Appendix F: Research Analysis Plan - Estimation of Awareness and Use of *IQOS*® among Underage Individuals 13-20 Years of Age

Please find on the following pages details about reporting plan for estimation of awareness and use of *IQOS*® among underage individuals 13-20 years of age.

RESEARCH ANALYSIS PLAN

ESTIMATION OF AWARENESS AND USE OF *IQOS* AMONG UNDERAGE INDIVIDUALS 13-20 YEARS OF AGE

Analysis of Relevant Data from the ALCS Underage Tobacco Use Survey (Short Title: Analysis of UTUS)

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VERSION HISTORY

Version	Version Date	Modification(s)	Reason(s) for Modification(s)
V1.0	8/6/2020	First Version	
V2.0	11/4/2020	• Removed logic skips so that *IQOS* awareness question will be asked to all participants. • Removed logic skips so that source of awareness for *IQOS* question will be asked to all participants who are aware of *IQOS*.	In response to FDA's feedback as communicated in its October 5, 2020 Information Request Letter, these changes enable the agency to accurately understand minors' awareness and use of *IQOS*.
		Added questions about recency and quantity of HeatSticks used specific to *IQOS*, which are solely conditioned on ever use of *IQOS*	These changes are made to provide information specific to *IQOS*.
		• Added questions about menthol and non-menthol HeatSticks used with *IQOS*. • Added stratified analyses in objectives 2 to 4 by menthol and non-menthol HeatSticks use	These changes are made to help assess the role menthol and non-menthol HeatSticks may play in youth initiation and other behaviors.
		Specified data quality check procedure	This information is added to provide a clear description of the data quality check procedure and to enable the agency to understand whether excluding potentially invalid data and imputing missing data influenced results substantively.
V3.0	12/22/2020	Added dual use of *IQOS* and cigarettes	To provide more specific information about dual use with *IQOS*
		Stratified Table 7 by combusted cigarette history and added daily *IQOS* users and daily cigarette users as demographic variables	To provide additional information about underage users of *IQOS*

Version	Version Date	Modification(s)	Reason(s) for Modification(s)
V4.0	4/5/2022	Removed oversample Changed sponsor contact Updated language in the introduction and appendix	To adjust to the current situation that *IQOS* is no longer marketed or available in the US, to reflect FDA's approval of version 3.0 of this analysis plan, and to reflect the modified risk granted order for *IQOS* 3.0.

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DEFINITIONS OF TERMS

Terms are arranged in alphabetic order. Users are defined by use behaviors; for example, a past 30-day user is an individual who used a tobacco product during the past 30 days prior to the assessment.

Ever Tobacco Product Use

Ever use refers to any use of a given tobacco product in one's lifetime.

Past 30-Day Tobacco Product Use

Past 30-day tobacco product use refers to any use of a given tobacco product during the 30 days prior to the assessment.

Tobacco Products

In this study, tobacco products include e-cigarettes, cigarettes, cigars, pipe tobacco, smokeless tobacco (snus, chewing tobacco, snuff or dip), oral nicotine products (excluding medicinal nicotine replacement products), hookah, and heated tobacco products.

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 of 2020 (version 2.4) and March 11 of 2022 (version 3.0), 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 Food and Drug Administration (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., has developed certain components of PMSS to assess the effect of the MRTP among U.S. consumers. The program, consisting of a collection of data over time that supports an assessment of *IQOS* in the postmarket setting, has been approved by the FDA. Given the recent Modified Risk Granted Order for *IQOS* 3.0, we present this analysis plan as one component of the PMSS program. Specifically, it describes the analyses we plan to continue to conduct using data relevant to *IQOS* from ALCS's ongoing Underage Tobacco Use Survey (UTUS) in order to address FDA's requirement for *IQOS* PMSS regarding assessing awareness and usage of *IQOS* among individuals who are 13-20 years of age[2] . This plan also describes the design adjustments that have been made to the UTUS study to reflect the current situation. It is of note that UTUS *IQOS*-specific questions are not specific to the version of the device. Therefore, we do not plan to make any adjustments to survey questions, which have been approved by the FDA (see Appendix 1).

[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 distribute and sell *IQOS* in the U.S. after FDA authorization. ALCS affiliate PM USA markets *IQOS* in the U.S. Therefore, PMSS that involves the study of consumers and consumption in the U.S. will be conducted by ALCS to be submitted as part of PMSS reporting by PMP S.A.

[2] In the "Modified Risk Granted Orders-Exposure Modification" (July 7, 2020), FDA indicated that "…, given the novelty of these products and the uncertainty related to the impact of modified risk information on youth, your studies must be designed to monitor individuals under the age of 18 to assess: (a) youth awareness of *IQOS*, to evaluate how effectively your marketing is limiting unintended exposure to youth, and (b) youth use of the *IQOS* system, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. Your surveys must also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20).

2 PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of this analysis plan is to estimate the awareness and use of *IQOS* among underage individuals based on relevant data from a nationwide population-based survey.

2.2 Objectives

The objectives of this analysis plan are to:

1) Estimate awareness of *IQOS* among underage individuals
2) Estimate ever and past 30-day *IQOS*® use among underage individuals
3) Estimate lifetime use behavior among underage ever users of *IQOS*
4) Estimate past 30-day use behavior among underage past 30-day *IQOS* users

Use behaviors include exclusive, dual and poly tobacco use with *IQOS* and frequency of use.

3 OVERVIEW OF THE UNDERAGE TOBACCO USE SURVEY

We will analyze data from the ALCS Underage Tobacco Use Survey, an on-going national cross-sectional survey of non-institutionalized household dwelling underage individuals (age 13-20) living in the United States (US).

ALCS developed the UTUS to support its underage tobacco prevention and regulatory research and engagement efforts. The UTUS was designed to provide a timely assessment of use behaviors among underage individuals across a range of tobacco product categories. ALCS communicated with FDA on November 15, 2019 its plan to launch the UTUS and shared relevant study materials, including the study protocol, questionnaire, and consent/assent forms.[3] The FDA acknowledged the communication and receipt of materials on Dec. 30, 2019.

ALCS conducted a pilot study during the first quarter of 2020. ALCS launched the full study in May 2020 (Q2 administration) and plans to carry out regular, quarterly survey administrations into the future.

The UTUS is designed to draw nationally representative samples of underage individuals 13-20 years of age using a probability-based sampling method. The target sample size is 5,000 each year. Probability-based sampling is known to enhance the representativeness of the sample compared to non-probability sampling methods because in probability-based sampling, each individual has a known chance of being selected, and results can be projected to the target population with a known level of precision. In contrast, in non-probability samples, where the chance of being selected is unknown, the degree of coverage bias and the exact nature of the bias will vary depending on the source.

[3] There have been some modifications to the study materials since then.

3.1 UTUS Sample Design

The UTUS sample design is a multi-stage stratified list-assisted address-based sampling (ABS) design, which utilizes housing unit addresses from the United States Postal Service (USPS) computerized delivery sequence file (CDS) and housing unit addresses flagged as being likely to have a person age 13 to 20 living at the address by the ABS vendor. Group quarters are not included on the sampling frame (e.g., military barracks, group homes, and correctional facilities). To sample housing units, addresses on the sampling frame are stratified by three age groups (13-15, 16-18, 19-20), four Census regions, and urban/rural classification, resulting in a total of 24 strata. Within each stratum, addresses are randomly selected. Within a sampled housing unit, a maximum of two individuals 13-20 years of age are randomly selected. The allowance of two persons per household is used in both US National Survey on Drug Use and Health, as well as the Population Assessment of Tobacco and Health survey.

3.2 UTUS Tobacco Categories

The following tobacco products are assessed in UTUS:

- Cigarettes
- Cigars
- Hookah
- Pipe tobacco
- E-cigarettes
- Snus
- Smokeless tobacco (snuff, dip, chewing tobacco)
- Oral nicotine products
- Heated tobacco products

For each of the above product categories, participants are asked about their awareness, usage, and consumption. Among past 30-day users, information about the brand of tobacco products used is collected. To further support *IQOS* MRTP postmarket surveillance, questions about the awareness, ever use, and past 30-day use of *IQOS* will be added to the survey in addition to questions about heated tobacco products at the category level. See Appendix 1 for the UTUS questions that are relevant to this analysis plan, including specification of the questions that will be added for the purpose of *IQOS* surveillance.

3.3 UTUS Study Duration

UTUS is fielded on a quarterly basis. For this analysis plan, data will be aggregated over the most recent 12-month period (i.e., four quarter-year surveys)

3.4 UTUS Recruitment

Once the sampled housing unit addresses are drawn, a series of four mailings are used to contact each sampled address. In addition, phone calls are made after the last mailing to housing units for which telephone numbers are available via the study vendor. In all cases, an

adult household member is required to respond to the survey invitation by providing a housing-unit-specific Access Code, which is included in the mailings. Upon successfully entering the unique Access Code, the responding adult household member enumerates household members to determine if there is at least one member of the household (including students away at college) whose age is between 13 and 20 years. Households containing at least one resident aged 13 to 20 are then administered a household roster to establish a list of eligible study participants in each household. Upon completion of the roster, a maximum of two eligible individuals are randomly selected.

If a selected potential participant is between the ages of 13-17, consent from the participant's parent or legal guardian is required. For all selected individuals, assent is required before taking the survey. Participants can either go to a study web-site to complete the questionnaire (online self-administration) or call a toll-free telephone number to speak to an interviewer to complete the questionnaire (computer-assisted phone interview). As a summary, the process includes the following steps to determine eligibility, select study participants, obtain informed consent/assent and proceed to the main questionnaire:

1. Person completing the screener is asked, "Including yourself, how many people, in each of the following age groups, live in your household at least 50% of the time, or are college students living away from home some of the time?
2. 12 or younger, 13-20, 21-34, 35-54, or 55 or older
3. Continue with the screener questionnaire if they have person age 13 to 20 in the household."
4. Household roster is established with age, and sex for each member of household that is age 13-20.
5. Up to 2 members of the household that are age 13-20 are randomly selected.
6. If 1 or 2 minors are selected, collect parental consent.
7. After collecting participant assent, complete the survey.

Both household roster and the main survey can be completed in English or Spanish.

Participants are able to obtain a token of appreciation upon completion of the questionnaire (in the form of Amazon or Target electronic gift cards). For participants aged 13-17 years, their parent/guardian is provided with instructions to obtain the token of appreciation and asked to pass it on to the child.

3.5 UTUS Inclusion Criteria

Participants must satisfy the following criteria to participate in the study:

a) English or Spanish speaking persons;

b) Have access to internet and/or telephone;

c) 13 to 20 years of age;

d) Sufficient abilities to complete the questionnaire (i.e., reading/responding to online survey instrument or listening/speaking to interviewer over the telephone);

e) 13-17-year-old individuals with consent from their parent/legal guardian and who assent

to participate; and

f) 18-20-year-old individuals who consent to participate.

3.6 Protection of Human Subjects in UTUS

The UTUS protocol is approved by a designated Institutional Review Board (IRB).

Participation in UTUS is voluntary. For study participants aged 13 to 17, parental/legal guardian consent is required and recorded through the survey instrument prior to administering the assent form to the minors. All study participants, including minors (age 13 to 17) and adults (age 18 to 20), are administered the informed assent form, and by stating that they would like to participate in the survey after being provided complete information about the study, they are providing their assent to participate. All participants and parents/guardians of 13-17 year-olds are able to obtain a copy of the assent or consent statements if they wish.

3.7 Survey Weighting

Survey weights are derived for the combined four quarters data. Survey weighting is carried out in the following stages:

Address Level

* Base Weights to reflect the selection probability for sampled addresses
* Exclusion of Non deliverable Addresses to restrict weighting to deliverable addresses present on sampling frame
* Adjustment for Screener Nonresponse to account for non-participation due to a screener not being completed

Person within Address Level

* Adjustment for Selection Within Household to reflect the selection probability for sampled persons within an address
* Adjustment for Parental Non-consent to account for non-participation due to parent/guardian not providing consent for selected minor to participate in survey
* Adjustment for Selected Person Nonparticipation to account for non-participation due to selected person not assenting to participate in survey or not providing a usable set of responses to the survey
* Adjustment to Person-Level Population Totals to control weighted counts of completed interviews to total population counts of persons age 13-20 by characteristics for which estimates are desired and/or which are associated with survey variables of interest (e.g., sex, age category, race/ethnicity, census region, and urban/rural residence)

Weights are trimmed as appropriate, to lessen the impact of extreme weights. Once survey weighting is completed, each participant who completed the survey has a weight which is used to generate survey estimates.

3.8 Considerations Related to Household Surveys

Our decision to conduct a household survey with online and phone administration is grounded in the following considerations. First, the target population of UTUS is individuals 13-20 years of age, including young adults 18-20 years of age. A substantial proportion of these young adults are not in high-school and can be difficult to reach in a school-survey context because they can be attending college, in the workforce, or neither; they are, conversely, typically affiliated with a household. It is noteworthy that we ask any college students away from home to be counted as a household member during the screening stage of the survey. Second, we consider household survey to be more feasible than school-based survey given that the survey is being sponsored by a tobacco manufacturer, and parental consent is necessary for participants 13-17 years of age. Third, while household surveys with in-house interviews are known to yield higher response levels compared to other administration modes, these interviews are not feasible for quarterly surveys because they are time- and resource-consuming. As described above, non-participation and selection probabilities will be accounted for during the weighting process, and post-stratification will be used to bring the sample into balance with the national population with respect to selected characteristics.

We are cognizant of other limitations associated with household surveys. One concern for household surveys is whether an underage individual has necessary privacy. In UTUS, we encourage the adult who completes the household roster to provide privacy for minors to fill out the survey. The adult can choose to send the survey link to selected participants via text messages or emails, which can facilitate the provision of privacy. We also consider the use of the online self-administration to facilitate privacy, and we note that UTUS can be completed on mobile devices. In addition, examination of current government-sponsored studies of tobacco use in the US shows that household surveys tend to result in lower prevalence estimates compared to results from school-based surveys. Nonetheless, both types of studies show similar trends over time and are valuable sources of surveillance information.

4 ANALYSIS PROCEDURES

Our analysis and reporting of *IQOS*-relevant information from UTUS for postmarket surveillance purposes will follow a step-wise process based on the number of *IQOS* users identified in the UTUS dataset.

The process will unfold as follows:

- The awareness of *IQOS* and use of *IQOS* (ever use and past 30-day use) among underage individuals will be reported following *IQOS* MTRP authorization for a time period specified in the Modified Risk Order (e.g., annual). The estimates will be based on data from the most recent four moving quarters.
- Outcomes based on subgroups of underage individuals (e.g., outcomes based only among those aware of *IQOS,* ever used *IQOS* or used *IQOS* in the past 30 days) will be reported when there are at least 50 respondents in that subgroup.

4.1 Sample Size Calculation and Rationale for Stepwise Reporting

A sufficient sample size is needed to ensure adequate precision of estimates (e.g., means and proportions) for the underage population as a whole and among *IQOS* users. With a sample size of approximately 5,000, estimates are generally with reasonable precision. For example,

when the point estimate is 1%, the 95% CI is (0.7%, 1.3%) for a sample size of 5,000. Therefore, we will report awareness and use (ever use and past 30-day use) outcomes (with their 95% CIs) in the first reporting period and thereafter. For outcomes relevant to a subsample (e.g., use behaviors among past 30-day users), we will start reporting the estimates when the sample size reaches 50 to balance between timeliness and precision. Our rationale is described below.

With respect to subsample analyses, based on our calculation described below, a sample size of n=100 is desirable to achieve a reasonable precision (NCSS Statistical software, 2017). Figure 1 and Table 1 shows 95% confidence intervals for various proportions and sample sizes. For example, with a sample size of 100, the width of 95% confidence interval will be 20% for a point estimate of 50%, which is typically acceptable. (Fleiss et al., 2003; Newcombe, 1998; Table 1 and Figure 1). As shown in Table 1, the precision increases with sample size. For continuous variables, a sample size of n=85 is desirable to produce sample means and standard deviations with reasonable precision (Piovesana et al., 2016). While a sample of 100 is desirable from a statistical perspective, we plan to report results based on a sample of 50 in order to balance between precision and timeliness of reporting. Therefore, we will start reporting the subset of estimates among ever or past 30-day *IQOS* users if there are at least 50 ever or past 30-day *IQOS* users in the annual dataset to balance between timeliness and precision. All estimates will be reported with their 95% confidence intervals to gauge the precision of estimates.

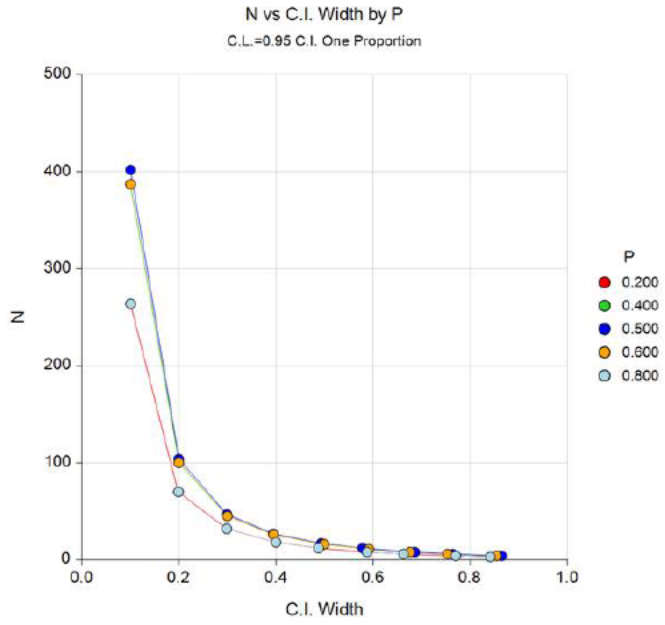

Figure 1: Estimated Sample Sizes for Various Confidence Interval Widths by Expected Proportions

Table 1: 95% Confidence Intervals at Various Proportion Points

n	Proportion									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
50	.005, .14	.03, .22	.06, .27	.10, .34	.13, .38	.18, .45	.21, .49	.26, .55	.30, .59	.36, .64
100	.02, .11	.05, .18	.09, .24	.13, .29	.17, .35	.21, .40	.26, .45	.30, .50	.35, .55	.40, .60
150	.02, .10	.06, .16	.10, .22	.14, .27	.19, .33	.23, .38	.28, .44	.32, .48	.37, .54	.42, .58
200	.02, .09	.06, .15	.10, .21	.15, .26	.19, .32	.24, .37	.28, .42	.33, .47	.38, .52	.43, .57
250	.03, .09	.07, .14	.11, .20	.15, .26	.20, .31	.24, .36	.29, .41	.34, .46	.39, .52	.44, .56
300	.03, .08	.07, .14	.11, .20	.16, .25	.20, .30	.25, .36	.30, .41	.34, .46	.39, .51	.44, .56
500	.03, .07	.08, .13	.12, .18	.17, .24	.21, .29	.26, .34	.31, .39	.36, .44	.41, .49	.46, .54

Table 2: Examples of the width of 95% confidence intervals for continuous variables given a sample size of 50 and 100.

Variable	Mean	Standard Deviation	95% Confidence Interval	
			n = 50	n = 100
Number of days you used heat sticks during the past 30 days	1.5	1.1	1.2, 1.8	1.3, 1.7

4.2 Estimated Timeline

We plan to report *IQOS*-related data from UTUS annually following *IQOS* MRTP authorization. Outcomes measured among the overall sample (e.g., awareness of *IQOS*, ever use and past 30-day use of *IQOS*) were reported in the first reporting period and thereafter. Outcomes measured among a population subgroup (e.g., use frequencies among past 30-day *IQOS* users) will be reported when the sample size of the subgroups reaches at least 50.

5 OUTCOME MEASURES

In this section, we provide detailed definitions of outcome measures to be reported for *IQOS* PMSS.

Objective 1: Estimate awareness and source of awareness of *IQOS* among underage individuals

- Awareness of *IQOS*: percentage of respondents who have seen or heard of *IQOS* (Table 1).
- Source of awareness of *IQOS*: percentages of respondents who indicated each option as the source of first awareness of *IQOS* among individuals who are aware of *IQOS* (Table 2).

Objective 2: Estimate ever and past 30-day *IQOS* use among underage individuals

- Prevalence of *past 30-day use* of *IQOS*: Percentage of respondents who used *IQOS* in the past 30 days. Past 30-day use of *IQOS* is operationalized as having ever used *IQOS* and used *IQOS* during the past 30 days (Table 3).

  Prevalence of past 30-day use will be estimated for overall *IQOS* use and for menthol and non-menthol HeatSticks used with *IQOS*, respectively.

- Lifetime *ever use*[4] of *IQOS*: Percentage of respondents who have ever used *IQOS* in their lifetime (Table 3).

  Ever use will be estimated for overall *IQOS* use and for menthol and non-menthol HeatSticks first used with *IQOS*, respectively.

Objective 3: Estimate lifetime use behavior among underage ever users of *IQOS*

- Lifetime consumption of heated tobacco: percentages of respondents who used 1, 2-10, 11-99, and 100+ of HeatSticks with *IQOS* in their lifetime among ever users of *IQOS* (Table 4) History of other tobacco use among ever *IQOS* users: percentages of respondents who have ever used (Table 4)
  - *IQOS* only
  - *IQOS* and at least one combusted tobacco product[5]
  - *IQOS* and at least one non-combusted tobacco product[6]
  - *IQOS* and both combusted and non-combusted tobacco products

  Estimates for outcomes listed in objective 3 will be stratified by whether the HeatStick first used was menthol or non-menthol when sample size allows.

Objective 4: Estimate past 30-day use behavior among underage past 30-day *IQOS* users

- Use frequency: median (with interquartile rage) and mean (with standard deviation) for the number of days of *IQOS* use during the past 30 days among past 30-day *IQOS* users (Table 6)
- Amount consumed on days used: percentages of respondents who consumed the following number of HeatSticks with *IQOS* on the days they used *IQOS* (Table 6):
  - ≤ 1 per day
  - 2-5 per day
  - 6-10 per day
  - >10 per day

[4] We do not consider lifetime ever use a prevalence measure because it deviates from the traditional definition of prevalence in significant ways and is better described as cumulative incidence among survivors (Streiner et al., 2009).

[5] Combusted tobacco products include cigarettes, cigars, hookah, pipe tobacco.

[6] Non-combusted tobacco products include E-cigarettes, snus, smokeless tobacco, and oral nicotine products.

- Exclusive, dual, and poly tobacco users among past 30-day *IQOS* users: percentages of respondents who used the following in the past 30 days (Table 6):
    - *IQOS* only
    - *IQOS* and at least one combusted tobacco product
    - *IQOS* and at least one non-combusted tobacco product
    - *IQOS* and both combusted and non-combusted tobacco products

  In addition, percentages of respondents who used both *IQOS* and cigarettes (regardless of other tobacco product use) will be reported (Table 6).

  Estimates for outcomes listed in objective 4 will be stratified by whether the HeatSticks used most often during the past 30-days were menthol or non-menthol when sample size allows.

Outcome measures will be reported for the total study population, and by population subgroups with respect to sex, age, and race/ethnicity when there are at least 50 individuals in a given subgroup (e.g., 13-17-year-olds or 18-20-year-olds).

In each reporting, we will provide a brief discussion about the above outcomes in light of data from national surveys (e.g., trends over time) as well as data from UTUS on the awareness and use of other tobacco products, with a focus on past 30-day use, and the correct identification of *IQOS* to contextualize these findings.

6 DATA MANAGEMENT AND QUALITY CHECKS

All original source information (i.e., the UTUS data sets) obtained or received to conduct the analyses will be maintained by the study lead analyst. UTUS does not collect any personally identification information (PII). All data collected during the conduct of UTUS are property of ALCS.

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.

In UTUS, a multi-pronged approach is used to detect falsification and assess data quality, with the following “tests” embedded in the main questionnaire:

- Speeding: Completing a questionnaire very quickly, without giving thought to answers. Respondents who complete the 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:
    - Used any products, but none in the past 30 days
    - Used only 1 product in the past 30 days
    - Used 2+ products in the past 30 days
    - Never used any of the products

The number of respondents that are flagged as "speeders" will be included in the report.

- Inattentiveness: UTUS contains a question at the end of the survey that reads "*Thank you for your answers so far. We appreciate your input. You're almost finished! Please select [insert color] to continue.*" Response list will include four colors (Red, Blue, Yellow and Green). Respondents who incorrectly answer this question will be flagged as "inattentive". The number of flags will be included in the report.

- Missing data: While respondents are not required to answer every question, the data will be examined to determine whether large amounts of missing values (due to skipping questions) presents a data quality concern. The final report will include:
    - The percentage of respondents that answered all of (100%) the questions that they were asked
    - The percentage of respondents that answered at least half (50% or more) of the questions that they were asked
    - The lowest percentage of questions that were answered by a respondent

The main analysis will be conducted with the full dataset and sensitivity analyses will be conducted without the flagged respondents (i.e., speeders and inattentive respondents) to determine if the potentially invalid data substantially influence the results. No respondents will be flagged based on the amount of missing data. The sensitivity analysis 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. The questionnaire is designed to minimize outliers by defining specific ranges for numeric responses and the use of categorical responses. For example, the number of days a person used a tobacco product in the past 30 days can only range from 1 to 30. Responses to lifetime consumption items are in categories. Therefore, we do not expect outliers relevant to this analysis plan.

7 DATA ANALYSIS

Descriptive statistics will be calculated, including medians and means for continuous or count variables (e.g., amount of tobacco use), as well as percentages and frequencies for categorical variables (e.g., yes/no ever used a tobacco product). Ninety-five percent (95%) confidence intervals will also be calculated when applicable.

Awareness and Use Measures. Estimates will be reported with 95% confidence intervals for the total sample and by major demographic categories (sex, age, and race/ethnicity). Analysis of a subgroup with sample size less than 50 will not be reported.

Demographic Characteristics. Descriptive statistics of the demographic characteristics (sex, age, and race/ethnicity) will be reported for *IQOS* ever users and past 30-day *IQOS* users, including sample sizes, central tendency measures (e.g. means, medians), variability measures (e.g. standard deviation, range) and 95% confidence intervals if/when there are at least 50 *IQOS* users in the dataset (Table 5 and Table 7). These descriptive statistics will be stratified by combusted cigarette history (Table 7).

8 ADMINISTRATIVE

The analyses shall be conducted as described in this plan. Any deviations from the planned analyses and reporting will be documented as amendments.

9 REFERENCES

Fleiss, J. L., Levin, B., & Paik, M. C. (2003). Statistical Methods for Rates and Proportions (Third ed.). New York: John Wiley & Son.

Food and Drug Administration, C. T. P. (2012). Guidance for Industry: Modified Risk Tobacco Product Applications. Rockville, MD: U.S. Department of Health and Human Services Retrieved from https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM297751.pdf.

NCSS Statistical software (Producer). (2017). PASS Sample Size, version 15.0.3. *Numeric Results for Determining Sample Size*.

Newcombe, R. G. (1998). Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. Statistics in Medicine, 17, 857-872.

Piovesana, A., & Senior, G. (2016). How Small Is Big: Sample Size and Skewness. *Assessment*. Doi:10.1177/1073191116669784

Streiner, D.L., Patten, S.B., Anthony, J.C. and Cairney, J. (2009) Has 'Lifetime Prevalence' Reached the End of Its Life? An Examination of the Concept. Int J Methods Psychiatr Res. 2009 Dec;18(4):221-8. Doi: 10.1002/mpr.296.

10 APPENDIX 1 – SELECTED UTUS QUESTIONS RELATED TO *IQOS* AND RELEVANT TO THIS ANALYSIS PLAN

This appendix provides a list of UTUS survey questions relevant to the current analysis plan. The questions that refer specifically to *IQOS* in the question stem had been added for purpose of *IQOS* surveillance and will continue to be included in the study for this purpose. The UTUS questionnaire is organized in two main parts: (1) awareness/ever use of various tobacco products and (2) category-specific modules with questions about tobacco use behaviors. To further support postmarket surveillance requirements, an *IQOS*-specific module was added to the questionnaire as indicated below.

AWARE / EVER USED

3h. And the next question is about heated tobacco products. Some people refer to these products as "heat-not-burn" tobacco products. "Heated tobacco products" heat tobacco sticks or capsules to produce a vapor. They are different from e-cigarettes, which heat a liquid to produce a vapor. Some brands of "heated tobacco products" include *IQOS*, glo™, and Eclipse®.

Have you ever seen or heard of "heated tobacco products" before this study?

Yes - 1

No - 2

(ASK Q.4h IF 'YES' AT Q.3h)

4h. Have you **ever used** a "heated tobacco product", even just one time?

Yes - 1

No - 2

3h1. Have you ever seen or heard of *IQOS* before this study?

Yes - 1

No - 2

Don't know -99

3h8. [Ask if 'Yes' at Q.3h1] How did you first see or hear of *IQOS*?

A friend/peer/classmate told me about it	-1
A family member told me about it	-2
Advertisement at gas stations, convenience stores, or other retail stores	-3
Advertisement in newspapers or magazines	-4
Advertisement at festivals, nightclubs, and bars	-5
Advertisement on websites or social media sites	-6
Heard or read a story in the news	-7
Saw *IQOS* in person in a store, mall, convenience store	-8
Saw someone else using *IQOS*	-9
Saw it on social media (e.g., YouTube or Instagram)	-10
Other, specify _____	-90
Don't know/don't recall	-99

3h9. [Ask if 'Yes' at Q.3h1] Which of the following best describes *IQOS*? [Rotate responses 1-4. Keep 1-3 together, rotating within these 3 responses. Always keep "Don't Know" last.]

This device only uses replaceable pods/cartridges/capsules	-1
This device only uses sticks containing actual tobacco	-2
This device uses both sticks containing actual tobacco ***and*** replaceable pods/cartridges/capsules	-3
This device is refilled using bottles of e-liquid	-4
[ALWAYS SHOW LAST] Don't Know	-99

4h1. [Ask if 'Yes' at Q.3h1] Have you ever used *IQOS* before this study, even just one time?

Yes	- 1
No	- 2
Don't know	-99

HEATED TOBACCO PRODUCT SECTION

These next questions are about the use of "heated tobacco products". Some people refer to these products as "heat-not-burn" tobacco products.

9h. [If Q4h is 'Yes'] When was the last time you used a heated tobacco product, even one or two times? (*Please select the first answer that fits.*)

Earlier today	-1
Not today but sometime during the past 7 days	-2
Not during the past 7 days but sometime during the past 30 days	-3
Not during the past 30 days but sometime during the past 6 months	-4
Not during the past 6 months but sometime during the past year	-5
1 to 4 years ago	-6
5 or more years ago	-7

12h. [If Q9h is 1-3] During the past 30 days, what brand or brands of heated tobacco products did you use? *(select all that apply)*

(Display brand list, only shows *IQOS* if 'Yes' at Q.4h1)

Eclipse	-1	
Glo	-2	
IQOS	-3	
PAX	-4	
Ploom Tech	-5	
Some other brand not listed here	-90	(specify) _____
Not sure	-99	

IQOS-SPECIFIC SECTION

21hi. You mentioned earlier that you have used *IQOS* before this study. The next questions are about *IQOS*.

[Ask if 'Yes' at Q4h1] How many HeatSticks have you used with *IQOS* in your **entire life**?

1	-1
2 to 10	-2
11 to 20	-3
21 to 50	-4
51 to 99	-5
100 or more	-6

22hi. [Ask if 'Yes' at Q4h1] Menthol HeatSticks are HeatSticks that taste like mint. Was the first *IQOS* HeatStick you used menthol or non-menthol (regular)?

Menthol	- 1
Non-Menthol	- 2
Not sure	-99

23hi. [Ask if 'Yes' at Q4h1 AND *IQOS* is not mentioned in Q12h; if *IQOS* is mentioned in Q12h, autofill this question with 'Yes' and move to 24hi] During the past 30 days, did you use *IQOS*?

Yes	- 1
No	- 2
Don't know	-99

24hi. [If 'Yes' at Q23hi OR *IQOS* is mentioned in Q12h] During the past 30 days, on how many days did you use *IQOS*?

_ _ Number of days (1-30)

25hi. [If 'Yes' at Q23hi OR *IQOS* is mentioned in Q12h] During the past 30 days, on the days you used *IQOS*, about how many HeatSticks did you use with *IQOS* per day?

Less than 1 per day	-1
1 per day	-2
2 to 5 per day	-3
6 to 10 per day	-4
11 to 20 per day	-5
More than 20 per day	-6

26hi. [If 'Yes' at Q23hi OR *IQOS* is mentioned in Q12h] During the past 30 days, was the HeatStick you usually used with *IQOS* menthol or non-menthol?

Menthol	-1
Non-Menthol	-2
I did not have a usual type	-97
Not sure	-99

11 APPENDIX 2 – EXAMPLE TABLE SHELLS

Objective 1. Estimate awareness of *IQOS*

Table 1: Estimated awareness of *IQOS* among 13-20 year olds		
Group	N	% (95% CI)
Overall		
Sex		
Males		
Females		
Age		
13-17 Years		
18-20 Years		
Race/ethnicity		
Non-Hispanic White		
Non-Hispanic Black		
Hispanic		
Others		
n is unweighted frequency; % is weighted percentage.		

Note: We intend to report results for a population subgroup when there are at least 50 individuals in the subgroup.

Table 2: Estimated source of awareness of *IQOS* among 13-20 year olds who are aware of *IQOS*		
Group	n	% (95% CI)
Saw *IQOS* in person in a store, mall, convenience store		
Saw someone else using *IQOS*		
Saw it on social media (e.g., YouTube or Instagram)		
Advertisement at gas stations, convenience stores, or other retail stores		
Advertisement on radio or in newspapers or magazines		
Advertisement at festivals, nightclubs, and bars		
Advertisement on websites or social media sites		
A friend/peer/classmate told me about it		
A family member told me about it		
Heard or read a story in the news		
Other, specify _____		
Don't know/do not recall		
n is unweighted frequency; % is weighted percentage.		

Note: We intend to complete the above table when there are at least 50 individuals who indicate they are aware of *IQOS*. Estimates will be produced for 13-17 year olds and 18-20 year olds separately when sample size permits (i.e., ≥50).

Objective 2. Estimate lifetime and past 30-day *IQOS* use

Table 3: Estimated ever and past 30-day use of *IQOS* by demographic characteristics					
Group	Ever *IQOS* use			Past 30-day *IQOS* use	
	n	% (95% CI)		n	% (95% CI)
Overall					
Sex					
Male					
Female					
Age					
13-17 Years					
18-20 Years					
Race/ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Others					
Group	Ever *IQOS* use with menthol HeatStick when first used			Past 30-day *IQOS* use with menthol HeatSticks used most often in past 30 days	
	n	% (95% CI)		n	% (95% CI)
Overall					
Sex					
Male					
Female					
Age					
13-17 Years					
18-20 Years					
Race/ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Others					
Group	Ever *IQOS* use with non-menthol HeatStick when first used			Past 30-day *IQOS* use with non-menthol HeatSticks used most often in past 30 days	

	n	% (95% CI)		n	% (95% CI)
Overall					
Sex					
Male					
Female					
Age					
13-17 Years					
18-20 Years					
Race/ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Others					
n is unweighted frequency; % is weighted percentage.					

Note: We intend to report results for a population subgroup when there are at least 50 individuals in the subgroup.

In addition, when there are at least 50 individuals in a population subgroup who respond 'I don't have a usual type' or 'not sure' in menthol vs. non-menthol questions, we will report results for these individuals.

Objective 3. Estimate lifetime use behavior among ever users of *IQOS*

The following tables will be included when there are at least 50 ever *IQOS* users in the UTUS dataset.

Table 4: Estimated lifetime use behavior among ever users of *IQOS* 13-20 years of age		
Overall *IQOS* use		
Outcome	n	% (95% CI)
Lifetime consumption of HeatSticks with *IQOS*		
1		
2-10		
11-99		
≥ 100		
Tobacco use history (based on ever use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		

First HeatStick used with *IQOS* was menthol		
Outcome	n	% (95% CI)
Lifetime consumption of HeatSticks with *IQOS*		
1		
2-10		
11-99		
≥ 100		
Tobacco use history (based on ever use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		
First HeatStick used with *IQOS* was non-menthol		
Outcome	n	% (95% CI)
Lifetime consumption of HeatSticks with *IQOS*		
1		
2-10		
11-99		
≥ 100		
Tobacco use history (based on ever use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		
n is unweighted frequency; % is weighted percentage.		

Note: Estimates will be produced for 13-17 year olds and 18-20 year olds separately when sample size permits (i.e., ≥ 50).

Table 5: Distribution of selected demographic characteristics of ever *IQOS* users 13-20 years of age						
Group	Overall		First HeatStick used was menthol		First HeatStick used was nonmenthol	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex						
Males						
Females						
Age						
13-17 Years						
18-20 Years						
Race/ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Others						
n is unweighted frequency; % is weighted percentage.						

Objective 4. Estimate past 30-day use behavior among past 30-day *IQOS* users

The following tables will be included when there are at least 50 past 30-day *IQOS* users in the UTUS dataset.

Table 6: Estimated past 30-day use behavior among past 30-day users of *IQOS* 13-20 years of age		
Outcome	n	Median (IQR)
Overall *IQOS* use		
# of days used heated tobacco products in the past 30 days		
	n	% (95% CI)
# of HeatSticks with *IQOS* consumed on days used in the past 30 days		
≤ 1 per day		
2-5 per day		
6-10 per day		
> 10 per day		
Tobacco use history (based on past 30-day use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		

IQOS and cigarettes		
Menthol HeatSticks used most often with *IQOS*		
Outcome	n	Median (IQR)
# of days used heated tobacco products in the past 30 days		
	n	% (95% CI)
# of HeatSticks with *IQOS* consumed on days used in the past 30 days		
≤ 1 per day		
2-5 per day		
6-10 per day		
> 10 per day		
Tobacco use history (based on past 30-day use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		
IQOS and cigarettes		
Non-Menthol HeatSticks used most often with *IQOS*		
Outcome	n	Median (IQR)
# of days used heated tobacco products in the past 30 days		
	n	% (95% CI)
# of HeatSticks with *IQOS* consumed on days used in the past 30 days		
≤ 1 per day		
2-5 per day		
6-10 per day		
> 10 per day		
Tobacco use history (based on past 30-day use)		
IQOS only		
IQOS and at least one combusted tobacco products		
IQOS and at least one non-combusted tobacco products		
IQOS and both combusted and non-combusted tobacco products		
IQOS and cigarettes		
n is unweighted frequency; % is weighted percentage.		

Note: Estimates will be produced for 13-17 year olds and 18-20 year olds separately when sample size permits (i.e., ≥ 50).

Table 7: Distribution of selected demographic characteristics and tobacco use among past 30-day *IQOS* users 13-20 years of age						
Group	Overall		Current Menthol HeatStick used most often		Current Non-Menthol HeatStick used most often	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex						
Males						
Females						
Age						
13-17 Years						
18-20 Years						
Race/ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Others						
History of cigarette smoking						
Never						
Ever						
Daily *IQOS* use						
Yes						
No						
Daily cigarette smoking						
Yes						
No						
Individuals who had never smoked a combusted cigarette						
Sex						
Males						
Females						
Age						
13-17 Years						
18-20 Years						
Race/ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Others						
Daily *IQOS* use						

Yes						
No						
Individuals who had ever smoked a combusted cigarette						
Sex						
Males						
Females						
Age						
13-17 Years						
18-20 Years						
Race/ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Others						
Daily *IQOS* use						
Yes						
No						
Daily cigarette smokers						
Yes						
No						
n is unweighted frequency; % is weighted percentage.						