PMI RESEARCH & DEVELOPMENT

Non-Interventional
Post-Market Study Protocol Concept
P1-NIS-03-US

Study Type: Behavioral Cohort Study

Study Title In-Market Adult Consumer Behavioral Cohort Study

Product: *iQOS* with *HeatSticks*

Country: United States

Sponsor: Philip Morris Products S.A.
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TABLE OF CONTENTS

PROTOCOL CONCEPT 3
Background 3
Objectives and Endpoint 3
Study Sampling and Population 4
Inclusion and Exclusion Criteria 4
Study Design 5
Study Instrument 6
Hypothesis 6
Sample Size 6
Statistical Methods 6
Human Subject Protection and Institutional Review Board (IRB) 7
ABBREVIATIONS 7
REFERENCES 7

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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 and 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. This study is a longitudinal cohort study designed to follow annual waves of new current *iQOS* with *HeatSticks* users (adult consumers who became current *iQOS* with *HeatSticks* users within the past 12 months) and compare them with a similar sample of current adult cigarette smokers, where appropriate, over a period of 12 months to assess intra-individual product use behaviors and trajectories.

Objectives and Endpoint

1. To characterize and describe patterns of use of tobacco and nicotine containing tobacco products
   - Types of products used within the past 30 days
   - Frequency of product use (number of days)
   - Volume of product use (number per day)
2. To identify intra-individual product use trajectories over time
   - Product switching patterns
   - Uptake of new products
   - Transitioning to more harmful tobacco products
   - Smoking cessation and cessation of all tobacco products
3. To characterize adult *iQOS* with *HeatSticks* users
   - Demographics and socioeconomic characteristics
   - Smoking history (e.g., lifetime, past year, past month)
   - Pre-*iQOS*, tobacco and nicotine containing tobacco product usage and behaviors
   - Reasons for *iQOS* use
4. To assess risk perceptions
   - Perceived Risk Instrument (PRI) to measure perception of risk associated with using cigarettes and *iQOS* with *HeatSticks*, using the Perceived Health Risk domain.

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5. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time
   - Signs and symptoms
   - Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
   - Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary disease (COPD), or other respiratory diseases, including asthma exacerbations
   - Malignancy diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)

Study Sampling and Population

Male and female adult cigarette smokers and *iQOS* users. This is an observational cohort study in which participants may change their tobacco product use during the course of the study; however, additional participants will not be enrolled to compensate for this tobacco product use switching.

The plan is to launch this study once the sale of *iQOS* is launched at a national level and the number of *iQOS* users is sufficient to support the design; however, the study could be launched sooner if there is a geographical region with a sufficient number of *iQOS* users. The enrollment in this study will be conducted in annual waves of new *iQOS* users (<12 months of *iQOS* use). The participants will be enrolled in 3 annual waves and followed for up to 12 months.

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 the United States (18-21 years of age depending on state and city)
- The participant is a resident of the United States
- The participant is willing to participate in the study and provides informed consent for participation.
- The participant has access to the internet for the purposes of completing the study assessments
- The participant is a new current *iQOS* with *HeatSticks* user or current cigarette smoker

A new current ***iQOS* with *HeatSticks* user** is someone who:

- Has used at least 100 *iQOS HeatSticks* in their lifetime,
- Currently (within the past 30 days) using *iQOS*, and
- Has used *iQOS* with *HeatSticks* for at least 2 months and no more than 12 months

NOTE: The use of *iQOS* with *HeatSticks* defines the user as an *iQOS* user, regardless of other tobacco or nicotine tobacco product use.

A current **Cigarette Smoker** is someone who:

- Has smoked at least 100 cigarettes in their lifetime
- Is currently (within the past 30 days) smoking cigarettes, and

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- Is not currently using *iQOS* with *HeatSticks*.

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 a tobacco industry employee
- The participant cannot read/understand English

Study Design

This is a prospective open enrollment, observational cohort study of American adults, legally authorized to purchase tobacco products in the US. The study will describe the patterns of use of tobacco and nicotine containing tobacco products and self-reported health outcomes and health-related events in *iQOS* with *HeatSticks* users and cigarette smokers.

Participants will be recruited into the cohort in 3 annual waves in a 3:1 ratio (*iQOS*:CC) until reaching the quota for each wave. We will seek to fill the adult cigarette smoker sample in each wave to have similar characteristics as observed in the *iQOS* sample. The aim of these annual waves is to ensure the recruitment of new current *iQOS* with *HeatSticks* users, as the demographic and other characteristics of new current *iQOS* with *HeatSticks* users may change over time. Annual waves will include up to 12 calendar months of recruiting consumers into the study.

Participants will be administered to the computer assisted self-interviews (CASIs) at Screening/Enrollment and then every 4 months for a total of 12 months.

The CASI will include questions related to: demographic information, socioeconomic status, smoking history, detailed product use including cessation intentions and behavior, and perception of risk, and self-reported health outcomes (symptoms and diagnoses).

The final study procedure is yet to be finalized, although it may unfold as follows: Potential participant will first be provided information about the study, and, if they are interested in participating, they will have to register and create an account using their email address and phone number. This registration process will include age verification from an independent 3rd party. Once the consumer is registered in the system, they will be provided the informed consent for participation and participant information. Participants who do not consent will have their accounts in the system deactivated, and the personal contact details removed from the database. Participants who do consent to participate in the study will be provided the eligibility domain of the CASI.

Participants that do not meet eligibility criteria for the study will be informed and will not be able to participate further in the study. Participants that meet the eligibility assessment, will provide the Baseline Domain, to capture their current information (as detailed above).

Participants in the study may be re-contacted by email, SMS, or telephone call (based on their preference), when their next assessment is required (4 months ± 1 month).

Participants can choose to withdraw from the study at any time, by logging into their account and choosing to stop participation in the study. At this time they will be asked the reason for discontinuation.

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

- Informed Consent
- Demographics (including age verification)
- Socioeconomic Status
- Lifestyle Assessment
- Tobacco Product Use History
- Intention to Quit
- Quit Attempts
- Perception of Risk
- Reason for Use
- Health Signs and Symptoms.

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

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

Sample Size
The total sample size of *iQOS* with *HeatSticks* users achieved in the current study may be affected by market penetration and product adoption. At this time, the target total sample size for *iQOS* with *HeatSticks* users is 3,000 participants, approximately 1,000 per annual wave. Therefore to account for drop-out and loss to follow-up of approximately 30% within the year, 4,500 participants will be enrolled over 3 annual waves (1,500 per wave). The sample size estimate is based on a precision based approach, so that tobacco use transitions rates and trajectories can be estimated with a precision of a 0.05 within each wave and sex. The sample size requirements for a precision of 0.05 on a probability of 50% with 95% confidence in a larger population is 385. Therefore given the unknowns of the population that will be enrolled in the study it is expected that if we have at least 1000 participants in a given wave and the sex distribution of the study is similar to that of conventional smoking then there would be more than a 95% probability of having at least 400 in each sex.

Statistical Methods
UData will be analyzed and summarized descriptively within each wave over the course of the study. There will be no hypothesis testing.

Standardization affects analysis by effectively removing the influence of changes in age and/or gender over time between the annual waves. The data from the annual waves will be age and sex standardized in compliance with the US population 2010 or a comparable, more recent reference (statistics by the U.S. census bureau).

The results will be summarized within each wave and across overall for the entire study.

The primary results from this study will be the tobacco use patterns and behaviors and the individual trajectories. The main presentation will focus on the endpoints at 12 months; however, the results will also be summarized for each 4 month collection period.

Tobacco use will be summarized by product (as well as by product combinations, as applicable) and each will be counted independently within that specific tobacco use pattern.

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Human Subject Protection and Institutional Review Board (IRB)

This study will be 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	
CASI	Computer assisted self-interviews
CASRO	Council of American Survey Research Organizations
CC	Conventional Cigarette
COPD	Chronic obstructive pulmonary disease
ESOMAR	European Society for Opinion and Marketing Research
FDA	Food and Drug Administration
IRB	Institutional Review Board
PMP	Philip Morris Products, SA
PRI	Perception of Risk Instrument

REFERENCES

[1] Association IE. Good epidemiological practice: IEA guidelines for proper conduct in epidemiologic research. 2007. (IEA 2007)

[2] 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)

[3] FDA (Food and Drug Administration), Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012. (FDA 2012)

[4] 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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