Swedish Match North America

Protocol for Observational Study

Perceptions and Behavioral Intentions Study for *General* Snus®

Protocol *SMNA 17-01GEN*

Status: Approved

Date: 28 May 2018

Prepared by: Kantar Health

Confidentiality Statement

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2 LIST OF ABBREVIATIONS AND DEFINITIONS

CAPTCHA	Completely Automated Public Turing Test To Tell Computers and Humans Apart
CASRO	Council of American Survey Research Organizations
CTP	Center for Tobacco Products
FDA	Food and Drug Administration
FTP	File Transfer Protocol
IRB	Institutional Review Board
MRTP	Modified Risk Tobacco Product
MRTPA	Modified Risk Tobacco Product Application
MTSS	Motivation to Stop Scale
NCHS	National Center for Health Statistics
OMB	Office of Management and Budget
PATH	Population Assessment of Tobacco and Health
PII	Personally Identifiable Information
PMTA	Premarket Tobacco Product Application
RESPONDENTS	Total sample which includes current, never, and former users of tobacco/nicotine products
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMNA	Swedish Match North America
TNP	Tobacco/Nicotine Products, including cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, and filtered cigars filled with tobacco, pipe tobacco, hookah and water pipe tobacco, and aids to help stop smoking
U.S.	United States
Video	*General* Snus® advertisement video

3 RESPONSIBLE PARTIES

3.1 Investigator and Contributors

Investigator: **Lulu Lee, PhD, Director, Health Outcomes Research**
Kantar Health, LLC

Kantar Health Project Team: (b)(6)

3.2 Sponsor

Swedish Match North America

Steve Seiferheld, Director of Market Research
steve.seiferheld@swedishmatch.com

4 SYNOPSIS

Title	Perceptions and Behavioral Intentions Study for *General* Snus®
Protocol version identifier	Version 1.0, Amendment 2
Date of last version of protocol	November 27, 2017
Protocol number	SMNA 17-01GEN
Author	Steve Seiferheld

Rationale and background	In November 2015, Swedish Match North America (SMNA) received market authorization for *General* Snus®, a smokeless tobacco product packaged in a small pouch that is placed under the upper lip, thereby eliminating the need for a user to spit or chew the product. In June 2014, SMNA had submitted modified risk tobacco product applications (MRTPAs) for *General* Snus® smokeless tobacco products. The FDA denied the request to remove a currently required warning stating that the products can cause gum disease and tooth loss. While the FDA did not rule on the mouth cancer warning or the "not a safe alternative" warning, the FDA did suggest alternative approaches which could provide sufficient evidence to support issuance of modified risk orders for the tobacco products.[2,3] Of particular note, the FDA suggested approaching MRTP designation through the use of claims that could be included in marketing and communication materials. SMNA has elected to submit an amended MRTPA for its *General* Snus® product line. This protocol summarizes consumer research that will be conducted and submitted in conjunction with the application amendment. For this purpose, the objective of the Perceptions and Behavioral Intentions Study for *General* Snus® is to determine how proposed modified risk claims impact various cohorts of adult consumers' perceptions of health risk of using *General* Snus® and their behavior intentions regarding tobacco and nicotine products (TNP).
Research question and objectives	The overarching research question within this study can be stated as follows: *How does the presence of a statement claiming reduced risk of General Snus® usage compared to cigarette smoking (the MRTP claim) affect intentions and behaviors of U.S. adult consumers, when compared with the absence of that same claim?* The question will be studied among both TNP users and non-users (all of whom are of legal age to use TNP in their residential geography). The effectiveness of the MRTP claim will be studied in the context of a single *General* Snus® description provided in a video advertisement (video). The study will utilize a test versus control methodology to assess the impact of three *General* Snus® videos, each containing one modified risk claim (serving as the test) and one *General* Snus® video not containing a modified risk claim (serving as the control), across three pairs of two-sample comparisons, each including one of three test groups and a control group.

	The **primary** objectives of this study are: 1. Compare the likelihood of various usage intentions and behaviors related to *General* Snus® and cigarettes between test (video with claim) and control (video without claim) sample groups. Specifically, after having viewed a single *General* Snus® video, compare: • Within TNP non-user groups o The likelihood to <u>initiate</u> TNP use with *General* Snus® between test and control sample groups, focusing on TNP non-user groups. o The likelihood to <u>re-initiate</u> TNP use with *General* Snus® between test and control sample groups, focusing on TNP non-user groups. • Within TNP user groups: o The likelihood to <u>use *General* Snus®</u> between test and control sample groups; o Among current smokers, the likelihood to <u>use cigarettes</u> between test and control sample groups; o The <u>intention to quit all current TNP</u> between test and control sample groups. 2. Examine perceptions of absolute risk associated with using General Snus®, smoking cigarettes, and never having used any TNP, between test and control sample groups among all respondents. The health conditions under consideration when assessing absolute risk: <u>Respiratory conditions:</u> ▪ Chronic bronchitis ▪ Emphysema ▪ Lung cancer ▪ Serious health problems <u>Non-respiratory conditions:</u> ▪ Gum disease ▪ Heart disease ▪ Mouth cancer ▪ Stroke

	3. Compare perceptions of the relative risks associated with using *General* Snus® with using • cigarettes • cigarettes and *General* Snus® • quitting all TNP, and • never having used any TNP, between test and control sample groups among all respondents. The health conditions under consideration when assessing relative risk: Respiratory conditions: ▪ Chronic bronchitis ▪ Emphysema ▪ Lung cancer ▪ Serious health problems Non-respiratory conditions: ▪ Gum disease ▪ Heart disease ▪ Mouth cancer ▪ Stroke 4. Assess the comprehension of the General Snus® modified risk claims between test and control sample groups. The **secondary** objectives of this study are: 5. Compare the likelihood of various usage intentions and behaviors related to *General* Snus® and other TNP (**e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, or filtered cigars filled with tobacco, pipe tobacco, and hookah or water pipe tobacco**) between test and control sample groups. Specifically, among TNP user groups, compare the likelihood to use current TNP between the test sample and the control sample (after having viewed a single *General* Snus® video). 6. Compare perceptions of the relative risks associated with using *General* Snus® with using • moist snuff • other brands of snus and • aids that help stop smoking, between test and control sample groups among all respondents.

	The health conditions under consideration when assessing relative risk: <u>Respiratory conditions:</u> ▪ Chronic bronchitis ▪ Emphysema ▪ Lung cancer ▪ Serious health problems <u>Non-respiratory conditions:</u> ▪ Gum disease ▪ Heart disease ▪ Mouth cancer ▪ Stroke 7. Assess the believability of the *General* Snus® modified risk claims between test and control sample groups.
Study design	A between-groups test versus control methodology will be utilized to assess the impact of the MRTP claims. The factorial study design includes 4 claims (3 tests claims and 1 control) x 4 warnings x 2 flavors, totaling 32 cells. The claims (3 test claims and 1 control) serve as the experimental stimulus, and the other factors are randomly distributed in a balanced way across respondents. Specifically, respondents within each of the six cohorts will be randomly assigned into one of 3 test cells (one for each modified risk claim to be tested) or 1 control cell for testing the absence of a modified risk claim. Claims are embedded in a video advertisement for *General* Snus®, with the control version having no such claim. Each of the video advertisements will also include 1 of the 4 mandated warning statements and 1 of 2 flavors of *General* Snus®. Within each test/control cell, each respondent will then be randomly assigned into 1 of the 8 total *General* Snus® video advertisements (4 warning statements by 2 flavors – see Table 1 "Study Design – Random Assignment into 3 Test Cells and 1 Control Cell"). The three modified-risk claims to be tested are: 1. Using *General* Snus® instead of cigarettes puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. 2. Using *General* Snus® instead of cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users 3. No tobacco is totally safe, but using *General* Snus® instead of

	cigarettes puts you at a lower risk of chronic lung disease and other tobacco-related ailments. The warning labels to be randomized within each test/control cell are: 1. *General* Snus® is not a safe alternative to cigarettes. 2. *General* Snus® can cause mouth cancer. 3. *General* Snus® can cause gum disease and tooth loss. 4. *General* Snus® is addictive. The flavors to be randomized within each test/control cell are: 1. Mint. 2. Wintergreen.
Population	The study will include 11,640 U.S. consumers who meet all the following criteria: • Minimum legal age for tobacco/nicotine use per local state requirements • Able to read and speak English • Currently a resident of the United States • Provide electronic informed consent Respondents who meet any of the following criteria will be excluded: • Respond as "don't know" or "decline to answer" to specific demographics (gender, geographical region, ethnicity, or education), used for balancing cohorts • Unwilling or unable to provide electronic informed consent • Individuals employed in any of the following fields or professions: market research, marketing, advertising, manufacturers of TNP, or physicians • Individuals who have taken part in a consumer research study on tobacco in the past 2 weeks Please see Data Sources for more detail about where the sample is sourced.
Variables	The primary intent of the survey will be to have respondents evaluate a single General Snus® description provided in a video. The videos run for about one minute, with the control versions of the videos running slightly shorter due to the absence of an MRTP claim. All videos provide background on General Snus®, how it is produced, and why it is a high-quality product. After exposure to a video, respondents will answer survey questions meant to measure the impact of the modified risk claims on TNP usage behaviors, and perceptions of health risks associated with TNP.

Data sources	Consumers will initially be recruited from verified online consumer panels from Lightspeed Research, Survey Sampling International, and Research Now. As verified panels, these are large commercial consumer panels that profile panelists on self-reported characteristics such as age, gender, location, income, ethnicity, household size, marital status, presence of young children, and education. Based on panelist self-reported background information, a representative sample reflecting socio-demographic characteristics of the adult population based on U.S. Census data will be selected from these panels, reflecting the marginal distribution of age, gender, geographical region, ethnicity, race, and education. Next, a sampling frame consisting of all legal age panelists from each state will be created. The invited sample will then be derived from a stratified sampling framework based on socio-demographic characteristics of the adult population from the Population Assessment of Tobacco and Health (PATH) study data[4]. Like the socio-demographic variables, panel source will also be balanced across cohorts through sample assignments, daily monitoring, and sample management, as well as extended duration of fielding. Although perfect balance is the goal with panel source, as with the socio-demographic variables, perfect balance is unlikely achievable in the recruitment for this study and will be discussed in the Limitations (Section 8.8). To ensure successful oversampling of key segments, an organization named Lucid will work with additional partners. Specifically, Lucid will be utilized for the current cigarette smokers from legal age to 24 years of age cohort and current smokeless tobacco user cohort. Lucid is an aggregator resource, with the ability to leverage sample from different sources, such as Branded Research Inc., for Good, P2, and Prodege. These sources recruit from social networks, targeted environments and websites, advertisement campaigns, reward companies, such as Swagbucks.com, to recruit hard-to-reach quota groups, especially younger age groups. All partners, like the online panels, have automated and manual sample quality assurance measures. The Limitations section (Section 8.8) will provide some further detail on the challenges associated with acquiring sample for difficult cohorts.

Study size	11,640 consumers will be recruited, 1,940 from each of the following six cohorts: • Never users of TNP from legal age to 24 years of age • Never users of TNP older than 24 years of age • Former cigarette smokers from legal age and older • Current cigarette smokers from legal age to 24 years of age • Current cigarette smokers older than 24 years of age • Current smokeless tobacco users from legal age and older
Data analysis	Cognitive interviews will be conducted prior to launching the web-based surveys. The series of individual comments obtained in the cognitive interviews, pertaining to separate questions across multiple interviews, will be compiled into a coherent set of summary findings that transcend the individual interview level. In-depth analysis will include looking for themes that indicate that respondents have issues with comprehension, retrieval, decision-judgment, and response for questions in the survey[18]. The results will then be compiled to determine which changes to the survey instrument are necessary for greater content validity. The main analyses for the quantitative study will focus on test versus control (exposed to test claims versus not) using independent measures. To meet the objectives of this study and test the hypotheses, the analysis will consist of bivariate analyses with corresponding significance testing to address the study hypotheses. Descriptive statistics will be calculated across all analyses and reported where valuable to interpretation of results. Bivariate analysis will include independent sample t-tests and two-sample binomial proportion tests will be conducted to examine statistical significance between test claims vs. control groups according to study hypotheses. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP).
Milestones	Start of data collection December 2017 End of data collection February 2018

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	11/27/17	Throughout	Amendment	Changes based on CTP feedback and redesign of the study
2	5/28/18	Throughout	Amendment	Changes based on new information and additional background obtained from: • January 24-25, 2018 Tobacco Products Scientific Advisory Committee Meeting • Public availability of Camel Snus/RJ Reynolds Tobacco Company MRTP application
…				

6 BACKGROUND AND RATIONALE

The Family Smoking Prevention and Tobacco Control Act, signed into law in 2009, gave the Food and Drug Administration (FDA) the power to regulate tobacco products and established the Center for Tobacco Products (CTP) within the FDA. The law gives the CTP authority to regulate the manufacturing, marketing/advertising content, and sale of tobacco/nicotine products (TNP). The FDA requires that the marketing of a new tobacco product be appropriate for the protection of the public health as determined "on the basis of well-controlled investigations" (Section 910 of the FD&C Act).[1]

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population, including users and non-users of the tobacco product[1]. Essentially, CTP will require research-based evidence that demonstrates, in general: (1) existing tobacco product users do not increase consumption, (2) non-tobacco users do not start using, and (3) former tobacco users do not re-start use of tobacco. Products marketed in the U.S. after February 15, 2007 must obtain a marketing authorization from the FDA (i.e., through a premarket tobacco product application [PMTA] application or a Substantial Equivalence [SE] report) or they can no longer be sold in the U.S.[1]

While all tobacco products pose risks, the modified risk tobacco product (MRTP) pathway outlined in the 2009 Family Smoking Prevention and Tobacco Control Act allows companies to submit applications for the FDA to evaluate whether a tobacco product may be sold or distributed as a product for use to reduce harm or the risk of tobacco-related disease and may use FDA-approved modified risk claims in marketing of the product.[2]

In November 2015, Swedish Match North America (SMNA) received market authorization for *General* Snus®, a smokeless tobacco product packaged in a small pouch that is placed under the upper lip, thereby eliminating the need for a user to spit or chew the product. In June 2014, SMNA had submitted modified risk tobacco product applications (MRTPAs) for *General* Snus® smokeless tobacco products. The FDA denied the request to remove a currently required warning stating that the products can cause gum disease and tooth loss. While the FDA did not rule on the mouth cancer warning or the "not a safe alternative" warning, the FDA did suggest alternative approaches which could provide sufficient evidence to support issuance of modified risk orders for the tobacco products.[2,3] Of particular note, the FDA suggested approaching MRTP designation through the use of claims that could be included in marketing and communication materials.

In conjunction with the notion of claims in support of MRTP status, the FDA cited that evidence "may support applications that seek to market the products with other claims about relatively lower risk … for *General* Snus® compared to other tobacco products."[3]

SMNA has elected to submit an amended MRTPA for its *General* Snus® product line. This protocol summarizes consumer research that will be conducted and submitted in conjunction with the application amendment. For this purpose, the objective of the Perceptions and Behavioral Intentions Study for *General* Snus® is to determine how proposed modified risk claims impact various cohorts of adult consumers' perceptions of health risk of using *General* Snus® and their behavior intentions regarding TNP.

7 OBJECTIVES AND HYPOTHESES

The overarching research question within this study can be stated as follows: *How does the presence of a statement claiming reduced risk of negative health conditions due to General Snus® usage compared to cigarette smoking (the MRTP claim) affect intentions and behaviors of U.S. adult consumers, when compared with the absence of that same claim?* The question will be studied among both TNP users and non-users (all of whom are of legal age to use TNP in their residential geography). The effectiveness of the MRTP claim will be studied in the context of a single *General* Snus® description provided in a video advertisement (video).

The study will utilize a test versus control methodology to assess the impact of three *General* Snus® videos, each containing one modified risk claim (serving as the test) and one *General* Snus® video not containing a modified risk claim (serving as the control), across three pairs of two-sample comparisons, each including one of three test groups and a control group. Objectives with corresponding hypotheses[a] are presented below.

7.1 Primary Objectives and Hypotheses

1. Compare the likelihood of various usage intentions and behaviors related to *General* Snus® and cigarettes between test (video with claim) and control (video without claim) sample groups. Specifically, after having viewed a single *General* Snus® video, compare:

   - Within TNP non-user groups
     - The likelihood to initiate[b] TNP use with *General* Snus® between test and control sample groups, focusing on TNP non-user groups.
     - The likelihood to re-initiate TNP use with *General* Snus® between test and control sample groups, focusing on TNP non-user groups.
   - Within TNP user groups:
     - The likelihood to use *General* Snus® between test and control sample groups;
     - Among current smokers, the likelihood to use cigarettes between test and control sample groups;
     - The intention to quit all current TNP between test and control sample groups.

[a] Certain study objectives seek support for the null hypothesis; we have complied with FDA's recommendations of using "valid measures of constructs," and that the study be "sufficiently statistically powered to detect differences should they exist."[1]

[b] The term "initiate" refers to entering the category of TNP user and is only pertinent to TNP never, i.e., those not currently using TNP. Similarly, the term "re-initiate" is only pertinent to TNP former users.

Hypotheses

1.1. Among TNP non-user groups, the likelihood to buy *General* Snus® among the test sample will be **equal or lower** than the control sample.

1.2. Among TNP user groups, the likelihood to buy *General* Snus® will be **higher** for the test sample than the control sample.

1.3. Among current smokers, the likelihood to smoke cigarettes moving forward will be **lower** for the test sample than the control sample.

1.4. Among current smokers, the likelihood to use aids to stop smoking moving forward will be **equal or higher** for the test sample than the control sample.

1.5. Among current smokers, the intention to quit smoking cigarettes will be **equal or higher** for the test sample than the control sample.

1.6. Among TNP user groups, the intention to quit all current TNP(s) (excludes aids to stop smoking) will be **equal or higher** for the test sample than the control sample.

2. Examine perceptions of absolute risk associated with using General Snus®, smoking cigarettes, and never having used any TNP, between test and control sample groups among all respondents.

   The health conditions under consideration when assessing absolute risk[c]

   Respiratory conditions:

   - Chronic bronchitis
   - Emphysema
   - Lung cancer
   - Serious health problems

   Non-respiratory conditions:

   - Gum disease
   - Heart disease
   - Mouth cancer
   - Stroke

Hypothesis

2.1. Among all respondents, perceived absolute risks of each health condition (respiratory and non-respiratory) from the daily use of only *General* Snus® and no other TNP will be **lower** for the test sample than the control sample.

3. Compare perceptions of the relative risks associated with using *General* Snus® with using

[c] Published literature would suggest misperceptions of the health risks of switching from cigarettes to smokeless tobacco, accordingly the eight health conditions will be categorized into respiratory and non-respiratory to better understand potential consumer misperceptions in this study.[20]

- cigarettes
- cigarettes and *General* Snus®
- quitting all TNP, and
- never having used any TNP,

between test and control sample groups among all respondents.

The health conditions under consideration when assessing relative risk:

Respiratory conditions:

- Chronic bronchitis
- Emphysema
- Lung cancer
- Serious health problems

Non-respiratory conditions:

- Gum disease
- Heart disease
- Mouth cancer
- Stroke

Hypotheses

3.1.1. Test sample will perceive the relative risks of each respiratory health condition as **lower** than the control sample, when comparing daily use of *General* Snus® vs. daily use of cigarettes.

3.1.2. Test sample will perceive the relative risks of each non-respiratory health condition as **equal or lower** than the control sample, when comparing daily use of *General* Snus® vs. daily use of cigarettes.

3.2.1. Test sample will perceive the relative risks of each respiratory health condition as **lower** than the control sample, when comparing daily use of *General* Snus® vs. daily use of both *General* Snus® and cigarettes.

3.2.2. Test sample will perceive the relative risks of each non-respiratory health condition as **equal or lower** than the control sample, when comparing daily use of *General* Snus® vs. daily use of both *General* Snus® and cigarettes.

3.3. Test sample will perceive the relative risks of each health condition (respiratory and non-respiratory) as **equal or higher** than the control sample, when comparing daily use of *General* Snus® vs. never having used any TNP.

3.4. Test sample will perceive the relative risks of each health condition (respiratory and non-respiratory) as **equal or higher** than the control sample, when comparing the act of quitting all TNP use except for *General* Snus® vs. the act of quitting all TNP use.

4. Assess the comprehension of the General Snus® modified risk claims between test and control sample groups.

Hypothesis

4.1 Among all respondents, the test sample will have a **higher** comprehension of the *General* Snus® claims than the control sample.

7.2 Secondary Objectives and Hypotheses

5. Compare the likelihood of various usage intentions and behaviors related to *General* Snus® and other TNP (**e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, or filtered cigars filled with tobacco, pipe tobacco, and hookah or water pipe tobacco**) between test and control sample groups. Specifically, among TNP user groups, compare the likelihood to use current TNP between the test sample and the control sample (after having viewed a single *General* Snus® video).

Hypothesis

5.1. Among TNP user groups, the likelihood to use TNP (**e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, or filtered cigars filled with tobacco, pipe tobacco, and hookah or water pipe tobacco**) moving forward will be **equal or lower** for the test sample than the control sample.

6. Compare perceptions of the relative risks associated with using *General* Snus® with using

   - moist snuff
   - other brands of snus and
   - aids that help stop smoking,

   between test and control sample groups among all respondents.

The health conditions under consideration when assessing relative risk:

Respiratory conditions:

- Chronic bronchitis
- Emphysema
- Lung cancer
- Serious health problems

Non-respiratory conditions:

- Gum disease
- Heart disease
- Mouth cancer
- Stroke

Hypotheses

6.1. Test sample will perceive the relative risks of each health condition (respiratory and non-respiratory) as **equal or lower** than the control sample, when comparing daily use of *General* Snus® vs. daily use of moist snuff.

6.2. Test sample will perceive the relative risks of each health condition (respiratory and non-respiratory) as equal or lower than the control sample, when comparing daily use of General Snus® vs. daily use of other brands of snus.

6.3. Test sample will perceive the relative risks of each health condition (respiratory and non-respiratory) as **equal or higher** than the control sample, when comparing daily use of *General* Snus® vs. daily use of aids that help stop smoking.

7. Assess the believability of the *General* Snus® modified risk claims between test and control sample groups.

Hypothesis

7.1. Among all respondents, the test sample will find the *General* Snus® claims **more** believable than the control sample.

8 RESEARCH METHODS

8.1 Data Source(s)

Data will be obtained using responses from a customized web-based survey of invited consumers who meet inclusion and exclusion criteria (explained in Sections 8.4.2 and 8.4.3) and who agree to participate. Consumers will initially be recruited from verified online consumer panels Lightspeed Research, Survey Sampling International, and Research Now. These large commercial consumer panels profile their panelists on self-reported characteristics such as age, gender, location, income, ethnicity, household size, marital status, presence of young children, and education. The panels are reflective of the U.S. population; however, they are not balanced to the U.S. census. They are sizeable enough to generate samples that are representative of the U.S. population. This ensures that our sample source is a reliable representation of the U.S. online population.

The online panels are opt-in panels where consumers who join make a conscious decision to participate regularly in surveys. Several methodologies, such as email, e-newsletter campaigns, banner placement, partnerships, direct mail, etc. are used by the panel companies to recruit panelists. Potential panelists are asked to complete an in-depth registration profile which includes numerous logic checks to ensure quality. Steps taken to ensure quality include, but are not limited to:

- Use of proxy detection, which detects a proxy server used to mask the registrant's true IP address and past fraudulent activity.
- IP GeoFencing, which detects the registrant's location via his/her IP address and determine his/her eligibility for registration based on location-specific rules.
- CAPTCHA technology, which prevents automated programs from joining our site through challenge-response tests.
- Email address verification, which queries our database to ensure the email address is unique (all registrants must verify their email addresses through a double opt-in registration process).

In addition, registrants' postal address and zip / postal code are verified against a current local address directory. Each computer is also tagged with a unique ID to ensure only one respondent per computer can participate in a survey. This ID would block survey respondents who attempt to complete the same survey from multiple panels and those who attempt to take a survey multiple times using different identities. Extensive analysis is conducted to understand and measure panelist activity. These analyses include the following: recruitment source, panel composition, longevity on panel, response, participation and dropout rate, and response quality.

The panel member details are maintained in confidence and are used purely for research purposes only. No information that could personally identify the respondent can be released, nor can personal information be sought from the panelists or about the panelists without their prior knowledge and consent.

Based on panelist self-reported background information, a representative sample reflecting socio-demographic characteristics of the adult population based on U.S. Census data will be selected from these panels, reflecting the marginal distribution of age, gender, geographical region, ethnicity, race, and education. Next, a sampling frame consisting of all legal age panelists from each state will be created. The invited sample will then be derived from a stratified sampling framework based on socio-demographic characteristics of the adult population from the Population Assessment of Tobacco and Health (PATH) study data[4]. Panelists with required demographic profiles will be randomly selected for inclusion in the invited sample until demographic profile quotas are met in each study cohort. This recruitment methodology is expected to provide socio-demographic profiles consistent with the adult population based on PATH study data for each of the study cohorts.

Online panel sampling tools will be used to generate traffic to the survey, based on the targeted demographics and considering expected response rates for the different demographic strata. During the fieldwork, sample performance will be monitored daily; analysis of response and qualifying rates will be done for each demographic quota within cohorts. The panels will utilize manual monitoring and dynamic automated tools to ensure that the sampling process results in the desired demographic quotas. As quota targets are achieved, the random sample selection process will be refined to target only panelists matching those demographic characteristics whose quotas have not yet been reached.

Like the socio-demographic variables, panel source will also be balanced across cohorts through sample assignments, daily monitoring, and sample management, as well as extended duration of fielding. Although perfect balance is the goal with panel source, as with the socio-demographic variables, perfect balance is unlikely achievable in the recruitment for this study and will be discussed in the Limitations (Section 8.8).

To ensure successful oversampling of key segments, an organization named Lucid will work with additional partners. Specifically, Lucid will be utilized for the current cigarette smokers from legal age to 24 years of age cohort and current smokeless tobacco user cohort. Lucid is an aggregator resource, with the ability to leverage sample from different sources, such as Branded Research Inc., for Good, P2, and Prodege. These sources recruit from social networks, targeted environments and websites, advertisement campaigns, reward companies, such as Swagbucks.com, to recruit hard-to-reach quota groups, especially younger age groups. All partners, like the online panels, have automated and manual sample quality assurance measures. The Limitations section (Section 8.8) will provide some further detail on the challenges associated with acquiring sample for difficult cohorts.

Prior to launching the study in full, Kantar will execute a soft launch. The primary objective of the soft launch process is to confirm that all facets of the data collection process function according to protocol; items of specific interest include the initial incidence rate, the length of interview, and the accuracy of the web-based instrument (i.e., survey), all of which work to ensure the primary objectives of the research are met. Soft launch data will be used as part of the final data set, unless quality control checks suggest an error or unintended issue that may have compromised the data.

In that event, the data will be saved but not included in the final data set. The soft launch will account for no greater than 10% of the total sample.

Once the accuracy of the web-based instrument is verified through soft launch, the study will be fully launched, with invitations being sent to a broader number of potential respondents. Potential respondents will receive their invitations from their respective panels to participate in the survey. To be clear that the study is relevant for all consumers, the invitation will specify that the opinions of both users and non-users of TNP will be important. The email will include the following: (1) general invitation; and (2) a link to the panelist welcome page. Approximately two to four days after the initial invitation, non-responders will be sent an e-mail reminder regarding the availability of the survey. New invitations will be sent until the target sample size is reached. Panelists previously invited will still able to participate if their desired quota is not reached.

If invited panelists are interested in participation, they click on the link at the bottom of the invitation, or copy and paste the link into their browser. The link takes respondents to the panelist welcome page where they are presented with another link to the screener, followed by the statement of informed consent for this study. The informed consent advises potential respondents that participation is voluntary and that responses will remain confidential. It also includes information about the goals of the study, the approximate length of the survey, and compensation for participation. Lastly, the statement of informed consent provides potential respondents with the contact information for panel managers to address any concerns they may have.

If potential respondents agree to participate in the study after reading the statement of informed consent, they will select "I agree to participate" and will then be taken to the survey instrument. Those who select "I do not agree to participate" will be thanked before exiting.

Respondents will be able to complete the online survey via computer, tablet, or smartphone. Following the completion of the survey by each of the respondents, a debriefing statement will be shown to clarify that the intent of the survey was not to market, sell or promote any tobacco or nicotine product, and that no products will be offered in exchange for survey completion. Respondents who complete the survey will receive compensation, typically reward points or currency offered by the panel of which they are a member, which are of fair market value for their time.

8.2 Study Design

Qualitative cognitive interviews will precede quantitative data collection. These cognitive interviews will walk through key components of the survey instrument to assess interpretation of each question by respondents. See Section 8.3 for more details about cognitive interviews.

A between-groups test versus control methodology will be utilized to assess the impact of the MRTP claims. The factorial study design includes 4 claims (3 tests claims and 1 control) x 4 warnings x 2 flavors, totaling 32 cells. The claims (3 test claims and 1 control) serve as the experimental stimulus, and the other factors are randomly distributed in a balanced way across respondents. Specifically, respondents within each of the six cohorts will be randomly assigned into one of 3 test cells (one for each modified risk claim to be tested) or 1 control cell for testing

the absence of a modified risk claim. Claims are embedded in a video advertisement for *General* Snus®, with the control version having no such claim. Each of the video advertisements will also include 1 of the 4 mandated warning statements and 1 of 2 flavors of *General* Snus®. Within each test/control cell, each respondent will then be randomly assigned into 1 of the 8 total *General* Snus® video advertisements (4 warning statements by 2 flavors – see Table 1 "Study Design – Random Assignment into 3 Test Cells and 1 Control Cell").

The three modified-risk claims to be tested are:

1. Using *General* Snus® instead of cigarettes puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.
2. Using *General* Snus® instead of cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users.
3. No tobacco is totally safe, but using *General* Snus® instead of cigarettes puts you at a lower risk of chronic lung disease and other tobacco-related ailments.

The warning labels to be randomized within each test/control cell are:

5. *General* Snus® is not a safe alternative to cigarettes.
6. *General* Snus® can cause mouth cancer.
7. *General* Snus® can cause gum disease and tooth loss.
8. *General* Snus® is addictive.

The flavors[d] to be randomized within each test/control cell are:

3. Mint.
4. Wintergreen.

Table 1: Study Design – Random Assignment into 3 Test Cells and 1 Control Cell

	CELL A (CLAIM 1)	CELL B (CLAIM 2)	CELL C (CLAIM 3)	CELL D (CONTROL)
Warning 1 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 2 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 3 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 4 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2

[d] Mint and wintergreen flavored *General* Snus® account for nearly 70% of product sales. Source: SMNA[8]

8.3 Cognitive Interviews

Cognitive interviews will be conducted prior to executing the quantitative phase of the Perceptions and Behavioral Intentions Study. The cognitive interviews will be conducted in accordance with the Office of Management and Budget (OMB) Statistical Policy Directive No. 2 Addendum: Standards and Guidelines for Cognitive Interviews.[5] Cognitive interviewing is used as a means for applying qualitative research methods to the understanding of the functioning of survey questions.[6] The premise of this approach is that intensive interviewing of a single individual provides rich information that is useful for providing the questionnaire designer with information concerning how questionnaires and individual survey questions, provide (or fail to provide) desired information.

The cognitive interviewing approach, used to evaluate sources of response error in survey questionnaires, has been tested and is used by the National Center for Health Statistics (NCHS) Centers for Disease Control and Prevention[7]. The cognitive assessments will determine any potential problems with how consumers understand, interpret, and answer each survey question, including questions or response options which may be confusing or misinterpreted.

To ensure that the materials are appropriate and sufficiently clear to consumers, the Perceptions and Behavioral Intentions online survey will be piloted among 20 respondents defined by the cohorts for this study across two rounds of qualitative in-depth, in-person, interviews, in two geographically distant cities. The second round of cognitive interviews will take place 2 weeks after the initial round of interviews to allow for revisions between rounds. We anticipate reaching saturation and not requiring additional rounds of cognitive testing; however, if saturation is not met, additional rounds of testing may be required.

The study team will collaboratively develop an interview guide around the survey instrument to standardize each interview with the purpose of collecting information with respect to the content validity of the instrument. As outlined by the guideline, the interview guide will "contain the questions to be evaluated along with interviewer instructions, such as follow-up probe questions." The purpose of the questions is to "to measure the processes by which a respondent interprets and responds to a question."

Recruitment of respondents will be a convenience sample. However, the cognitive testing sample will be recruited to best represent the population of interest including age, gender, race/ethnicity, education, and tobacco/nicotine use behavior. Recruitment will be done by Fieldwork Research, in Seattle, and Schlesinger Associates, in Philadelphia, at a local level, utilizing their databases of consumers. Panel members will be contacted via email with a web-based link to an online screener. The email would include a general introduction to the availability of a new study, those interested would complete an online screener for qualification based on cohorts as well as all the inclusion and exclusion criteria (see section 8.4.2 and section 8.4.3). The screener will also include an introduction explaining the purpose and scope of the study. Once qualified, consumers will indicate interest and the field agency will schedule the in-person interview.

Table 2: Cognitive Interview Sample Plan by Cohort

	Number of Respondents		
	Seattle	**Philadelphia**	**TOTAL**
Never tobacco users from legal age to 24 years of age	1	1	2
Never tobacco users older than 24 years of age	2	2	4
Former cigarette smokers from legal age and older	2	2	4
Current cigarette smokers from legal age to 24 years of age	1	1	2
Current cigarette smokers older than 24 years of age	2	2	4
Current smokeless tobacco users from legal age and older	2	2	4
TOTAL NUMBER OF RESPONDENTS	**10**	**10**	**20**

8.4 Study Population

The study population consists of the U.S. adult population of legal age for TNP use. To meet the objectives of the Perceptions and Behavioral Intentions Study for *General* Snus®, the research will include respondents from the following cohorts:

Never Tobacco Users	• Have **NEVER** used the following products: ▪ Cigarettes ▪ E-cigarettes ▪ Cigars, cigarillos, filtered cigars ▪ Pipe filled with tobacco ▪ Hookah or water pipe filled with tobacco ▪ Smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco) • **OR** all of the following: o Smoked fewer than 100 cigarettes during their lifetime AND now do not smoke cigarettes every day or some days **AND** o For each of the following products, have never been a regular user AND now do not use the product every day or some days: ▪ E-cigarettes ▪ Cigars, cigarillos, filtered cigars ▪ Pipe filled with tobacco ▪ Hookah or water pipe filled with tobacco ▪ Smokeless tobacco (snus pouches, moist snuff, dip or chewing tobacco)

Former cigarette smokers	• Have smoked 100 or more cigarettes during lifetime **AND** currently do not smoke cigarettes every day or some days
Current cigarette smokers	• Have smoked 100 or more cigarettes during lifetime **AND** currently smoke cigarettes every day or some days
Current smokeless tobacco users	• Have regularly used smokeless tobacco (snus pouches, moist snuff, dip or chewing tobacco) **AND** currently uses smokeless tobacco products every day or some days **AND** • Have smoked cigarettes during lifetime **AND** currently do not smoke cigarettes every day or some days **OR** have never smoked

The definition of users and the product types constituting TNP for this study are consistent with the PATH study, where a threshold of lifetime use is established for cigarette use and for all other TNP, based on recollection of ever using TNP fairly regularly and if they now use the product every day or some days.[4] If a respondent is both a former cigarette smoker and a current smokeless tobacco user, the respondent will be recruited as part of the current smokeless group, as that is the lower incidence group.

8.4.1 Study Sample Size

Power analyses were conducted to verify the following. First, given the study sample size, there will be a sufficiently high probability that tests will be able to detect significant differences when they exist (i.e., mitigate Type II error; β). Second, given the number of significance tests performed, there will be a sufficiently low probability of rejecting the null hypothesis when it is true (Type I error; α).

The hypotheses specified in Section 7 require comparing responses between test and control samples. Considering an initial Type 1 error rate of .05, 85% power, and a small effect size of 0.20 based on Cohen's d, which is a standardized measure of effect defined as the difference between two means divided by their pooled standard deviation,[9] a sample of n=485 for each test and control sample cell was calculated. The detailed list of assumptions is below:

- A comparison of means of a continuous measurement across independent samples t-tests.
- A conventional small effect size (Cohen's d) of .20.
- Type 1 error rate of 0.05, adjusted for 3 multiple comparisons using the Holm procedure. This adjustment leads to a minimum type 1 error rate of 0.0167 from simultaneously assessing results of the 3 test claims.
- A power level of .85
- One-tailed hypothesis test, appropriate due to the a priori directionality of predicted findings as specified in the hypotheses.

In total, the planned study sample is n=11,640 respondents with n=1,940 respondents in each cohort, as shown in Table 3 below. Within each sample cohort respondents will be randomly assigned into 4 cells: 3 tests and 1 control; each of these randomly assigned cells will contain n=485 respondents (see Figure 1: 32 Video Advertisements to be Tested Across 3 Test Cells and 1 Control Cell Within 6 Study Cohorts). Combining respondents from four sample cells (485 x 4) gets us back to the 1,940 respondents per cohort.

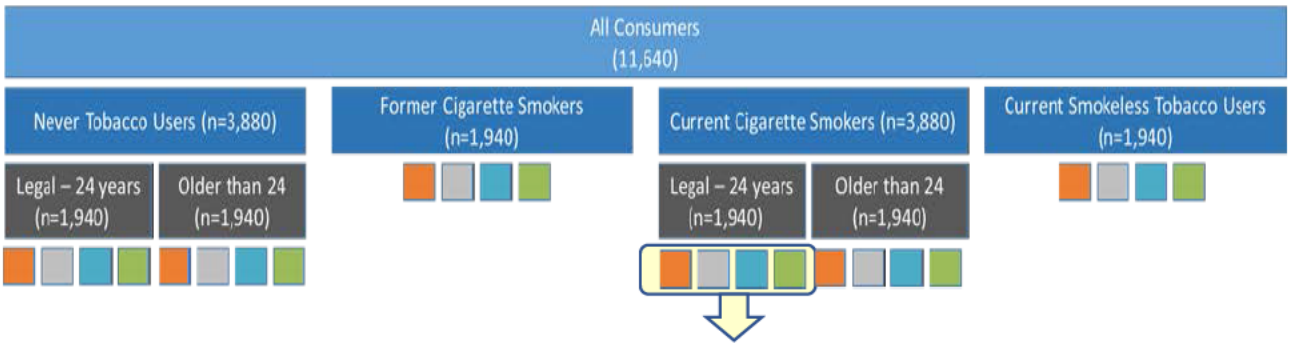
Table 3: Sample Size

	N=11,640	Percent of Sample	Percent of Adult Population[4]
Never tobacco users from legal age to 24 years of age	1,940	17%	6%
Never tobacco users older than 24 years of age	1,940	17%	43%
Former cigarette smokers from legal age and older	1,940	17%	20%
Current cigarette smokers from legal age to 24 years of age	1,940	17%	3%
Current cigarette smokers older than 24 years of age	1,940	17%	16%
Current smokeless tobacco users from legal age and older	1,940	17%	3%

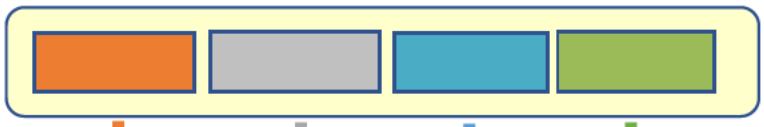
The age breaks are based on those used in PATH.[4]

The primary intent of the survey will be to have respondents evaluate different *General* Snus® communication executions (see Figure 1 for stimulus assignment for each study cohort) to elicit their perception of health risk and intended TNP behavior.

Figure 1: 32 Video Advertisements to be Tested Across 3 Test Cells and 1 Control Cell Within 6 Study Cohorts



Colored boxes represent the columns of the table below referencing the random assignment into test cells and the control cell and across the 4 warning labels and 2 flavor constants (see Table 1 in Study Design).



	CELL A (CLAIM 1)	CELL B (CLAIM 2)	CELL C (CLAIM 3)	CELL D (CONTROL)
Warning 1 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 2 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 3 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2
Warning 4 series →	Flavor 1	Flavor 1	Flavor 1	Flavor 1
	Flavor 2	Flavor 2	Flavor 2	Flavor 2

In compliance with the CTP's guidance[10] regarding intended use and risk assessment in vulnerable populations, this study will oversample the young adult population among never users and current cigarette smokers, specifically people who fall between the legal age for tobacco use in their states and age 24.

8.4.2 Subject Selection: Inclusion Criteria

In addition to the cohort requirements specified earlier, respondents must meet the following criteria to be included:

- Minimum legal age per local requirements.
- Able to read and speak English.
- Currently a resident of the United States.
- Required to provide electronic informed consent.

8.4.3 Subject Selection: Exclusion Criteria

The exclusion criteria for this research study are the following.

- Respond as "don't know" or "decline to answer" to specific demographics (gender, geographical region, ethnicity, or education), necessary for balancing cohorts.
- Unwilling or unable to provide electronic informed consent.
- Individuals employed in any of the following fields or professions: market research, marketing, advertising, manufacturers of TNP, or physicians.
- Individuals who have taken part in a consumer research study on tobacco in the past 2 weeks.

8.5 Outcomes

The length of interview for this survey instrument is estimated to be 15 minutes among non-users and former users, and 20 minutes among current users. Outcome variables supporting attainment of the study objectives are as follows.

Note that for all questions following the review of the *General* Snus® video, respondents will be able to click a link to review the video again, if needed.

Likelihood to buy *General* Snus® will be assessed with the 11-point Juster Scale. The Juster Scale is a probability scale that can be used to produce estimates of the average probability that a population will perform a certain behavior by a future time.[11] As the Juster Scale measures probability, the mean response predicts the proportion of the population that will perform the behavior.[12] Research has shown that the Juster Scale is effective in predicting consumers' future purchasing behaviors.[13] See Figure 2 for an example.

Figure 2: Likelihood to Buy Example

Q. How likely are you to buy *General* Snus® for yourself if sold in a store where you usually shop? You may need to scroll to see all options and to continue.

[SELECT ONE]

No chance, almost none [1 in 100]	Very slight possibility [1 in 10]	Slight possibility [2 in 10]	Some possibility [3 in 10]	Fair possibility [4 in 10]	Fairly good possibility [5 in 10]	Good possibility [6 in 10]	Probable [7 in 10]	Very probable [8 in 10]	Almost sure [9 in 10]	Certain, practically certain [99+ in 100]
0	1	2	3	4	5	6	7	8	9	10

Likelihood to use TNP(s) will be measured separately for each TNP with a custom, single-choice 4-point ordinal scale assessing the use of each TNP moving forward (after viewing *General* Snus® video). See Figure 3 for an example.

Figure 3: Likelihood to Use TNP(s) Example

Q. How will you use **[PRODUCT]** moving forward?

[SELECT ONE PER ROW]

		Quit Completely	Cut Back Use	Use the Same Amount	Use More	Don't Know	Decline to Answer
1	cigarettes	1	2	3	4	99	999
2	e-cigarettes	1	2	3	4	99	999
3	moist snuff (available in loose form, also known as dip, and in pouches)	1	2	3	4	99	999
4	chewing tobacco (also known as loose leaf chewing tobacco)	1	2	3	4	99	999
5	snus (pouch tobacco product, different than moist snuff)	1	2	3	4	99	999
6	aids that help stop smoking (e.g. Nicorette, Nicoderm CQ)	1	2	3	4	99	999
7	cigars, cigarillos, or filtered cigars filled with tobacco	1	2	3	4	99	999
8	pipe tobacco	1	2	3	4	99	999
9	hookahs or water pipe tobacco	1	2	3	4	99	999

Intention to quit is measured by the one-item validated instrument, Motivation to Stop Scale (MTSS).[14] The MTSS consists of one item with seven response categories ranging from 1 (lowest) to 7 (highest level of motivation to stop smoking). Scale developers found that odds of quit attempts increased linearly with increasing levels of motivation. In the current study, the MTSS is used for assessing intention to quit cigarettes and/or other TNPs. Consistent with published research using the MTSS, we will report the mean MTSS score.[15] See Figure 4 for an example.

Figure 4: Intention to Quit (MTSS)

Q. Which of the following describes you?
You may need to scroll to see all options and to continue.

[SELECT ONE]

1	I don't want to stop smoking
2	I think I should stop smoking but don't really want to
3	I want to stop smoking but haven't thought about when
4	I REALLY want to stop smoking but I don't know when I will
5	I want to stop smoking and hope to soon
6	I REALLY want to stop smoking and intend to in the next 3 months
7	I REALLY want to stop smoking and intend to in the next month

99	Don't know

Perceptions of absolute health risk associated with daily use of *General* Snus® and no other TNP will be assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= very low chance to 5= very high chance, also including "don't know" and "decline to answer") for each of 8 health conditions (chronic bronchitis, emphysema, gum disease, heart disease, lung cancer, mouth cancer, stroke and serious health problems). This scale was modified from the risk perception scale used in HINTS.[16] The 5-point Likert scale used in HINTS had response options where 1= much less harmful to 5= much more harmful; we changed the response options to fit with the structure of the question in the survey. See Figure 5 for an example.

Figure 5: Perception of Absolute Health Risk Example

Q: If a typical person **uses *General* Snus® every day and no other tobacco products,** what is the chance that person would suffer from the following health conditions during his/her lifetime?

		Very Low Chance	Low Chance	Moderate Chance	High Chance	Very High Chance	DK	Decline to Answer
1	Chronic bronchitis	1	2	3	4	5	99	999
2	Emphysema	1	2	3	4	5	99	999
3	Gum disease	1	2	3	4	5	99	999
4	Heart disease	1	2	3	4	5	99	999
5	Lung cancer	1	2	3	4	5	99	999
6	Mouth cancer	1	2	3	4	5	99	999
7	Stroke	1	2	3	4	5	99	999
8	Serious health problems	1	2	3	4	5	99	999

Perceptions of relative health risk will be assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= a much lower chance to 5= a much higher chance, also including "don't know" and "decline to answer") for each of the 8 health conditions (chronic bronchitis, emphysema, gum disease, heart disease, lung cancer, mouth cancer, stroke, and serious health problems) contrasting *General* Snus® use to several other risk exposures. The risk exposures assessed for each health condition included daily use of *General* Snus® vs. the daily use of other TNP, aids to help stop smoking, both cigarettes and *General* Snus®, never having used any TNPs, and quitting all TNP relative to quitting all TNP except for *General* Snus®. This scale was modified from the risk perception scale used in HINTS.[16] The 5-point Likert scale used in HINTS had response options where 1= much less harmful to 5= much more harmful; we changed the response options to fit with the structure of the question in the survey. See Figure 6 for an example.

Figure 6: Perception of Relative Health Risk Example

PRODUCT LIST:

1. **Cigarettes.**
2. **Moist snuff.**
3. **Other brands of snus.**
4. **Aids to help stop smoking.**
5. **Both cigarettes and *General* Snus®.**
6. **Never having used any tobacco or nicotine products.**

Q: Compared to the **daily use of only [INSERT PRODUCT FROM LIST ABOVE, NUMBER 1-4], the daily use of only *General* Snus®** has

[SHOW IF PRODUCT FROM LIST IS #5 "both cigarettes and *General* Snus®]
Compared to the **daily use of both cigarettes and *General* Snus®, the daily use of only *General* Snus®** has

[SHOW IF PRODUCT FROM LIST IS #6 "never having used..."]
Compared to **never having used any tobacco or nicotine products, the daily use of only *General* Snus®** has

1	2	3	4	5
a much lower chance	a lower chance	the same chance	a higher chance	a much higher chance

99	999
don't know	decline to answer

of causing **[INSERT CONDITION]**

Q. Assume two people are exactly the same in every way, except:

- One has decided to quit the use of all tobacco and nicotine products and use nothing; and
- The other has decided to quit the use of all tobacco and nicotine products except for the daily use of *General* Snus®.

Compared to the person **who has quit** all tobacco and nicotine products and uses nothing, **the person who has quit all tobacco and nicotine products except for the daily use of *General* Snus® has**

1	2	3	4	5
a much lower chance	a lower chance	the same chance	a higher chance	a much higher chance

99	999
don't know	decline to answer

of suffering from **[INSERT CONDITION]**

Comprehension of the modified test claims will be assessed with 9 items measuring comprehension of the various pieces of information presented in the modified test claims. The multiple-choice response options include 6 or 7 response options with one correct answer along with "don't know" and "decline to answer." The "don't know" response will be coded as incorrect. This approach was based on feedback on the Study Protocol (June 2017), from the FDA.[17] See Figure 7 for an example.

Figure 7: Comprehension of the Modified Test Claims Example

Q: Using *General* Snus® instead of cigarettes…

1	puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
2	does not affect your risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
3	puts you at higher risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
4	None of the above

99	Don't know
999	Decline to answer

Believability of the test claims will be assessed with 3 items measuring believability (4-point ordinal scale same as used in HINTS[16]; from 1= not at all believable to 4= very believable, also including "don't know" and "decline to answer") for each of the three modified test claims. See Figure 8 for an example.

Figure 8: Believability of Test Claims Example

Q: How believable do you find each of the following statements about *General Snus*®?

		Not At All Believable	A Little Believable	Somewhat Believable	Very Believable	DK	Decline to Answer
1	Using *General* Snus® instead of cigarettes puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis	1	2	3	4	99	999
2	Using *General* Snus® instead of cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users	1	2	3	4	99	999
3	No tobacco is totally safe, but using *General* Snus® instead of cigarettes puts you at a lower risk of chronic lung disease and other tobacco-related ailments	1	2	3	4	99	999

8.5.1 Potential Confounders

As discussed in Data Sources, section 8.1, the sampling approach will ideally mitigate potential confounding factors. Nevertheless, confounding variables may include respondent demographics (age, gender, ethnicity, education, and geographic region), frequency of tobacco use, current tobacco products used, intentions to quit, and method of recruitment. Although efforts will be made to ensure a representative sample using stratified sampling, the precise ratio of subgroups which may appear in the population cannot be fully controlled. If deemed appropriate, weighting socio-demographic variables will be employed to bring the sample more in line with the distribution of the underlying population and mitigate the effects of over- and under-representation.

Further, as compared to the other four study cohorts, an additional data source (Lucid) will be used to obtain the required sample in the current cigarette smokers from legal age to 24 years of age and current smokeless tobacco user cohorts. While the utilization of an additional data source for these cohorts may also introduce potential confounding factors when comparing outcomes across cohorts, confounding factors should be limited for test versus control comparisons within cohort. A description of potential impact and subsequent handling of confounding variables will be described in the Statistical Analysis Plan (SAP) which will be submitted as a follow-up to the study protocol.

8.5.2 Other Variables

Baseline characteristics of age, gender, ethnicity, education, and geographical region will be collected to help achieve a representative sample.

8.6 Data Management

Kantar Health will be responsible for all study data management. The protocol specifies data sources, data collection modes, software products and servers used for data collection, data management and data transfer procedures, as well as the measures that will be taken to protect the security and integrity of the data as they are collected and stored during the study.

Kantar Health subscribes to Safe Harbor and pledges to follow the Council of American Survey Research Organizations (CASRO) Code of Conduct, both providing principles and guidelines to ensure respondent confidentiality and privacy. Examples of best practices include but are not limited to:

- The implementation of controls and procedures to maintain the confidentiality, integrity, and availability of personal information in accordance to company policy and applicable local legislation;
- Data handling procedures ensuring secure transfer and storage of personal identifiable information;

- Restricting access to personal information to only those who require access to perform their job;
- Properly informing respondents about the survey's aim and how their personal information will be used and protected.

8.6.1 Data Quality Control

The data collected for this study will be monitored for adherence with to this study protocol. All data will be collected using a programmed web survey. Prior to initiating the study, appropriate edit programming will be conducted to ensure the final dataset requires minimal cleaning of invalid responses. The questionnaire will be designed so that instructions are as easy to understand and clear as possible to help avoid missing data. These programming procedures for the web-based survey data entry tool will include response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or data manipulations will be cross checked by Kantar Health team members who independently replicate the results and/or verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before any further analysis is completed.

Other quality control procedures include the identification of respondents with little variability in their responses, for example due to disinterest in the project ("straight liners"), respondents that complete the survey much faster than expected ("speeders"), and/or that provide disproportionate or nonsensical numeric responses compared to the average (outliers). Removed respondents will be held in a separate data file with documentation identifying the reason for their removal from the data file containing the n=11,640 respondents that will be utilized for the analysis.

In addition, respondents with clearly inconsistent responses will be removed and replaced from the main study. Problematic cases will be monitored during field and considered for deletion. Deleted cases will be replaced during field to ensure the completion of the sample. A separate file with the removed cases will be stored for future reference. Further explanation of the handling of suspect respondents will be provided in the study SAP.

8.6.2 Data Base Lock

After data collection is complete, data quality and completeness will be evaluated. Once the data quality check is complete, the database will be locked, and the data will no longer be subject to change.

8.6.3 Data Transfer

Until the approval and signing of the SAP by SMNA, the data will remain blinded and locked to the analytical team.

Once data are transferred, the analytical team will perform further checks prior to conducting data analyses specified in the SAP.

Kantar Health will transfer final data files to SMNA in a zipped file via a secure FTP site after the study. SMNA will confirm receipt of these files. File name will include the study name and date of transfer.

8.6.4 Data Storage and Archiving

All electronic data files will be kept on secure servers, with backup processes in place. Paper data files will be scanned and filed accordingly.

Only de-identified data will be transferred for analysis purposes.

Personally Identifiable Information (PII) will be stored separately from the study data. Electronic records of data files and study documents will be transferred in a secure manner to SMNA and retained and stored on a secured server maintained by SMNA as required by law.

8.7 Data Analysis

A formal and more detailed SAP will be prepared by Kantar Health.. This SAP will be submitted as a follow-up to the study protocol.

8.7.1 Cognitive Interview Data Analysis

The cognitive interviews will be conducted in accordance with the Office of Management and Budget (OMB) Statistical Policy Directive No.2 Addendum: Standards and Guidelines for Cognitive Interviews.[5] Systematic content analysis will provide the data to be analyzed, thus ensuring we are hearing the participants' own words as they "think aloud" while completing the survey. The series of individual comments obtained in the cognitive interviews, pertaining to separate questions across multiple interviews, will be compiled into a coherent set of summary findings that transcend the individual interview level. In-depth analysis will include looking for themes that indicate that respondents have issues with comprehension, retrieval, decision-judgment, and response for questions in the survey[18]. If a question or element in the survey is misunderstood from what was intended, the moderator will identify the statements/descriptions/ terms that caused the misunderstanding. These will then be reworked or adjusted and reassessed, so that the terms achieve universal understanding of the intent of the question. The results will then be compiled to determine which changes are necessary for greater content validity. From this analysis, recommendations will be made to revise the language and content of study materials.

8.7.2 Quantitative Data Analysis

The main analyses for this study will consist of bivariate comparisons with corresponding significance testing to address the study hypotheses. Descriptive statistics will be calculated across all analyses and reported where valuable to interpretation of results. Sample cohort comparisons (e.g., younger vs. older groups) are not planned, and no hypotheses were formed based on sample characteristics. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The final SAP may require modification of plans outlined in the protocol; any major modifications of primary outcome definitions or their analyses would be reflected in a protocol amendment.

Kantar Health will lead quality control (QC) of the data. QC will focus on identifying potential outliers that exist in the dataset. Identification of outliers will be based on investigation of the underlying distribution of the variable. Respondents with values on particular variables that are extreme, as determined by the underlying distribution, will be considered for removal prior to performing the main analyses. This said, the *a priori* assumption for all data collected is that it is true and accurate.

In the quantitative survey phase, the study team will format and properly label the data sets (including all responses from respondents and the date that the survey was completed) in a statistical package (IBM SPSS Statistics v23)[19], so that the data are suitable for analysis. The data sets will contain a subject ID number and will not contain any information that could be used to identify individual respondents. Additional detail on data quality measures can be found in Section 8.7.4 "Quality Control".

8.7.3 Statistical Considerations

The analysis will focus on test versus control (exposed to test claims versus not) using independent measures. Statistical considerations are described below.

8.7.3.1 Descriptive Analysis

Descriptive analyses will provide summary statistics for all variables collected for the entire sample and each of the six cohorts. Summary statistics will include counts and percentages for categorical variables and means, standard deviations, medians, minimums, and maximums for numeric variables.

8.7.3.2 Bivariate Analysis

Independent sample t-tests and two-sample binomial proportion tests will be conducted to examine statistical significance between test claims vs. control groups according to study hypotheses.

All results will be presented in tables organized by primary and secondary objectives, and statistical significance will be determined with an initial α=.05 significance level adjusted for multiple comparisons using the Holm Procedure. Each potentially confounding variable (e.g.,

socio-demographics, etc.) along with each outcome variable supporting the primary objectives (see Outcomes 8.5), will be included in the bivariate analysis. Further details regarding methodology and statistical analyses of data collected in this study for primary and secondary objectives will be documented in the final SAP.

8.7.4 Quality Control

There are several aspects to quality control as described below:

Survey Instrument Programming

- The web-based survey will be created by the Kantar programming team using the Decipher® software for web-based survey programming (v117, Fresno, CA).
- After the survey has been programmed and tested, the survey link and content will be reviewed by a separate team within Kantar Health's fielding operations group from the perspective of the respondent (i.e. the link is reviewed online and not within the Decipher® software).
- Prior to initiating the study, appropriate edit programming will be conducted to assure the final dataset requires minimal cleaning of invalid responses. These programming procedures for the web-based survey data entry tool will include response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or creation of grouping variables will be cross checked by Kantar Health operations team members who independently replicate the results and/or verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before data are provided to Kantar Health's analytical team to begin study analysis.

Qualitative Study

- As mentioned in Cognitive Interviews, Section 8.3, a qualitative study will be conducted to assess the online survey instrument in a live setting with 20 respondents matching the inclusion and exclusion criteria. During this time, any areas in the survey instrument that require clarification or improvements will be updated.

Data Management and Analyses

- When conducting online research, invariably some respondents will find a way to complete the survey without attempting to provide accurate, relevant responses. To ensure that those respondents do not compromise the integrity of the data, measures are taken to identify them in a systematic and objective way prior to actual analyses. No respondent will be removed from the full study analyses. However, should the process below identify outliers, sensitivity analyses will be conducted without these respondents to determine whether results differ from the full sample analyses. The process will seek to identify the following respondent types:

- Respondents who lack variability in their responses to a battery of questions ("straight liners") will be identified using standard deviations customized for each outcome found in the survey. Respondents whose responses have a standard deviation of zero or greater than four times the overall standard deviation will be flagged and examined individually.
- Similarly, respondents who demonstrate a discernable pattern in their answers inconsistent with any coherent understanding of the question (e.g., selecting 1, 2, 3, 4, 5, 1, 2, 3, 4, 5, 1… etc.) will also be flagged and examined individually.
- Respondents who are straight lining or giving patterned responses consistently throughout the survey (i.e., across multiple sections of the survey) will be individually scrutinized.

- Respondents found to lack credibility will be identified, handled consistently and transparently, and documented in the final report. This said, the a priori assumption is that all data reported is true and accurate, and preliminary outliers will be identified based on the underlying distribution of the data and through descriptive analysis.
- Data from non-credible respondents will be flagged in the data file. Additionally, the number of respondents flagged and the rationale for their identification as outliers will be reported in the final report.

8.8 Limitations of the Research Methods

The data collected will be based on responses post-exposure to a video advertisement for *General* Snus®. The perceived health risk assessments are intended to simulate real world perceptions after exposure to real world information on *General* Snus® but obviously do not have the same contextual, social, and emotional consequences of actual decisions. Similarly, one can only expect so much accuracy and extrapolation while capturing behavioral intentions, as unforeseen market factors can impact actual behaviors. Potential hypothetical bias can be limited by constructing questions that mimic realistic perceptions and behaviors as closely as possible.

In addition, since data from this study will depend on respondent self-reporting, subsequently reported variables may also be subjected to recall bias. Self-reported data collection is a standard approach, and any potential problems with recall bias are anticipated to be constant across time points.

Respondents will be recruited based on their membership with an online market research panel. As a result, recruitment could be considered a convenience sample. While multiple panels will be used, similar to any other data source used (e.g. random dialing), consumers who are not part of these data sources will not have the opportunity to participate. Further, due to sample selection during recruitment, respondents who are more interested in research or, perhaps healthy enough to participate, may be over-represented, hence the possibility of selection bias. Although these issues raise concerns about the external validity of the findings (e.g., our sample may not be fully generalizable to all consumers), the recruitment plan is designed to mirror the underlying

populations (see Section 8.4 "Study Population" for more detail). Even with efforts to ensure a representative sample using stratification, the precise proportion of subgroups which will appear in the study sample cannot be completely controlled. In fact, regardless of how respondents are recruited, there will always exist the possibility that the people who decline the opportunity to participate in the research differ in a systematic way from the people who accept the opportunity. Weighting may be used to bring the study sample more in line with the distribution of the population, and mitigate the effects of over-representation.

9 PROTECTION OF HUMAN SUBJECTS

This study is an observational study; there is no assignment of a respondent to any TNP, or vice versa. No additional diagnostic or monitoring process is required for participation or during the study. The risks and warning executions respondents will be exposed to are very similar to print, product, and video advertisements of TNP that respondents will be exposed to in retail, internet, or other real-world settings. This study will test the effect of different combinations of claims, warnings, flavors, and type of media on health risk perceptions and behavior intentions. All stimuli will be presented in such a way that all information is visible and legible to respondents and ensures the respondent views the modified risk claim as it would appear in the real world. Additionally, the study will end with a debriefing statement to inform all respondents that all information within stimuli is for market research purposes only and not approved or endorsed by the FDA.

9.1 Regulatory Authority Approvals/Authorizations

The study will be carried out within an approved indication and in accordance with CTP guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole[1]. Additionally, Kantar Health conducts all our research in accordance with the requirements of our Quality System, which confirms to ISO 20252:2012 the International Standard for Market Research, Certification Number: 1019.

9.1.1 Institutional Review Board (IRB)

Documented approval from an appropriate IRB in the U.S. will be obtained prior to study start. When necessary, an extension, amendment or renewal of the IRB approval will be obtained and forwarded to SMNA. The IRB will supply to SMNA, upon request, a list of the IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to applicable laws and regulations.

9.1.2 Respondent Information and Consent

Prior to beginning the survey, potential respondents will be provided with a statement of informed consent. The consent informs potential respondents that participation in the study is voluntary, and that responses will remain confidential. It also includes information about the goals of the study, the approximate length of the survey, and incentives for participation. Lastly, the statement of informed consent provides potential respondents with the resource references to address any

concerns they may have. A link to each panel is given if the respondent has any specific questions about the survey instrument or incentives for participation.

After potential respondents read the statement of informed consent, they will be asked, "Do you voluntarily agree to participate in this study?".Respondents who select "I agree to participate" will be able to complete the survey. At any time during survey completion, the respondent may choose to exit the survey should they decide not to participate any further. Data provided by a respondent who exits the survey prematurely will not be utilized in any analyses. Respondents who select "I do not agree to participate" will be thanked for their time before exiting. IRB written approval/ favorable opinion of the electronic informed consent form and any other written information provided to respondents will be obtained prior to the initiation of the study.

9.1.3 Confidentiality

Swedish Match North America and all investigators ensure adherence to applicable data privacy protection regulations. Data are transferred in encoded form only. The entire documentation made available to Swedish Match North America does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Respondent names will not be supplied to SMNA. If the respondent name appears on any document, it must be obliterated before a copy of the document is supplied to SMNA. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable respondents' records to be identified in case of queries.

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INVESTIGATOR SIGNATURE

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Investigator (Main Author):

Name (typed or printed): **Lulu Lee, PhD., Director, Health Outcomes Research**

Institution: **Kantar Health, Inc.**

Signature: (b)(6) **Date:** 31 May 2018

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to SMNA; a protocol amendment will not be required.

SPONSOR SIGNATURE

This Protocol has been subjected to an internal Swedish Match North America review.

I agree to the terms of this Study protocol.

Sponsor:

Name (typed or printed): **Steve Seiferheld, Director, Market Research**

Company: Swedish Match North America

Signature: (b)(6) **Date:** 31 May 2018

(Day Month Year)