

2.2 Survey Development and Testing Overview

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

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

Demographics and Population Characteristics Module

Demographic and population characteristic module items will include:

- Sex
- Age
- Race
- Ethnicity
- Education level
- Income
- Marital Status
- Pre-existing medical conditions or co-morbidities
    - Cardiovascular disease
    - Respiratory disease
    - Cancer

  - Diabetes
- Mental illness
- Pregnancy status (among women 21 to 49 years of age)
- Military or Veteran Status
- Sexual Identity

Tobacco Use Behaviors Module

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

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

Tobacco Dependence Module

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

Quitting Behaviors Module

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

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

Risk Perceptions Module

Risk perceptions will be collected through the Perceived Health Risk Scale (PRI-G; Cano et al., 2018). The risk perceptions module will include items related to general risks to health.

Perception and Understanding of IQOS® and Exposure Reduction

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

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

Quality of Life, Signs and Symptoms

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

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

Diagnoses Module

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

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

2.3 Survey Duration

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

Survey 1 (Time 0)

- Demographics module
- Tobacco use behaviors module

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

Survey 2 (Time 3 months)

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

Survey 3 (Time 6 months)

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

Survey 4 (Time 12 months)

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

Survey 5 (Time 18 months)

- Tobacco use behaviors module
- Tobacco dependence module
- Quitting behaviors module
- Perception and understanding of IQOS® and exposure reduction module

- Quality of life, signs, and symptoms module

Survey 6 (Time 24 months)

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

3 STUDY GROUPS AND SAMPLE SIZE

3.1 Study Groups

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

- **IQOS® Users (Test Group):** The IQOS® user group will be comprised of adults who report: (1) using IQOS® "every day" or "some days", (2) having used IQOS® during the past 30 days, (3) having used IQOS® for a period of 6 months or less (irrespective of use of any other tobacco product), and (4) having used at least 100 Marlboro HeatSticks® in their lifetime
- **Cigarette Smokers (Reference Group):** The cigarette smoker group will be comprised of adults who report: (1) never trying IQOS®, (2) having smoked at least 100 cigarettes in their lifetime, (3) smoke "every day" or "some days", and (4) having smoked cigarettes in the past 30 days (irrespective of use of any other tobacco product)

Group assignment will be determined using responses to survey 1. An evaluation in change of group membership (i.e. Current Cigarette Smoker at enrollment who at any subsequent interval tries/uses IQOS®) will be conducted at each interval. Based on the proportion of these changes, a determination will be made as to how to address the associated statistical analyses.

3.2 Propensity Score as a Covariate

Propensity scores, or the probability of treatment group assignment, can be used to reduce confounding between groups and limit bias when randomization is not possible (Austin et al., 2011; Rosenbaum et al., 1983).

Propensity scores will be calculated using a logistic regression from demographic characteristics and other variables likely to predict current IQOS® or cigarette use, which is consistent with other tobacco-related observational analyses (da Veiga et al., 2008; Leas et al., 2017; Timberlake et al., 2009). The following variables will be used as predictors in the logistic regression with group membership (IQOS® versus cigarette smokers) as the dependent variable:

- Demographic (age, sex, race/ethnicity, education, marital status)
- Smoking exposure related (years smoked, tobacco poly-use)
- Behavioral related (binge drinking, mental health concern, cessation advice from a health professional)
- Health related (presence of any chronic health condition)
- Other variables may be included if significant and meaningful differences are seen between groups

The propensity score model will be developed and based on the above characteristics of the IQOS® User Group at time of study enrollment (survey 1). Covariate balance will be assessed to determine if the propensity scores adequately remove confounding.

Once propensity scores are calculated, propensity scores will be used as a replacement of covariates during the analysis of outcome measures comparing the IQOS® and smoker groups, when relevant.

3.3 Sample Size and Power Considerations

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

Proportion Difference (SAS Institute Inc.). If sample size requirements for the IOQS user group are not met through IQOS® Cross-sectional PACS recruitment, then additional participants will be recruited though an internal database of IQOS® users.

Sample Size & Categorical Data

Unless otherwise stated, proportions for categorical variables will be summarized with point estimates and 95% asymptotic confidence intervals. Table 1 presents the confidence interval sizes for an example (b) (4) given different sample proportions. Exact estimation methods will be used instead of asymptotic estimation methods to construct confidence intervals when either *pn* or *qn*[4] is less than (b) in these cases, the exact binomial confidence interval (specifically, Clopper-Pearson) will be presented instead.[5] See Section 9.3.1 for details of statistical analyses of categorical data.

Table 1: 95% Asymptotic confidence intervals for binomial proportions

Binomial Proportions %	Asymptotic Confidence Interval (b) (4) %
(b) (4)	

Sample Size & Continuous Data

For continuous variables, the estimated width at 95% confidence for two example variables are presented in Table 2. See Section 9.3.2 for details of statistical analyses of continuous variables.

[4] *pn* = proportion * sample size, *qn* = (1-proportion)*sample size

[5] Gravetter, F.J. & Wallnua, L.B. (2014). *Essentials of Statistics for the Behavioral Sciences: 8th Edition.* Belmont, CA: Wadsworth.

Table 2: Estimated 95% confidence width with (b) (4) for example of continuous variables

Variable	Mean	Standard Deviation	Standard Error (b) (4)
(b) (4)			

3.4 Recruitment Method

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

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

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

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

4 OUTCOME MEASURES

Outcome measures, organized by study objectives, are presented in this section. The survey intervals (survey 1, survey 2, etc.) at which each outcome is measured is referenced, as applicable. Additionally, the planned statistical analyses associated with each measure, as outlined in Section 5, is indicated.

4.1 Characterization of tobacco use behaviors

Tobacco use outcomes include:

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

  The current use categories will be stratified by predominant use of menthol or regular HeatSticks® and use of a cessation treatment.
- **Cigarettes per day change among dual users** – Percent of prior wave IQOS® and cigarette dual users from the IQOS® user group who at surveys 2, 3, 4, 5, or 6 have either reduced cigarettes per day by at least 50%, increased cigarettes per day by at least 50%, or had the same cigarettes per day (less change than ±50%) compared to the prior wave and baseline accounting for predominant use of menthol or regular HeatSticks® and cigarettes and use of a cessation treatment
- **Cigarettes per day over time among dual users** – Mean cigarettes per day among IQOS® and cigarette dual users in the IQOS® user group at each follow-up survey, after controlling for cigarettes per day at baseline and accounting for predominant use of menthol or regular HeatSticks® and cigarettes and use of a cessation treatment

- **Average Number of Days Used IQOS®/Cigarettes per 30 days** – Number of days used in the past 30 days will be reported using mean and standard deviations, median and interquartile range for IQOS® and cigarettes at survey 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks® and cigarettes
- **Median Number of Units (e.g., sticks) of IQOS®/Cigarettes Used per Day in Past 30 Days** – Number of uses per day on days used in the past 30 days reported using median and interquartile range for IQOS® and cigarettes at survey 1, 2, 3, 4, 5, and 6 stratified by predominant use of menthol or regular HeatSticks® and cigarettes
- **Current Use of Cigarettes** – Percent of participants in the IQOS® user and cigarette smoker groups who are current established cigarette smokers at each survey, after accounting for predominant use of menthol or regular HeatSticks® and cigarettes, and use of a cessation treatment[6]. Comparisons will be conducted within and across study groups – at survey 1, 2, 3, 4, 5, and 6

4.2 Characterization of product use transitions

Change among dual users:

- **Change among dual users of IQOS® and Cigarettes** – Percent and count of prior wave IQOS® and cigarette dual users from the IQOS® user group who at surveys 2, 3, 4, 5, or 6 are exclusive IQOS® users, exclusive smokers, IQOS® and smoking dual users, or users of neither product, irrespective of other tobacco product use and stratifying by predominant use of menthol or regular HeatSticks® and cessation treatment

Complete switching outcomes:

- **Complete Switching from Cigarettes to IQOS®** – Percent of established smokers from the IQOS® user and cigarette smoker groups who, at a future survey, report current established IQOS® use and no cigarette use accounting for predominant use of menthol or regular HeatSticks® and cigarettes, and use of a cessation treatment
- **Complete Switching from IQOS® to Cigarettes** – Percent of established IQOS® users in the IQOS® user group who, at a future survey, report current established smoking and no IQOS® use accounting for predominant use of menthol or regular HeatSticks® and cigarettes, and cessation treatment

Initiation outcomes[7]:

- **Ever Use of a [Tobacco Product] Never Used at Baseline** – Percent of participants in the IQOS® user and cigarette smoker groups who report ever use (even one time) at surveys 2, 3, 4, 5, or 6 of a [Tobacco Product] never used, even one time, at survey 1 accounting for predominant use of menthol or regular HeatSticks®

---

[6] This measure includes smoker group members who have since quit. See Section 4.2 for details regarding the covariates and statistical model.

[7] Initiation outcomes will include descriptive statistics stratified by IQOS® HeatStick preference.

- **Established Use of a [Tobacco Product] Never Used at Baseline** – Percent of participants in the IQOS® user and cigarette smoker groups who report ever established use at surveys 2, 3, 4, 5, or 6 of a [Tobacco Product] never used, even one time, at survey 1 accounting for predominant use of menthol or regular HeatSticks®

Smoking relapse and re-initiation outcomes[8]:

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

Quitting behaviors[9]:

- **Quit Smoking After First Trying IQOS® as Assessed at Survey 1** – Percent and count of the IQOS® user group who were established smokers and smoked in the 30 days before first trying IQOS® and quit smoking at survey 1 stratified by predominant use of menthol or regular HeatSticks® and baseline use of a cessation treatment
- **Quit Attempts** – Percent of established smokers from the IQOS® user and cigarette smoker groups who attempted to quit smoking cigarettes in the past 12 months at survey 1 and at each interval between subsequent surveys, accounting for predominant use of menthol or regular HeatSticks®
- **Use of Cessation Treatment** – Percent of participants from the IQOS® user and cigarette smoker groups who report use of a cessation treatment at baseline (more than 12 months ago, over 30 days but less than 12 months, past 30 days, never) and incident use of a cessation treatment at surveys 2, 3, 4, 5, or 6
- **Completely Quit Smoking** – Percent of established smokers from the IQOS® user and cigarette smoker groups who completely quit smoking cigarettes at surveys 2, 3, 4, 5, or 6, accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment
- **Completely Quit IQOS®** – Percent of established IQOS® users who completely quit IQOS® at surveys 2, 3, 4, 5, or 6 accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment

[8] Smoking relapse and re-initiation outcomes will include descriptive statistics stratified by IQOS® HeatStick preference.

[9] Quitting outcomes will include descriptive statistics stratified by IQOS® HeatStick preference.

- **Completely Quit All Tobacco** – Percent of participants in the IQOS® user and cigarette smoker groups who completely quit all tobacco products at surveys 2, 3, 4, 5, or 6, accounting for predominant use of menthol or regular HeatSticks® and use of a cessation treatment

4.3 Assessment of health-related quality of life, signs and symptoms

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

- **Health-related Quality of Life (physical)** – Mean physical health T-score in the IQOS® user group relative to the mean physical health T-score in the cigarette smoker group at each follow-up survey, after controlling for the mean physical health T-score at baseline and years smoked cigarettes
- **Health-related Quality of Life (mental)** – Mean mental health T-score in the IQOS® user group relative to the mean mental health T-score in the cigarette smoker group at each follow-up survey, after controlling for the mean mental health T-score at baseline and years smoked cigarettes

The signs and symptoms outcomes will include:

- **Cardiovascular Signs and Symptoms** – Mean number of cardiovascular symptoms present in the IQOS® user group relative to the mean number of cardiovascular symptoms present in the cigarette smoker group at each follow-up survey, after controlling for cardiovascular symptoms at baseline and years smoked cigarettes
- **Respiratory Signs and Symptoms** – Mean number of respiratory symptoms present in the IQOS® user group relative to the mean number of respiratory symptoms present in the cigarette smoker group at each follow-up survey, after controlling for respiratory symptoms at baseline and years smoked cigarettes

4.4 Assessment of Risk perceptions of IQOS® and cigarettes and perception and understanding of IQOS® and exposure reduction

- **Risk Perceptions** – Mean, standard deviation, median, and interquartile range of the risk perceptions (PRI-G) composite score of IQOS® and cigarettes among the IQOS® user group and the cigarette smoker group
- **Perception of IQOS® Exposure Reduction** – Percent and count of participants in the IQOS® user and cigarette smoker groups perception that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure at surveys 2, 3, 4, 5, or 6
- **Understanding of What to do to Reduce Exposure** – Percent and count of participants in the IQOS® user and cigarette smoker groups understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure (among

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

participants who perceive that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure) at surveys 2, 3, 4, 5, or 6

5 PLANNED STATISTICAL ANALYSIS[11]

Analyses within this section align with the outcomes in Section 4. Overall, the data analyses will consist of the following steps:

1. Participation proportions will be reported in total and by sex and age
2. Descriptive statistics will be calculated for demographics at baseline and all study outcomes for each time period specified by study group where appropriate (e.g., use history, current tobacco use, days used and units used, risk perception, perception and understanding of IQOS® and exposure reduction), including means, medians, standard deviations, and interquartile range for continuous variables (e.g., age) and proportions and frequencies for categorical variables (e.g., sex).
3. A series of GEE models (e.g., GEE log-binomial regression, GEE Poisson regression) will be employed to address study objectives with comparisons between groups or over time (e.g., tobacco use, transitions, health-related quality of life, signs and symptoms). Some outcomes are only relevant to certain tobacco subpopulations; the population(s) included in the analysis is described within the outcome.

GEE models will be employed using the GENMOD procedure. LSMEANS and ESTIMATE statements will be constructed to estimate statistics of interest (e.g., group and time-specific proportions and means) as well as to test specific contrasts (e.g., mean differences between groups across time points). For all GEE models, the covariance structure will employ an exchangeable covariance structure. The tenability of all assumptions will be evaluated. In the event assumptions are not met, more appropriate statistical models will be utilized.

All statistical tests will be conducted at a Type I Error Rate of (b) (4) Corrections for the potential inflation of Type I Error will not be made due to the potential inflation of Type II error (Perneger, 1998). Significant *p*-values will be reported with high precision (to the 4th decimal place) to allow reviewers to evaluate significance after applying a Bonferroni correction, if desired. Estimates with denominator sample sizes less than (b) or having a relative standard error greater than 30% will be reported with a note of low statistical precision. Estimates with denominator sample sizes less than (b) will not be reported with a note of small sample size.

5.1 Characterization of tobacco use behaviors

1. **Tobacco use status prior to first trying IQOS®** – Descriptive statistics will be employed to summarize the percent and count of participants who report use of tobacco products before first trying IQOS® that characterizes them into one of the following

[11] All references to Baseline within this section = survey 1-Time 0

groups: Never tobacco user; long term former tobacco user; current smoker; other current tobacco user (Table 3).

Current Use of Tobacco Products – Descriptive statistics will be employed to summarize the percent and count of participants who report current use of tobacco products that characterizes them into one of the following groups: IQOS® only; Cigarettes only; IQOS® and cigarettes; IQOS® and one other tobacco product (excluding cigarettes); IQOS® and two or more other tobacco products, including cigarettes; IQOS® and two or more other tobacco products, excluding cigarettes. The current use categories will be stratified by predominant use of menthol or regular HeatSticks® and use of a cessation treatment (Table 4).

2. **Cigarettes per day change among dual users** – A GEE with a cumulative logit link will be employed to estimate the changes in cigarettes per day categories among Test participants who dual use IQOS® and cigarettes who report reduced cigarettes per day by at least 50%, the same cigarettes per day (less change than ±50%), or increased cigarettes per day by at least 50% compared to the prior wave. The model will include predominant use of menthol or regular HeatSticks® and cigarettes and use of a cessation treatment. The dependent variable will be change in cigarettes per day: reduced cigarettes per day by at least 50%, the same cigarettes per day (reference), or increased cigarettes per day by at least 50% (Descriptive statistics, Table 5; Model results, Table 6).

   The standardized calculation for cigarettes per day for this measure is defined as:

$$\left(\begin{array}{c}\text{Cigarettes used per}\\ \text{day on days used}\\ \text{in the past 30 days}\end{array} \times \begin{array}{c}\text{Days used in}\\ \text{the past 30 days}\end{array} \right) \div 30$$

   Standardized cigarettes per day is then grouped into change categories compared to the prior wave.

3. **Cigarettes per day over time among dual users** – A GEE traditional linear model will be employed to estimate the cigarettes per day among baseline IQOS® and Cigarette dual users by time point. The model will include time predominant use of menthol or regular HeatSticks® and cigarettes and use of a cessation treatment. The parameters derived from the statistical model will be used to estimate and test for differences in average standardized cigarettes per day over time compared to baseline (Descriptive statistics, Table 7; Model results, Table 8).

   The standardized calculation for cigarettes per day for this measure is defined as:

$$\left(\begin{array}{c}\text{Cigarettes used per}\\ \text{day on days used}\\ \text{in the past 30 days}\end{array} \times \begin{array}{c}\text{Days used in}\\ \text{the past 30 days}\end{array} \right) \div 30$$

4. **Average Number of Days Used IQOS®/Cigarettes per 30 days** – Descriptive statistics will be employed to summarize the mean number of days [out of 30 days] Test and Reference participants reported using each tobacco product [IQOS® and cigarettes] at each time point stratified by predominant use of menthol or regular

HeatSticks® and cigarettes. The mean number of days used tobacco products is defined as the sum of the number of days product used for each participant divided by the number of participants who reported having used the tobacco product during the past 30 days (Table 9).

Formula: $\bar{x} = \frac{\sum x}{n}$

Where:

x = number of days product used for each participant

n = participants who reported having used the tobacco product during the past 30 days

Summary Statistics will include means, standard deviations, medians and interquartile range.

5. **Median Number of Units (e.g., sticks) of IQOS®/Cigarettes Used per Day in Past 30 Days** – Descriptive statistics will be employed to summarize the median number of units (e.g., sticks) of each tobacco product [IQOS® and cigarettes] Test and Reference participants used in a given day [out of 30 days] at each time point stratified by predominant use of menthol or regular HeatSticks® and cigarettes. The median number of units (e.g., sticks) of each tobacco product will be calculated among participants who used the tobacco product on at least one day in the past 30 days. Summary Statistics will include median and interquartile range (Table 10).
6. **Current Use of Cigarettes** – A GEE log-binomial regression model will be employed to estimate the percent of participants who are current established cigarette smokers by group and time point. The model will include group (Test, Reference), time and group-BY-time, years smoking cigarettes, HeatStick preference, menthol cigarette preference, use of a cessation treatment, and propensity score. The dependent variable will be yes/no endorsement of current established cigarette smoking. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, current use Table 11; Descriptive statistics, current menthol and regular Heatstick and Cigarette use Table 12; Model results, Table 13).

5.2 Characterization of product use transitions

1. **Change among dual users of IQOS® and Cigarettes** – Descriptive statistics will be employed to summarize the percent and count of prior wave IQOS® and cigarette dual users from the IQOS® user group who at surveys 2, 3, 4, 5, or 6 are exclusive IQOS® users, exclusive smokers, IQOS® and smoking dual users, or users of neither product, irrespective of other tobacco product use and stratifying by predominant use of menthol or regular HeatSticks® and use of a cessation treatment (Table 14).
2. **Complete Switching from Cigarettes to IQOS®** – A GEE log-binomial regression model will be employed to estimate the percent of participants who use IQOS® while transitioning from cigarettes to not at all use of cigarettes. The model will include time and menthol or regular HeatStick preference, menthol cigarette preference, and use of a cessation treatment (at baseline). The dependent variable will be calculated based on

(1) were smoking cigarettes during the 30 days before first trying IQOS®, and became former smokers after first trying IQOS® at baseline and (2) report not at all use of cigarettes and current established use of IQOS® in a subsequent survey(s) (Descriptive statistics, Table 15; Model results, Table 16)

3. **Complete Switching from IQOS® to Cigarettes** – A GEE log-binomial model will be employed to estimate the percent of participants in the IQOS® user group who, at a future survey, report current established smoking and no IQOS® use. The model will include time and menthol or regular HeatStick preference, menthol cigarette preference, and use of a cessation treatment (at baseline). The dependent variable will be calculated based on (1) current established use of IQOS® at baseline and (2) report not at all use of IQOS® and current established use of cigarettes in a subsequent survey(s) (Descriptive statistics, Table 17; Model results, Table 18).

4. **Ever Use of a [Tobacco Product] Never Used at Baseline** – A GEE log-binomial model will be employed to estimate the percent of participants who report ever use at surveys 2, 3, 4, 5, or 6 of a [Tobacco Product] never used, even one time, at survey 1 by group and time point. The model will include group (Test, Reference), time, group-BY-time, menthol or regular HeatStick preference, and propensity score. The dependent variable will be whether or not participants who initiated use of a tobacco product during the study. The parameters derived from the statistical model will be used to estimate and test for differences in proportions across time points by group (Descriptive statistics, with IQOS® HeatStick preference, Table 19; Model results, Table 20).

5. **Established Use of a [Tobacco Product] Never Used at Baseline** – A GEE log-binomial model will be employed to estimate the percent of participants who report ever established use at surveys 2, 3, 4, 5, or 6 of a [Tobacco Product] never used, even one time, at survey 1 by group and time point. The model will include group (Test, Reference), time, group-BY-time, menthol or regular HeatStick preference, and propensity score. The dependent variable will be whether or not participants who initiated use and reached lifetime established use criterion for a tobacco product during the study. The parameters derived from the statistical model will be used to estimate and test for differences in proportions across time points by group (Descriptive statistics, with stratification of IQOS HeatStick preference, Table 21; Model results, Table 22).

6. **Smoking Relapse** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the IQOS® user group that experience smoking relapse. The model will include time, years smoked cigarettes, menthol or regular HeatStick preference, and use of a cessation treatment. The dependent variable will be percent of participants who report established use of cigarettes but report not currently using cigarettes at survey 1, and at a subsequent survey report resuming current use of cigarettes within 12 months of not using (Descriptive statistics, with stratification of IQOS HeatStick preference, Table 23; Model results, Table 24).

7. **Smoking Re-initiation** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the IQOS® user group that experience smoking re-initiation. The model will include time, years smoked cigarettes, menthol or regular HeatStick preference, and use of a cessation treatment. The dependent variable will be

percent of participants who report established use of cigarettes but report not currently using cigarettes at survey 1, and at a subsequent survey report resuming current use of cigarettes 12 months or more after not using (Descriptive statistics, with stratification of IQOS HeatStick preference, Table 25; Model results, Table 26).

8. **Quit Smoking After First Trying IQOS® as Assessed at Survey 1** – Descriptive statistics will be employed to summarize the percent and count of the IQOS® user group who were established smokers and smoked in the 30 days before first trying IQOS® and quit smoking at survey 1 stratified by predominant use of menthol or regular HeatSticks® and baseline use of a cessation treatment (Table 27).
9. **Quit Attempts** – A GEE log-binomial regression model will be employed to estimate the percent of baseline smokers who attempted to quit smoking cigarettes in the past 12/6/3 months at survey 1 and at each interval between subsequent surveys between groups over time. The model will include group (Test, Reference), time, group-BY-time, quit status, years smoking cigarettes, predominant use of menthol or regular HeatSticks®, and propensity score. The dependent variable will be yes/no response to past 12/6/3 month quit attempts for cigarettes. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, with stratification of IQOS HeatStick preference, Table 28; Model results, Table 29).
10. **Use of Cessation Treatment** – Descriptive statistics will be employed to summarize the percent and count of participants who report use of a cessation treatment at baseline (Never, Past 30 Days, >30 Days -12 Months, >12 Months) (Table 30), use (past 30 day, > past 30 day to last assessment), and incident use of a cessation treatment (Yes/No) at surveys 2, 3, 4, 5, or 6 (Table 31).
11. **Completely Quit Smoking** – A GEE log-binomial regression model will be employed to estimate the percent of baseline smokers who completely quit smoking cigarettes between groups over time. The model will include group (Test, Reference), time, group-BY-time, years smoking cigarettes, menthol or regular HeatStick preference, use of a cessation treatment, and propensity score. The dependent variable will be yes/no response to completely quit smoking cigarettes. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, Table 32; Model results, Table 33).
12. **Completely Quit IQOS®** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the IQOS® user group who completely quit IQOS® use over time. The model will include time and years of IQOS® use, menthol or regular HeatStick preference, and use of a cessation treatment. The dependent variable will be yes/no response to completely quit IQOS® (Descriptive statistics, with stratification of IQOS HeatStick preference, Table 32; Model results, Table 34).
13. **Completely Quit All Tobacco** – A GEE log-binomial regression model will be employed to estimate the percent of established IQOS® users and cigarette smokers who completely quit all tobacco products at surveys 2, 3, 4, 5, or 6. The model will include group (Test, Reference), time, group-BY-time, menthol or regular HeatStick preference, use of a cessation treatment, and propensity score. The dependent variable will be coded yes/no based on whether the participant met the criteria for "completely

quit" all tobacco products. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, Table 32; Model results, Table 35).

5.3 Assessment of health-related quality of life, signs and symptoms

1. **Health-related Quality of Life (physical)** – A GEE traditional linear model will be employed to estimate the mean physical health T-score between groups over time. The model will include group (Test, Reference), time, and group-BY-time, years smoked cigarettes, number of diagnoses, and propensity score. The dependent variable will be the physical health T-score. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 36; Model results, Table 37).
2. **Health-related Quality of Life (mental)** – A GEE traditional linear model will be employed to estimate the mean mental health T-score between groups over time. The model will include group (Test, Reference), time, and group-BY-time, years smoked cigarettes, number of diagnoses, and propensity score. The dependent variable will be the mean mental health T-score. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 36; Model results, Table 37).
3. **Cardiovascular Signs and Symptoms** – A GEE Poisson regression model will be employed to estimate the mean number of cardiovascular symptoms present between groups over time. The model will include group (Test, Reference), time, group-BY-time, years smoked cigarettes, number of diagnoses, and propensity score. The dependent variable will be the number of cardiovascular symptoms present. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 36; Model results, Table 37).
4. **Respiratory Signs and Symptoms** – A GEE Poisson regression model will be employed to estimate the mean number of respiratory symptoms present between groups over time. The model will include group (Test, Reference), time, group-BY-time, years smoked cigarettes, number of diagnoses, and propensity score. The dependent variable will be the number of respiratory symptoms present. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 36; Model results, Table 37).

5.4 Assessment of risk perceptions and perception and understanding of IQOS® and exposure reduction

1. **Risk Perceptions** – Descriptive statistics will be employed to summarize the means, standard deviations, medians and interquartile range number of the PRI-G composite score of [IQOS® and cigarettes] among the IQOS® user group and the cigarette smoker at Survey 1, 4 and 6 (Table 38). Summary Statistics will include means, standard deviations, medians and interquartile range.

2. **Perception of IQOS® Exposure Reduction** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the IQOS® user and cigarette smoker groups perception that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure over time compared to baseline. The model will include time. The dependent variable will be correct perception/misperception response to reduced harmful or potentially harmful chemical exposure perception. (Descriptive statistics, with complete distribution of response options, Table 39; Model results, Table 40).
3. **Understanding of What to do to Reduce Exposure** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the IQOS® user and cigarette smoker groups understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure over time compared to baseline. The model will include time. The dependent variable will be correct perception/misperception response to what smokers must do to reduce harmful or potentially harmful chemical exposure. This model will include participants who perceive that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure. (Descriptive statistics, with complete distribution of response options, Table 41; Model results, Table 42).

6 ADDITIONAL DATA SUMMARIES

6.1 Participation Proportions

The following proportions will be reported in total and by sex, age, and study group (as applicable).

- **Contact Proportion**: The number of persons screened for eligibility divided by the total number of persons attempted to be reached for eligibility screening (i.e., the number of invitations sent)
- **Eligibility Proportion**: The number of persons eligible for enrollment (i.e., persons who meet all inclusion criteria and no exclusion criteria) divided by the total number of persons screened for eligibility
- **Completion Proportion**: The number of completed interviews divided by the number of attempted interviews (completed plus partial)
- **Response Proportion**: The number of completed interviews divided by the number of invitations sent.

7 SURVEY PERFORMANCE EVALUATION

7.1 Overview

Survey development, testing, and evaluation are viewed as iterative processes that frequently entail examining the performance of the survey instruments (FDA, 2009). The purpose of this section is to provide an analytical plan to evaluate the performance of the survey instruments

used in this study. The summary of results will be reported as part of the Detailed Study Report. The full report of the survey performance evaluation will be provided under separate cover.

7.2 Examine Survey Administration Meta-Data

The survey administration meta-data file contains the number of seconds a participant takes to complete each question across each entire survey. Survey administration meta-data (e.g., the average and fastest survey completion time by study group) will be examined for irregularities to identify issues associated with how participants engaged with the survey.

a. The total time required to complete each survey will be calculated and depicted graphically using histograms in total and by study group. Means, medians, standard deviations, minimums and maximums will also be reported in total and by study group.

b. The 5% fastest participants for each survey will be identified and their demographics and tobacco product use patterns will be examined for irregularities relative to the other participants.

7.3 Data Quality Checks

A variety of data quality checks will be implemented to identify and flag records that contain forms of data falsification or missing data. These records will be examined to understand their influence on study results and for possible exclusion from analysis. Data falsification forms include "speeding," nondifferentiation, and gibberish/non-sensical verbatim response. The number of respondents that are flagged for each data falsification form will be included in the final survey report.

"Speeding" is completing a questionnaire very quickly, without giving thought to answers. In this study, a participant who completes the main questionnaire in less than 30% of the median completion time of participants with a similar number of tobacco products used is flagged for review. The amount of time to complete each questionnaire is expected to vary depending on the number of tobacco products used. Median questionnaire duration will be calculated and compared among participants that:

- Use no tobacco products
- Use one tobacco product
- Use two tobacco products
- Use more than two tobacco products

Nondifferentiation of rating, or "straightlining" is when a participant does not differentiate between response options and selects the same response for multiple questions (e.g., selecting the first option for a question series). Participants who have answers with 100% similarity for scaled attribute questions with 15 or more dimensions are flagged for review.

Free text fields and verbatim responses that are poor quality (e.g. gibberish, non-sensical responses, single characters, profanity) are flagged for possible removal. The main questionnaire does not contain open-ended questions and includes program logic to ensure valid values, so this review will be applied to typed-in "other" responses. The questionnaire is

designed to minimize outliers by defining ranges for numeric responses. For example, cigarettes smoked per day has a minimum of '<1' and a maximum of 'more than 50,' and the number of days used in the past 30 days can only range from 0 to 30. Therefore, we do not expect any outliers relevant to this analysis plan.

The main analysis will be conducted with the full dataset and sensitivity analyses will be conducted without the flagged responses to determine if the potentially invalid data substantially influence the results. These sensitivity analyses will be performed to assess the robustness of the results with the exclusion of flagged data. If there are no substantial changes observed, results are considered robust to invalid data. Treatment of invalid data and inconsistencies will be noted in the Final Study Report as applicable.

8 ADDITIONAL ANALYSES

As needed, additional analyses may be conducted to clarify or further contextualize study outcomes measures. These analyses may be exploratory in nature. These additional supportive analyses will be documented, amended to the SAP and reported in the final study report.

9 STATISTICAL METHODOLOGIES

9.1 General Consideration

The data will be analyzed and reported both descriptively – primarily using percentages, frequency distributions, means, standard deviations and medians, and through the use of inferential statistics such as generalized linear models.

9.2 Missing Data

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

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

on the weighted data will be provided in the appendix. This analysis will be repeated separately at each time point.

To address the potential bias due to attrition in the GEE models, the weighted GEE estimator originally proposed by Robins, Rotnitzky, and Zhao (1995) will be performed.[12] 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.

9.3 Statistical Analysis of Data

9.3.1 Analysis of Categorical Data

All summaries of categorical data will present sample sizes, proportions, and 95% confidence intervals for each study group.

9.3.2 Analysis of Continuous Data

All summaries of continuous data will present sample sizes, mean, standard deviation, median, interquartile range and 95% confidence intervals by study group.

9.3.3 Analysis Using GEE Models

All summaries of models will include number of observations used, estimate, standard error, Z value, and *p*-value for the model and variables in the model.

9.4 Coding of Open-Ended Data

Certain survey questions allow participants to provide an answer other than what is pre-listed in the response set (e.g., signs and symptoms). These verbatim responses are 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 are "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" are categorized, and frequency of these responses are evaluated. Responses with a frequency beyond a certain threshold (e.g., 2-5%) are then assigned a code, and the coded response is analyzed and reported as part of the response set for that question. Responses with frequencies below the threshold are reported as "other."

9.5 Reporting Conventions

All summary statistics, including percentages, means, standard deviations, medians and confidence intervals will be reported to the second decimal place. Standard rounding

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

conventions will be used (e.g. 12.567 rounded to 12.57; 12.564 rounded to 12.56). Significant *p*-values will be reported with high precision (to the 4th decimal place) to allow reviewers to evaluate significance after applying a Bonferroni correction, if desired.

10 FIGURES AND TABLES

Examples of table shells for the analyses are provided.

Table 3: Tobacco use status prior to first trying IQOS® – Test Group (Descriptive Statistics)

Measure	Baseline % (CI)
Base: Test Group Participants	*n=xxx*
Never tobacco user	
Long term former tobacco user	
Current smoker	
Current tobacco user	

Table 4: Current Use of Tobacco Products – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Tobacco Use Behaviors						
IQOS® only						
By HeatStick Preference						
By Cessation Treatment Use						
Cigarettes only						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and one other tobacco product, excluding cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and two or more other tobacco products, including cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and two or more other tobacco products, excluding cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Tobacco Use Behaviors						
IQOS® only						
By HeatStick Preference						
By Cessation Treatment Use						
Cigarettes only						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and cigarettes						

By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and one other tobacco product, excluding cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and two or more other tobacco products, including cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						
IQOS® and two or more other tobacco products, excluding cigarettes						
By HeatStick Preference						
By Cessation Treatment Use						

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 5: Cigarette per day change among dual users – Test Group (Descriptive Statistics)

Measure	Cigarette Per Day Category		
	Reduced cigarettes per day by at least 50% **Number, % (CI)**	Same cigarettes per day (less change than ±50%) **Number, % (CI)**	Increased cigarettes per day by at least 50% **Number, % (CI)**
Baseline IQOS® and cigarette dual users who, at Wave 2, are classified as:			
By HeatStick Preference			
Menthol Cigarette Preference			
By Cessation Treatment Use			
Wave 2 IQOS® and cigarette dual users who, at Wave 3, are classified as:			
By HeatStick Preference			
Menthol Cigarette Preference			
By Cessation Treatment Use			
Wave 3 IQOS® and cigarette dual users who, at Wave 4, are classified as:			
By HeatStick Preference			
Menthol Cigarette Preference			
By Cessation Treatment Use			
Wave 4 IQOS® and cigarette dual users who, at Wave 5, are classified as:			
By HeatStick Preference			
Menthol Cigarette Preference			
By Cessation Treatment Use			
Wave 5 IQOS® and cigarette dual users who, at Wave 6, are classified as:			
By HeatStick Preference			
Menthol Cigarette Preference			
By Cessation Treatment Use			

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 6: Results from Generalized Estimating Equation: Cigarette per day change among dual users

Term	Estimate	SE	Z value	*p* value
Threshold 1				
Threshold 2				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
HeatStick Preference				
Menthol Cigarette Preference				
Cessation Treatment				
Fit Statistics				
Deviance				
AIC				
BIC				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 7: Cigarettes per day over time among dual users – Test Group (Descriptive Statistics)

	Survey Wave					
Measure	**Baseline**	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Average cigarettes per day						
Mean (CI)						
Standard deviation						
Median						
Interquartile Range						

This table repeated for: HeatStick Preference, Menthol Cigarette Preference, Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 8: Results from Generalized Estimating Equation: Cigarettes per day over time among dual users

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
HeatStick Preference				
Menthol Cigarette Preference				
Cessation Treatment				
Fit Statistics				
Deviance				
AIC				
BIC				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 9: Average Number of Days Used IQOS®/Cigarettes per 30 days – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Participants who used IQOS® on at least one day in the past 30 days	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Number of days (out of 30 days) IQOS® is used						
Mean (CI)						
Standard deviation						
Median						
Interquartile Range						
Base: Participants who smoked a cigarette on at least one day in the past 30 days	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Number of days (out of 30 days) cigarettes are smoked						
Mean (CI)						
Standard deviation						
Median						
Interquartile Range						

This table repeated for: Reference Group, HeatStick Preference, Menthol Cigarette Preference

Table 10: Median Number of Units (e.g., sticks) of IQOS®/Cigarettes Used per Day on days used in Past 30 Days – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Participants who used IQOS® on at least one day in the past 30 days	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Number of Marlboro HeatSticks® used per day on days used						
Median						
Interquartile Range						
Base: Participants who smoked a cigarette on at least one day in the past 30 days	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Number of cigarettes used per day on days used						
Median						
Interquartile Range						

This table repeated for: Reference Group, HeatStick Preference, Menthol Cigarette Preference

Table 11: Current Use of Cigarettes (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Current established cigarette smokers						
By HeatStick Preference						
By Menthol Cigarette Preference						
By Cessation Treatment						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Current established cigarette smokers						
By HeatStick Preference						
By Menthol Cigarette Preference						
By Cessation Treatment						

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 12: Current Menthol and Regular Heatstick and Cigarette Use (Descriptive Statistics)

		Cigarette Use Status			
		Current Non-menthol Smoker Number, %	**Current Menthol Smoker Number, %**	**Non-current Smoker Number, %**	**Total**
HeatStick Use Status	**Current Non-menthol HeatStick User Number, %**				
	Current Menthol HeatStick User Number, %				
	Non-current HeatStick User Number, %				
	Total				

Table repeated for: Reference group and Wave

Table 13: Results from Generalized Estimating Equation: Current Use of Cigarettes

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 3* Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
Years smoked cigarettes				
HeatStick Preference				
Menthol Cigarette Preference				
Cessation Treatment				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Baseline)				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 14: Change among dual users of IQOS® and Cigarettes – Test Group (Descriptive Statistics)

Measure	Current IQOS® and Cigarette Use Status				
	Exclusive IQOS® users **Number, % (CI)**	Exclusive smokers **Number, % (CI)**	IQOS® and smoking dual users **Number, % (CI)**	Users of neither product **Number, % (CI)**	Total **Number**
Baseline IQOS® and cigarette dual users who, at Wave 2, are classified as:					
By Menthol HeatStick Preference					
By Cessation Treatment Use					
Wave 2 IQOS® and cigarette dual users who, at Wave 3, are classified as:					
By Menthol HeatStick Preference					
By Cessation Treatment Use					
Wave 3 IQOS® and cigarette dual users who, at Wave 4, are classified as:					
By Menthol HeatStick Preference					
By Cessation Treatment Use					
Wave 4 IQOS® and cigarette dual users who, at Wave 5, are classified as:					
By Menthol HeatStick Preference					
By Cessation Treatment Use					
Wave 5 IQOS® and cigarette dual users who, at Wave 6, are classified as:					
By Menthol HeatStick Preference					
By Cessation Treatment Use					

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is Never, >12 Months, >30 Days -12 Months, Past 30 Days. Behavior classification are irrespective of other tobacco product use other than IQOS® and cigarettes.

Table 15: Complete Switching from Cigarettes to IQOS® (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total switched from cigarettes to IQOS®						
By HeatStick Preference (at baseline)						
By Menthol Cigarette Preference (at baseline)						
By Cessation Treatment (at baseline)						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total switched from cigarettes to IQOS®						
By HeatStick Preference (at baseline)						
By Menthol Cigarette Preference (at baseline)						
By Cessation Treatment (at baseline)						

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is Never, >12 Months, >30 Days -12 Months, Past 30 Days. Behavior classification are irrespective of other tobacco product use other than IQOS® and cigarettes.

Table 16: Results from Generalized Estimating Equation: Complete Switching from Cigarettes to IQOS®

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
HeatStick Preference (at baseline)				
Menthol Cigarette Status (baseline)				
Cessation Treatment (at baseline)				
Fit Statistics				
Deviance				
AIC				
BIC				

This table repeated for: Reference Group

Table 17: Complete Switching from IQOS® to Cigarettes (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
By HeatStick Preference (at baseline)	NA					
By Menthol Cigarette Preference (at baseline)	NA					
By Cessation Treatment (at baseline)	NA					

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is Never, >12 Months, >30 Days -12 Months, Past 30 Days. Behavior classification are irrespective of other tobacco product use other than IQOS® and cigarettes. NA=Not applicable.

Table 18: Results from Generalized Estimating Equation: Complete Switching from IQOS® to Cigarettes

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
HeatStick Preference (at baseline)				
Menthol Cigarette Status (at baseline)				
Cessation Treatment (at baseline)				
Fit Statistics				
Deviance				
AIC				
BIC				

Table 19: Ever Use of a [Tobacco Product] Never Used at Baseline – (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Ever use (even one time) of a [Tobacco Product] never used, even one time, at survey 1						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-vapor products	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					
By HeatStick Preference	NA					
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Ever use (even one time) of a [Tobacco Product] never used, even one time, at survey 1						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-vapor products	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					

Note: HeatStick Preference is Menthol, Regular. NA=Not applicable

Table 20: Results from Generalized Estimating Equation: Ever Use of a [Tobacco Product] Never Used at Baseline

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
HeatStick Preference				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

This table repeated for: Each tobacco category

Table 21: Established Use of a [Tobacco Product] Never Used at Baseline – (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Ever use (even one time) of a [Tobacco Product] never used, even one time, at survey 1						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-vapor products	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					
By HeatStick Preference	NA					
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Ever use (even one time) of a [Tobacco Product] never used, even one time, at survey 1						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-vapor products	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					

Note: HeatStick Preference is Menthol, Regular. NA=Not applicable

Table 22: Results from Generalized Estimating Equation: Established Use of a [Tobacco Product] Never Used at Baseline

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
HeatStick Preference				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

This table repeated for: Each tobacco category

Table 23: Smoking Relapse – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total Relapse to Cigarette Smoking	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up. NA=Not applicable

Table 24: Results from Generalized Estimating Equation: Smoking Relapse

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years smoked cigarettes				
HeatStick Preference				
Cessation Treatment				
Fit Statistics				
Deviance				
AIC				
BIC				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 25: Smoking Re-initiation – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total Re-initiation to Cigarette Smoking	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up. NA=Not applicable

Table 26: Results from Generalized Estimating Equation: Smoking Re-initiation

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years smoked cigarettes				
HeatStick Preference				
Cessation Treatment				
Fit Statistics				
Deviance				
AIC				
BIC				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at baseline and at each follow-up.

Table 27: Quit smoking after first trying IQOS® as assessed at survey 1 – Test Group (Descriptive Statistics)

Measure	Baseline % (CI)
Base: Test Group Participants who were established smokers and smoked in the 30 days before first trying IQOS	*n=xxx*
Total Quit smoking at survey 1	
By HeatStick Preference	
By Menthol Cigarette Preference	
By Cessation Treatment	

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is Never, >12 Months, >30 Days -12 Months, Past 30 Days.

Table 28: Quit Attempts – Test Group (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	Month 3 % (CI)	Month 6 % (CI)	Month 12 % (CI)	Month 18 % (CI)	Month 24 % (CI)
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Attempted to quit smoking cigarettes in the past 12 months at Survey 1 and at each interval between subsequent surveys						
Menthol HeatStick Preference						
Regular Heatstick Preference						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Attempted to quit smoking cigarettes in the past 12 months at Survey 1 and at each interval between subsequent surveys						
Menthol HeatStick Preference						
Regular Heatstick Preference						

Table 29: Results from Generalized Estimating Equation: Quit Attempts

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 3* Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
Quit status				
Years smoked cigarettes				
HeatStick Preference				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Baseline)				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

Table 30: Use of Cessation Treatment at Baseline: (Descriptive Statistics)

Measure	Baseline % (CI)
Base: Test Group Participants	*n=xxx*
Never cessation treatment	
Cessation treatment in past 30 days	
Cessation treatment >30 days -12 months ago	
Cessation treatment >12 months ago	
Base: Reference Group Participants	*n=xxx*
Never cessation treatment	
Cessation treatment in past 30 days	
Cessation treatment >30 days -12 months ago	
Cessation treatment >12 months ago	

Table 31: Use of a Cessation Treatment: Use and Incident Use at Each Survey Period (Descriptive Statistics)

Measure	Survey Wave				
	Month 3 % (CI)	Month 6 % (CI)	Month 12 % (CI)	Month 18 % (CI)	Month 24 % (CI)
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Use of a cessation treatment in the past 30 days					
Use of a cessation treatment from > 30 days to last assessment					
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Use of a cessation treatment in the past 30 days					
Use of a cessation treatment from > 30 days to last assessment					
Base: Test Group Participants without history of prior use of a cessation treatment	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Incident use of a cessation treatment					
Base: Reference Group Participants without history of prior use of a cessation treatment	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Incident use of a cessation treatment					

Table 32: Completely Quit (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3 % (CI)**	**Month 6 % (CI)**	**Month 12 % (CI)**	**Month 18 % (CI)**	**Month 24 % (CI)**
Base: Test Group Established Smokers at baseline	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total completely quit smoking cigarettes	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total completely quit smoking cigarettes	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total completely quit IQOS	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total completely quit all tobacco	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Total completely quit all tobacco	NA					
By HeatStick Preference	NA					
By Cessation Treatment	NA					

Note: HeatStick Preference is Menthol, Regular; Use of a Cessation Treatment is past 30 days (Yes/No) at each follow-up. NA=Not applicable.

Table 33: Results from Generalized Estimating Equation: Completely Quit Smoking

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
Years smoked cigarettes				
HeatStick Preference				
Cessation Treatment				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at each follow-up.

Table 34: Results from Generalized Estimating Equation: Completely Quit IQOS®

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years of IQOS® use				
HeatStick Preference				
Cessation Treatment				
Fit Statistics				
Deviance				
AIC				
BIC				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at each follow-up.

Table 35: Results from Generalized Estimating Equation: Completely Quit All Tobacco

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
HeatStick Preference				
Cessation Treatment				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

Note: Use of a Cessation Treatment is past 30 days (Yes/No) at each follow-up.

Table 36: Health-related Quality of Life, Signs and Symptoms (Descriptive Statistics)

Measure	Survey Wave					
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Physical health T-score						
Mean (CI)						
Standard deviation						
Median						
Interquartile Range						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Physical health T-score						
Mean (CI)						
Standard deviation						
Median						
Interquartile Range						

This table repeated for:

- Mental health T-score
- Number of cardiovascular symptoms
- Number of respiratory symptoms

Table 37: Results from Generalized Estimating Equation: Health-related Quality of Life, Signs and Symptoms

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Test				
Month 3* Test				
Month 6* Test				
Month 12* Test				
Month 18* Test				
Month 24* Test				
Years smoked cigarettes				
Diagnoses				
Propensity score				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Baseline)				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

This table repeated for:

- Mental health T-score
- Number of cardiovascular symptoms
- Number of respiratory symptoms

Table 38: Risk Perception Composite Score – Test Group (Descriptive Statistics)

Measure	Survey Wave		
	Baseline	**Month 12**	**Month 24**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*
PRI-G composite score - Cigarettes			
Mean (CI)			
Standard deviation			
Median			
Interquartile Range			
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*
PRI-G composite score - IQOS®			
Mean (CI)			
Standard deviation			
Median			
Interquartile Range			

This table repeated for: Reference Group

Table 39: Perception of IQOS® and Exposure Reduction (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Test Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Have more exposure to harmful or potentially harmful chemicals						
Have the same exposure to harmful or potentially harmful chemicals						
Have less exposure to harmful or potentially harmful chemicals (correct answer)						
Have no exposure to harmful or potentially harmful chemicals						
Don't know						
Base: Reference Group Participants	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Have more exposure to harmful or potentially harmful chemicals						
Have the same exposure to harmful or potentially harmful chemicals						
Have less exposure to harmful or potentially harmful chemicals (correct answer)						
Have no exposure to harmful or potentially harmful chemicals						
Don't know						

Table 40: Results from Generalized Estimating Equation: Perception of IQOS® and Exposure Reduction

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Fit Statistics				
Deviance				
AIC				
BIC				

Table 41: Understanding of What to do to Reduce Exposure (Descriptive Statistics)

Measure	Survey Wave					
	Baseline % (CI)	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Base: Test Group Participants who perceive that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Stop smoking cigarettes completely and only use IQOS (correct answer)						
Smoke fewer cigarettes and also use IQOS						
Keep smoking the same amount of cigarettes and also use IQOS						
Don't know						
Base: Reference Group Participants who perceive that switching completely to IQOS® results in reduced harmful or potentially harmful chemical exposure	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*	*n=xxx*
Stop smoking cigarettes completely and only use IQOS (correct answer)						
Smoke fewer cigarettes and also use IQOS						
Keep smoking the same amount of cigarettes and also use IQOS						
Don't know						

Table 42: Comprehension: Must Switch Completely from Cigarettes to IQOS® (Descriptive Statistics)

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Fit Statistics				
Deviance				
AIC				
BIC				

11 SUMMARY OF CHANGES TO THE PROTOCOL AND/OR STATISTICAL ANALYSIS PLAN

Version	Date of Revision	Revision	Reason for Revision
1.0	8/6/2020	(b) (4)	
2.0	11/4/2020		In its October 5th letter, FDA determined that these changes are necessary to monitor participants' understanding of the risks of using IQOS at baseline and over time.

		(b) (4)	To better understand the role menthol plays in behaviors
			Reduce respondent burden
			Understand role of menthol HeatSticks in increasing IQOS adoption and complete switching in menthol cigarette smokers
			To understand if cessation therapies are being used alongside tobacco products including IQOS and to assess the overall history of cessation treatment use among IQOS users
			To account for additional analyses of regular and menthol HeatStick flavors.
			To better interpret the public health implications
			To ensure study validity
			To enable the agency to understand whether excluding potentially invalid data and imputing missing data influenced results substantively

12 REFERENCES

Austin, P. C. 2011. 'An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies', Multivariate Behav Res, 46: 399-424.

Berg, C. J., D. B. Barr, E. Stratton, C. Escoffery, and M. Kegler. 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: 789-800.

Cano, S., Chrea, C., Salzberger, T., Alfieri, T., Emilien, G., Mainy, N., 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. doi:10.1186/s12955-018-0997-5.

Campagna, D., F. Cibella, P. Caponnetto, M. D. Amaradio, M. Caruso, J. B. Morjaria, M. Malerba, and R. Polosa. 2016. 'Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes', Eur J Clin Invest, 46: 698-706.

Caponnetto, P., R. Auditore, C. Russo, G. C. Cappello, and R. Polosa. 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: 446-61.

Choi, K., and J. L. Forster. 2014. 'Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults', Am J Prev Med, 46: 175-8.

Cibella, F., D. Campagna, P. Caponnetto, M. D. Amaradio, M. Caruso, C. Russo, D. W. Cockcroft, and R. Polosa. 2016. 'Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes', Clin Sci (Lond), 130: 1929-37.

da Veiga, P. V., and R. P. Wilder. 2008. 'Maternal smoking during pregnancy and birthweight: a propensity score matching approach', Matern Child Health J, 12: 194-203.

Dobbie, F., R. Hiscock, J. Leonardi-Bee, S. Murray, L. Shahab, P. Aveyard, T. Coleman, A. McEwen, H. McRobbie, R. Purves, and L. Bauld. 2015. 'Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS): a prospective cohort study', Health Technol Assess, 19: 1-156.

Farsalinos, K. E., G. Romagna, D. Tsiapras, S. Kyrzopoulos, and V. Voudris. 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: 4356-73.

Grana, R. A., L. Popova, and P. M. Ling. 2014. 'A longitudinal analysis of electronic cigarette use and smoking cessation', JAMA Intern Med, 174: 812-3.

Gravetter, F.J. & Wallnua, L.B. (2014). Essentials of Statistics for the Behavioral Sciences: 8th Edition. Belmont, CA: Wadsworth.

Halpern, S. D., M. O. Harhay, K. Saulsgiver, C. Brophy, A. B. Troxel, and K. G. Volpp. 2018. 'A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation', N Engl J Med, 378: 2302-10.

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. Addiction, 84, 791–800.

Hyland, A., B. K. Ambrose, K. P. Conway, N. Borek, E. Lambert, C. Carusi, K. Taylor, S. Crosse, G. T. Fong, K. M. Cummings, D. Abrams, J. P. Pierce, J. Sargent, K. Messer, M. Bansal-Travers, R. Niaura, D. Vallone, D. Hammond, N. Hilmi, J. Kwan, A. Piesse, G. Kalton, S. Lohr, N. Pharris-Ciurej, V. Castleman, V. R. Green, G. Tessman, A. Kaufman, C. Lawrence, D. M. van Bemmel, H. L. Kimmel, B. Blount, L. Yang, B. O'Brien, C. Tworek, D. Alberding, L. C. Hull, Y. C. Cheng, D. Maklan, C. L. Backinger, and W. M. Compton. 2017. 'Design and methods of the Population Assessment of Tobacco and Health (PATH) Study', Tob Control, 26: 371-78.

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):15-9.

Leas, E. C., J. P. Pierce, T. Benmarhnia, M. M. White, M. L. Noble, D. R. Trinidad, and D. R. Strong. 2017. 'Effectiveness of Pharmaceutical Smoking Cessation Aids in a Nationally Representative Cohort of American Smokers', J Natl Cancer Inst.

Mantey, D. S., M. R. Cooper, A. Loukas, and C. L. Perry. 2017. 'E-cigarette Use and Cigarette Smoking Cessation among Texas College Students', Am J Health Behav, 41: 750-59.

McKeganey, N., J. A. Miler, and F. Haseen. 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.

McRobbie, H., A. Phillips, M. L. Goniewicz, K. M. Smith, O. Knight-West, D. Przulj, and P. Hajek. 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: 873-8.

Nides, M. A., S. J. Leischow, M. Bhatter, and M. Simmons. 2014. 'Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system', Am J Health Behav, 38: 265-74.

Norton, K. J., K. M. June, and R. J. O'Connor. 2014. 'Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes', Tob Induc Dis, 12: 17.

O'Connor, R. J., A. Hyland, G. A. Giovino, G. T. Fong, and K. M. Cummings. 2005. 'Smoker awareness of and beliefs about supposedly less-harmful tobacco products', Am J Prev Med, 29: 85-90.

O'Connor, R. J., K. J. Norton, M. Bansal-Travers, M. C. Mahoney, K. M. Cummings, and R. Borland. 2011. 'US smokers' reactions to a brief trial of oral nicotine products', Harm Reduct J, 8: 1.

Pacifici, R., S. Pichini, S. Graziano, M. Pellegrini, G. Massaro, and F. Beatrice. 2015. 'Successful Nicotine Intake in Medical Assisted Use of E-Cigarettes: A Pilot Study', Int J Environ Res Public Health, 12: 7638-46.

Parsons, V. L., C. Moriarity, K. Jonas, T. F. Moore, K. E. Davis, and L. Tompkins. 2014. 'Design and estimation for the national health interview survey, 2006-2015', Vital Health Stat 2: 1-53.

Perneger, T. V. 1998. 'What's wrong with Bonferroni adjustments', BMJ, 316: 1236-8.

Polosa, R., P. Caponnetto, M. Maglia, J. B. Morjaria, and C. Russo. 2014. 'Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit', BMC Public Health, 14: 1159.

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

Polosa, R., J. Morjaria, P. Caponnetto, M. Caruso, S. Strano, E. Battaglia, and C. Russo. 2014. 'Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal', Int J Environ Res Public Health, 11: 4965-77.

Pulvers, K., A. S. Emami, N. L. Nollen, D. R. Romero, D. R. Strong, N. L. Benowitz, and J. S. Ahluwalia. 2016. 'Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes', Nicotine Tob Res.

Pulvers, K., R. B. Hayes, T. S. Scheuermann, D. R. Romero, A. S. Emami, K. Resnicow, E. Olendzki, S. D. Person, and J. S. Ahluwalia. 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: 1085-95.

Rosenbaum, P. R, and D Rubin. 1983. 'The central role of the propensity score in observational studies for causal effects', Biometrika, 70: 41-55.

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.

SAS Version 9.4 of the SAS System for Windows. Copyright© 2002-2012 by SAS Institute Inc., Cary, NC, USA.

Substance Abuse and Mental Health Services Administration. 2017. "National Survey on Drug Use and Health." In, translated and edited by U.S. Department of Health and Human Services. Rockville, MD: The Substance Abuse and Mental Health Services Administration.

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. Tob Control January 2020 Vol 29 No s1.

Timberlake, D. S., J. Huh, and C. M. Lakon. 2009. 'Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking', Nicotine Tob Res, 11: 455-62.

U.S. Department of Health and Human Services. 2014. 'The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General.' in Centers for Disease Control and Prevention U.S. Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health (ed.) (Rockville, MD).

World Health Organization. 1998. 'The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties', Soc Sci Med, 46: 1569-85.

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, Communications in Statistics - Simulation and Computation, 48(9), 2812-2829.

Zhu, S. H., Y. L. Zhuang, S. Wong, S. E. Cummins, and G. J. Tedeschi. 2017. 'E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys', BMJ, 358: j3262.