PMI RESEARCH & DEVELOPMENT

Non-Interventional
Post-Market Study Protocol Concept
P1-NIS-01-US

Study Type: Cross-Sectional Adult Consumer Survey

Study Title: In-Market Adult Consumer Study: Ongoing, Cross-Sectional Tracking of Adult Consumer Tobacco Behavior

Product: *iQOS* with *HeatSticks*

Country: United States

Sponsor: Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Version Status: FINAL
Version: 1.0
Version Date: 10/7/2016

Confidentiality Statement

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PROTOCOL CONCEPT

Background

Philip Morris Products S.A. (PMP S.A.) is developing novel tobacco and nicotine containing products with the potential to reduce harm or the risk of tobacco-related disease associated with smoking cigarettes. In accordance with the United States Food and Drug Administration (FDA), PMP must demonstrate that "the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (FDA 2012)

iQOS with *HeatSticks* is one of these novel tobacco products. Altria Clients Services (ALCS) is planning to adapt existing or develop new research infrastructure to conduct this study – a cross-sectional survey that will be repeated over time to monitor and assess at a population-level the prevalence of use of tobacco and nicotine containing tobacco products.

Objectives and Endpoint

1. Describe and track the prevalence of tobacco use behaviors, by product type
   Endpoints:
   - Tobacco or nicotine containing tobacco product use (lifetime, past year, past 30 days, past week)
2. Describe the tobacco or nicotine containing tobacco product use (by type or combinations of tobacco products)
   Endpoints:
   - Frequency of product use
   - Volume of product use
3. Describe the patterns of product use
   Endpoints:
   - Tobacco or nicotine containing tobacco product use (single, dual and poly product use)
4. Estimate the rates of initiation, cessation and product switching
   Endpoints:
   - Initiation with tobacco or nicotine containing tobacco product
   - Cessation from cigarettes
   - Cessation from all tobacco or nicotine containing tobacco products
   - Tobacco product category and segment switching

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Study Sampling and Population

The population is a probability sample that is representative of the U.S. adult population. We plan to oversample in the geography in which *iQOS* with *HeatSticks* is marketed to estimate prevalence of *iQOS* users, as feasible.

- A probability sample of adults of legal age to purchase tobacco products in the geography being surveyed. Age will be participant self-verified.
- The final sampling frame will be defined based on a mixed mode of cell and landline random-digit dialing telephone interviewing, existing tobacco tracking research and study specifications.
- The population will include approximately 45,000 respondents per annual sample. The annual sample may be collected in waves of participants enrolled over time.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria envisioned at this time include:

Inclusion Criteria:

- The participant is a civilian, non-institutionalized adult, legally authorized to buy tobacco and nicotine containing tobacco products in their city and state of residence within the United States (18-21 years of age depending on state and city)
- The participant is a resident of the <<City>> or <<State>> or <<United States>> (*Note: this will be dependent on the marketing of iQOS and the scope of the survey*)
- The participant is willing to participate in the study and provides informed consent[1] for participation

Exclusion Criteria:

- The participant is an employee, contractor or consultant of the Sponsor or third-party organization responsible for conducting the study
- The participant cannot understand English

Study Design

This study will be conducted using a mixed mode of cell and landline telephone interviewing (random-digit dialing) that will be balanced and regularly updated based on US Government statistics on phone usage. The study will be conducted continuously throughout the year.

The study will be balanced based on a number of variables, including:

- Sex
- Age
- Race

[1] Given the nature of the study design, consent is provided by participants by their agreement to participate in the study. According to Good Epidemiological Practice (IEA 2007), "Formal written consent is unnecessary if the research is carried out in settings that pose no threat to the potential participants, when it is stated that taking part is voluntary and it is obvious that no benefits are at risk of being lost if potential participants refuse to take part. Such situations often arise in studies based on self-administered questionnaires or telephone interviews where providing the data involves giving de facto consent."

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The participant will be informed about the voluntary nature of their participation and data privacy/confidentiality. After agreeing to participate, the participant completes the "Screener Survey", eligible participants then complete the "Main Survey".

Study Instrument
The study instruments will be developed to include the following elements:

- Survey introduction - informed consent
- Demographics and geography (age, race, sex, educational attainment, US Census Region, urban/rural)
- Tobacco and nicotine containing tobacco product use (current, lifetime, past year, past 30 days, past week)
- Tobacco and nicotine containing tobacco product use behaviors (days used, amount used per average day, total amount used in past week)
- Brand use (regular and alternate for each tobacco category and segment)
- Product characteristics (form, flavor etc.)

(Please see Section 8.4.3, for more details on certain survey elements.)

Hypothesis
This study is descriptive in nature; therefore no statistical hypotheses will be tested.

Sample Size
The target sample size is 45,000 participants per annual sample. As the statistical analysis will be descriptive in nature, the sample size was determine by evaluating how many smokers would likely be sampled and, based on the number of smokers, evaluating the number of potential *iQOS* users that may be included in the sample based on the potential prevalence of *iQOS* with *HeatSticks* use in the population sampled.

The prevalence of *iQOS* with *HeatSticks* use will be dependent on several factors, including the manner in which the product is brought to market. To provide a sense of scale, Table 1 assumes a full, national distribution of *iQOS* with *HeatSticks* and shows estimated numbers of *iQOS* users surveyed based on a sample size of 45,000 participants. Table 1 further assumes a current smoking prevalence of 16.8% in the adult US population (CDC 2015), and a prevalence of *iQOS* with *HeatSticks* use among smokers between 0.5% and 5% (0.5%, 1.0%, 2.5%, and 5.0%).

For example, based on a sample size of 45,000 participants in the population we could expect that we would have more than a 95% probability of obtaining a sample of at least 7,425 smokers and 63 *iQOS* users if the prevalence of *iQOS* with *HeatSticks* use among smokers was 1.0%.

Table 1. Sample Size Calculations – Number of *iQOS* Users in the Sample

Probability of the Sample Size	*iQOS* with *HeatSticks* use Prevalence			
	0.5%	**1.0%**	**2.5%**	**5.0%**
80%-95%	29-32	63-67	168-174	347-355

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Statistical Methods

UData will be analyzed and summarized descriptively within each annual sample. Results will be summarized based on the raw data as well as age and sex standardized.

There will be no hypothesis testing.

Due to the possibility of low numbers of participants in some of the tobacco use groups, stratification will only be applied to those groups where there is a reasonable number of participants, at least n = 30 participants.

To fully understand the nature and integrity of the sampling, participation rates will include contact rate, response rate, eligibility rate, and completion rate.

Smoking prevalence may be influenced by population-level changes in age and/or gender over time; therefore, given that this study will be conducted over time, annual results will also be standardized by age, gender and age by gender combinations using the US population 2010 (statistics by the U.S. census bureau).

After having completed the first two annual samplings time series comparisons will also be performed by presenting the tabulations and graphical displays, by sample. The trends of each prevalence rates and behaviors will be presented.

Human Subject Protection and Institutional Review Board (IRB)

This study will submitted to an Institutional Review Board and approved or determined to be exempt prior to conducting the study. The study will be conducted in accordance with the Guidelines for Good Epidemiological Practice (GEP) (IEA 2007), Council of American Survey Research Organization's (CASRO) Code of Standards and Ethics (CASRO 2016), and the International Chamber of Commerce/European Society for Opinion and Marketing Research's (ESOMAR) International Code on Market and Social Research (ESOMAR 2016).

ABBREVIATIONS	
CASRO	Council of American Survey Research Organizations
ESOMAR	European Society for Opinion and Marketing Research
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
IRB	Institutional Review Board
PMP S.A.	Philip Morris Products, S.A.

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REFERENCES

[1]	Association IE. Good epidemiological practice: IEA guidelines for proper conduct in epidemiologic research. 2007. (IEA 2007)
[2]	Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2005–2014. Morbidity and Mortality Weekly Report 2015; 64(44):1233–40. (CDC 2015)
[3]	Council of American Survey Research Organizations. Code of Standards and Ethics. http://c.ymcdn.com/sites/www.casro.org/resource/resmgr/Code/Code_of_Standards_and_Ethics.pdf (accessed 09/13/16) (CASRO 2016)
[4]	FDA (Food and Drug Administration), Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012. (FDA 2012)
[5]	International Chamber of Commerce/ESOMAR. International Code on Market and Social Research (2008). https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ICCESOMAR_Code_English_.pdf (accessed 09/13/16) (ESOMAR 2016)

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PMI RESEARCH & DEVELOPMENT

Non-Interventional
Post-Market Study Protocol Concept
P1-NIS-02-US

Study Type: Cross-Sectional Adult Consumer Survey

Study Title: In-Market Adult Consumer Study: Cross-Sectional Survey of Adult *iQOS* with *HeathSticks* Consumers

Product: *iQOS* with *HeatSticks*

Country: United States

Sponsor: Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Version Status: FINAL
Version: 1.0
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PROTOCOL CONCEPT

Background

Philip Morris Products S.A. (PMP S.A.) is developing novel tobacco and nicotine containing products with the potential to reduce harm or the risk of tobacco-related disease associated with smoking cigarettes. In accordance with the United States Food and Drug Administration (FDA), PMP must demonstrate that "the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (FDA 2012)

iQOS with *HeatSticks* is one of these novel tobacco products. Altria Client Services LLC (ALCS) plans to develop this study – a cross-sectional survey that will be repeated over time to obtain detailed information on current and former *iQOS* users and how they interact with the product.

Objectives and Endpoint

1. Characterize *iQOS* with *HeatSticks* use patterns, ever-triers and current users
   Endpoints:
   - Types of tobacco products ever tried
   - Types of tobacco products used in past 30 days
   - Number of tobacco products used in the past 30 days
   - Frequency of use (number of days in the past 30 days)
   - Amount of use (number per day)
2. Characterize *iQOS* users reasons for using *iQOS* with *HeatSticks*
   Endpoints:
   - Reason for *iQOS* with *HeatSticks* use
3. Describe the risk perceptions among *iQOS* Users
   Endpoints:
   - Perception of the health risk associated with cigarettes and *iQOS* with *HeatSticks* as assessed with the "Perception of Health Risk" score from the Perception of Risk Instrument Global (PRI-G)
4. Characterize initiation, re-initiation, switching and cessation behaviors
   Endpoints:
   - Initiation - (first tobacco product ever tried; first tobacco product ever used on a consistent basis, including assessment of *iQOS* with *HeatSticks* as first tobacco product ever tried/ever used on a consistent basis)
   - Re-Initiation with *iQOS* with *HeatSticks* - (first trial of *iQOS* with *HeatSticks* after quitting cigarettes for more than 6 months, first trial of *iQOS* with *HeatSticks* after quitting all tobacco products for more than 6 months)
   - Re-Initiation of cigarette smoking or another tobacco product after trying *iQOS* with *HeatSticks*
   - Switching - (switching from cigarettes to *iQOS* with *HeatSticks*, switching from all tobacco products to *iQOS* with *HeatSticks*, switching from *iQOS* with *HeatSticks* to

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one or more tobacco products [*iQOS* with *HeatSticks* ever trier only], switching from *iQOS* with *HeatSticks* to cigarettes [*iQOS* with *HeatSticks* ever trier only])
- Cessation from all tobacco products after first trying *iQOS* with *HeatSticks* (*iQOS* with *HeatSticks* ever triers only)
- Cessation from cigarettes after first trying *iQOS* with *HeatSticks* (*iQOS* with *HeatSticks* ever triers only)

5. Correlations between intent to quit, nicotine dependence and quit attempt(s)
Endpoints:
- Fagerström Test for Cigarette Dependence (FTCD) (Fagerström 2011)
- Quit attempts in the past 12 months
- Plan to quit

Study Sampling and Population

The population will be a non-probability sample of adult *iQOS* users and ever-triers and a sample of adult current cigarette smokers who never tried *iQOS* with *HeatSticks*. The sample will be restricted to residents of the geographic locations where *iQOS* with *HeatSticks* is marketed.

- A convenience sample of adults of legal age to purchase tobacco products in the geography being surveyed identified using two sources of potential participants (1) a database of *iQOS* users and (2) commercial, on-line panels. (*Other potential recruiting sources may be considered.*)
- The age of participants will be verified using an external vendor prior to enrolling the participant into the study.
- The details of the sampling frame and mix of recruiting modes will be defined based on specific needs of the study. The recruiting modes will be defined in the final protocol.
- The population will include approximately 2,000 respondents per annual sample.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria envisioned at this time include:

Inclusion Criteria:
- The participant is an adult, legally authorized to buy tobacco products in their city and state of residence within the United States (18-21 years of age depending on state and city)
- The participant is a resident of the <<City>> or <<State>> within the study geography
- The participant is willing to participate in the study and provides informed consent for participation

Exclusion Criteria:
- The participant is an employee, contractor or consultant of the Sponsor or third-party organization responsible for conducting the study
- The participant is institutionalized
- The participant cannot read/understand English
- The participant cannot access the internet to complete the survey

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Study Design
This study will be conducted using an online survey system and will consist of two surveys (1) Screener Survey (including the informed consent) and (2) Main Survey.

Once a potential participant is interested to participate in the study, they will be provided the informed consent providing a summary of the study including the aim of the study, the voluntary nature of their participation, and data privacy/confidentiality.

After agreeing to participate in the study, the participant will complete the Screener Survey to determine their eligibility for the study. As part of the process of determining eligibility the participant's age will be verified to ensure that they meet the inclusion criteria.

Eligible participants then are presented with the "Main Survey" which will collect the detailed study information to assess the study objectives.

Study Instrument
The study instruments will be developed to include the following elements:

- Survey introduction - informed consent
- Demographics (including age verification)
- Socioeconomic Status
- Tobacco Product Use (first product use, ever trial and use within past 30 days)
- Intention to Quit and Quit Attempts
- Perception of Risk
- Reason for Use

(Please see Section 8.4.3, for more details on certain survey elements.)

Hypothesis
This study is descriptive in nature; therefore no statistical hypotheses will be tested.

Sample Size
The target sample size is 2,000 participants will be enrolled per annual sample. As the sample is to characterize segments of the population and not to assess the prevalence, the sample size of each segment is defined as:

- Current *iQOS* Users (n=1,000) – having used at least 100 *iQOS HeatSticks* in their lifetime and used *iQOS* with *HeatSticks* within the past 30 days
- *iQOS* Ever Trier (n=500) – have tried or used *iQOS* with *HeatSticks*, but no *iQOS* with *HeatSticks* use within the past 30 days
- Current Cigarette Smokers (n=500) – report never trying *iQOS* with *HeatSticks* and having smoked at least 100 cigarettes in their lifetime and smoked cigarettes in the past 30 days

The demographic distribution within the *iQOS* segments is unknown, however, the sample size is large enough to describe this distribution.

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Statistical Methods

UData will be analyzed and summarized descriptively within each annual sample. Results will be summarized based on the raw data as well as age and sex standardized. Data presentations will also be stratified by sex, age group and in some cases by smoking consumption (heavy versus light smokers). Due to the possibility of low numbers of participants in some of the tobacco use groups, stratification will only be applied to those groups where there is a reasonable number of participants, at least n = 30 participants.

There will be no hypothesis testing.

To fully understand the nature and integrity of the sampling, participation rates including contact rate, response rate, eligibility rate, and completion rate will be summarized.

Demographics of *iQOS* users may change over time; therefore, given that this study will be repeated over time, results will be reported by age, gender and age by gender combination.

Smoking prevalence may be influenced by population-level changes in age and/or gender over time; therefore, given that this study will be conducted over time, annual results will also be standardized by age, gender and age by gender combinations using the US population 2010 (statistics by the U.S. census bureau).

After having completed the first two annual samplings time series, comparisons will also be performed by presenting the tabulations and graphical displays, by sample. The trends for behavior measures will be presented.

Categorical data summaries: will presented as sample size, frequency counts and point estimates of proportions, and 95% confidence intervals will be reported for all study groups. Continuous data summaries will present sample sizes, and will be presented as the number of non-missing values, mean, median, standard deviation, minimum, maximum and 95% confidence intervals by study group.

Human Subject Protection and Institutional Review Board (IRB)

This study will submitted to an Institutional Review Board and approved or determined to be exempt prior to conducting the study. The study will be conducted in accordance with the Guidelines for Good Epidemiological Practice (GEP) (IEA 2007), Council of American Survey Research Organization's (CASRO) Code of Standards and Ethics (CASRO 2016), and the International Chamber of Commerce/European Society for Opinion and Marketing Research's (ESOMAR) International Code on Market and Social Research (ESOMAR 2016).

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ABBREVIATIONS	
ALCS	Altria Client Services, LLC
CASRO	Council of American Survey Research Organizations
ESOMAR	European Society for Opinion and Marketing Research
FDA	Food and Drug Administration
FTCD	Fagerstrom Test for Cigarette Dependence
GEP	Good Epidemiological Practice
IRB	Institutional Review Board
PMP S.A.	Philip Morris Products, S.A.
PRI-G	Perceived Risk Instrument – General Risk

REFERENCES

[1]	Association IE. Good epidemiological practice: IEA guidelines for proper conduct in epidemiologic research. 2007. (IEA 2007)
[2]	Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2005–2014. Morbidity and Mortality Weekly Report 2015;64 (44):1233–40. (CDC 2015)
[3]	Council of American Survey Research Organizations. Code of Standards and Ethics. http://c.ymcdn.com/sites/www.casro.org/resource/resmgr/Code/Code_of_Standards_and_Ethics.pdf (accessed 09/13/16) (CASRO 2016)
[4]	Fagerström, K. Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. Nicotine & Tobacco Research 2011: 14(1):75-8. (Fagerström 2011)
[5]	FDA (Food and Drug Administration), Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012. (FDA 2012)
[6]	International Chamber of Commerce/ESOMAR. International Code on Market and Social Research (2008). https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ICCESOMAR_Code_English_.pdf (accessed 09/13/16) (ESOMAR 2016)

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