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	(b) (4)	
V2.0	11/4/2020		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*.
			These changes are made to provide information specific to IQOS®.
			These changes are made to help assess the role menthol and non-menthol HeatSticks may play in youth initiation and other behaviors.
			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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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, 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 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., 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.

Together with PMP SA, ALCS developed this analysis plan as one component of the PMSS program. Specifically, it describes the analyses we intend 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 are intended to be made to the UTUS study to better address these requirements.

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[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 M RTPs 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 (b) (4) 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.

As described in this plan, to better support surveillance of IQOS® following the MRTP authorization, ALCS intends to incorporate an annual oversample of (b) (4) underage

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

individuals 13-20 living in US geographies where IQOS® is currently available for sale. Thus, analysis of UTUS data will provide information on IQOS® at both the national and targeted geography levels.

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.

We intend to enhance the UTUS sample design to include an oversampling of participants in geographies where IQOS® is sold to better support surveillance of IQOS®. Currently, IQOS® is in very limited distribution in the United States. IQOS® was first launched into a single market, Atlanta, GA, in September 2019 and into a second market, Richmond, VA, in November 2019. IQOS® launched into a third market, Charlotte, NC, in July 2020. Future expansion is planned to occur, but the pace and breadth of expansion may depend on learning achieved from the early market launches. To account for the limited distribution of IQOS®, we will oversample in Atlanta, Richmond, and Charlotte for IQOS® postmarket surveillance purposes[4]. The target annual sample size for the oversample is (b) (4) for all locations combined. Estimates will be reported for the national sample and the oversample separately.

3.2 UTUS Tobacco Categories

The following tobacco products are assessed in UTUS:

- Cigarettes
- Cigars
- Hookah
- Pipe tobacco
- E-cigarettes
- Snus

[4] We have implemented the oversampling approach in the current Q4 2020 administration of UTUS. The UTUS questionnaire in field includes heated tobacco category-level assessments. The IQOS®-specific questions described in this analysis plan will be included in the next possible quarterly administration pending FDA approval of those questions.

- 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)[5].

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:

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[5] For the first reporting period, we will include data from the most recent survey(s) with proposed IQOS®-specific questions upon FDA's approval of the analysis plan. If FDA approves this analysis plan by December 15, 2020, we will be able to add IQOS®-specific questions in the quarter 1 survey of 2021 and include those data in the 2021 Postmarket Annual Report. Otherwise, we will introduce the IQOS®-specific questions in the next earliest quarterly administration following FDA approval and include the results in the 2022 Postmarket Annual Report. Until the IQOS®-specific questions are deployed, we will, however, be able to share heated tobacco category-level data with FDA, including brand of heated tobacco product used in the past 30 days.

(b) (4)

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:

(b) (4)

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 national sample and oversample will be reported separately, and each will adhere to the process below.

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[6].
- 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 (b) 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 (b) (4) (the national sample) and (b) (4) (the oversample), estimates are generally with reasonable precision. For example, when the point estimate is 1%, the 95% CI is (0.7%, 1.3%) and (0.5%, 2.0%) for a sample size of (b) (4) and (b) (4) respectively. 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 (b) to balance between timeliness and precision. Our rationale is described below.

[6] As described in the previous footnote, the inclusion of data from the IQOS®-specific questions in the 2021 Postmarket Annual Report will depend on whether those questions are deployed in the quarter 1 2021survey administration.

With respect to subsample analyses, based on our calculation described below, a sample size of (b) (4) 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 (b) 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 (b) (4) is desirable to produce sample means and standard deviations with reasonable precision (Piovesana et al., 2016). While a sample of (b) is desirable from a statistical perspective, we plan to report results based on a sample of (b) 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 (b) 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.

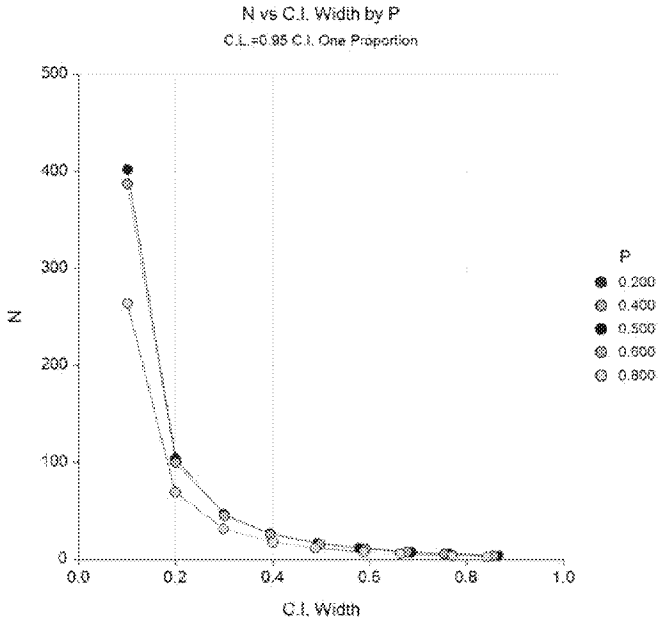

Figure 1: Estimated Sample Sizes for Various Confidence Interval Widths by Expected Proportions

Table 1: 95% Confidence Intervals at Various Proportion Points

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

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

Variable	Mean	Standard Deviation	95% Confidence Interval	
			(b) (4)	(b) (4)
(b) (4)				

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®) will be 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 (b). Sets of estimates will be reported for the national sample and the oversample separately.

5 OUTCOME MEASURES

In this section, we provide detailed definitions of outcome measures to be reported for IQOS® PMSS. Outcomes will be reported separately for the national sample and the oversample where IQOS® is distributed.

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*[7] 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 products[8]
  - IQOS® and at least one non-combusted tobacco products[9]
  - 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

[7] 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).

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

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

- 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
- 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 products
    - IQOS® and at least one non-combusted tobacco products
    - IQOS® and both combusted and non-combusted tobacco products

  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 (b) 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 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 (b) 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 (b) IQOS® users in the dataset (Table 5 and 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

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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. Questions to be added specifically for IQOS® PMSS purposes are highlighted in yellow and will be added upon FDA's approval of this analysis plan. 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 will be added to the questionnaire as indicated below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

11 APPENDIX 2 - EXAMPLE TABLE SHELLS

Each of the following tables will be repeated for the national sample and the oversample.

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 (b) 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 (b) 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., (b)).

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 (b) individuals in the subgroup.

In addition, when there are at least (b) 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 (b) 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., (b)).

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 (b) 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		
Menthol HeatSticks used most often with IQOS®		
# 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		
Non-Menthol HeatSticks used most often with IQOS®		
# 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		
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., (b) (4)).

Table 7: Distribution of selected demographic characteristics of 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						
n is unweighted frequency; % is weighted percentage.						