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Swedish Match North America, Inc.

Protocol for Observational Study

ZYN[®] Patterns of Use Study

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Prepared by: (b) (4)

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Swedish Match North America, its parent and affiliate companies.

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
BRINC	Branded Research Inc.
CA	California
CAPTCHA	Completely Automated Public Turing Test To Tell Computers & Humans Apart
CO	Colorado
CTP	Center for Tobacco Products
DIR	Directions in Research
FDA	Food and Drug Administration
FTP	File Transfer Protocol
ICF	Informed Consent Form
ID	Idaho
IP	Internet Protocol
IRB	Institutional Review Board
LSR	Lightspeed Research
MRTP	Modified Risk Tobacco Product
MSG	Marketing Systems Group
MT	Montana
MTSS	Motivation To Stop Scale
NCHS	National Center for Health Statistics
NE	Nevada
NM	New Mexico
OMB	Office of Management and Budget
OR	Oregon
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

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SMNA	Swedish Match North America, Inc.
SSI	Survey Sampling International
TNP	Tobacco/Nicotine Products, including cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, nicotine pouches, 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
UT	Utah
WA	Washington
WY	Wyoming
ZYN[®] non-users	ZYN [®] non-users who use tobacco products

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3. RESPONSIBLE PARTIES

3.1. Investigator and Contributors

Investigator:

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(b) (4)

Project Team:

(b) (4), (b) (6)

3.2. Sponsor

Swedish Match North America

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4. SYNOPSIS

Title	ZYN[®] Patterns of Use Study
Protocol version identifier	Version 1.0, Amendment 2
Date of last version of protocol	November 13, 2017
Protocol number	(b) (4)
Author	(b) (6)

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Rationale and background	<p>Swedish Match North America (SMNA) began selling ZYN[®] in 2014. ZYN[®] delivers nicotine derived from tobacco, but the ZYN[®] product itself does not contain tobacco leaves. It comes in a small pouch that contains nicotine flavoring elements and other ingredients required to ensure shelf stability. SMNA has no current intention of marketing ZYN[®] as a smoking cessation product, but rather as a nicotine-delivery product that requires no spitting, produces no off-putting odors, is smoke-free, and comes in a variety of flavors and nicotine strengths. The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA.</p>
Research question and objectives	<p>The overarching research questions within this project can be stated as follows: (i) <i>How do ZYN[®] users and ZYN[®] non-users use TNP, and (ii) how do they perceive health risks associated with TNP?</i> These questions will be studied by means of a retrospective assessment of TNP use among both ZYN[®] users and ZYN[®] non-users (the Retrospective Study); all study participants are of legal age to use TNP in their residential geography. Included as part of this project is a 10-week prospective study among ZYN[®] users and ZYN[®] non-users (the Prospective Study); SMNA is including objectives and related findings from the Prospective Study as part of the secondary objectives, since the specific sample size or composition from that study are unknown. No formal hypotheses are specified for the ZYN[®] Patterns of Use study.</p> <p><u>Primary Objectives</u></p> <p>Utilizing data from the Retrospective Study:</p> <ol style="list-style-type: none"> 1. Compare TNP patterns of use between ZYN[®] users and ZYN[®] non-users over the past 30 days. <p>The study will examine usage patterns among respondents and, in particular, examine how ZYN[®] users utilize other TNP products, compared with ZYN[®] non-users. Of specific interest will be usage patterns of cigarettes, smokeless tobacco, aids to help stop smoking, and ZYN[®] itself.</p> <ol style="list-style-type: none"> 2. Among ZYN[®] users, compare TNP patterns of use over the last 30 days with TNP patterns of use during the weeks prior to using ZYN[®]. <p>Within the cohort of ZYN[®] users, the study will explore how usage of TNP products might have changed from the period prior to starting ZYN[®] to the last 30 days. Of particular interest will be whether usage of ZYN[®] offsets usage of products such as cigarettes and smokeless tobacco.</p>

	<p>3. Evaluate the level of compliance among ZYN[®] users with ZYN[®] usage instruction over the last seven days.</p> <p>Focusing on the last seven days, the study will explore how ZYN[®] users report using the product. Specifically of interest will be compliance with usage instructions and presence/absence of product misuse.</p> <p><u>Secondary Objectives</u></p> <p>Utilizing data from the Retrospective Study:</p> <ol style="list-style-type: none"> 1. Assess perceptions of absolute risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) among ZYN[®] users and ZYN[®] non-users. <p>The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN[®] daily, smoking only cigarettes daily, and never having used any TNPs. Discussion sections will highlight any observed divergence between ZYN[®] users with ZYN[®] non-users.</p> <ol style="list-style-type: none"> 2. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with ZYN[®] as compared with using other TNP, aids that help stop smoking, and never having used any TNPs. <p>The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN[®] daily relative to using only other TNP daily, daily use of aids to help stop smoking, or never having used any TNPs.</p> <ol style="list-style-type: none"> 3. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with adding ZYN[®] use to existing TNP use. <p>The study will measure the perceived relative risk of the aforementioned health conditions attributed to using both ZYN[®] and other TNP compared with using other TNP alone. From there, further analysis will delve into how adding ZYN[®] to existing TNP use alters perceived risk.</p>
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	<p>4. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) to a person who quits use of all TNP compared with a person who quits all TNP except for daily use of ZYN[®].</p> <p>The study will measure the perceived relative risk of the aforementioned health conditions attributed to quitting all TNP except for the daily use of ZYN[®] compared with quitting all TNP use.</p> <p>Utilizing data from the Prospective Study:</p> <p>5. Explore daily TNP patterns of use among ZYN[®] users and ZYN[®] non-users, including reasons for ZYN[®] use, over a prospective 10-week observational period.</p> <p>6. Compare the tendencies of ZYN[®] users to quit TNP or use the product in an incremental fashion, in a supplemental fashion, or in complete substitution of other TNP.</p>
Study design	<p>The ZYN[®] Patterns of Use Study consists of two separate projects, meant to gain an understanding of how ZYN[®] is and has been used among consumers. Each project includes ZYN[®] users and non-users, to allow for more informed investigation. Each study relies upon its own survey instrument; cognitive interviews inform the retrospective and prospective surveys to ensure clear communication of survey items to respondents. The Retrospective Study utilizes a cross-sectional design to measure recalled TNP usage among ZYN[®] users and ZYN[®] non-users. The Prospective Study longitudinally evaluates TNP patterns of use among ZYN[®] users and ZYN[®] non-users over a 10-week observation period.</p>

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Population	<p>The study will include respondents of legal age for TNP use across the 11 U.S. states where ZYN[®] is currently available for retail sale, listed below.</p> <p>Respondents must meet all of the following inclusion criteria to be included in the study:</p> <ul style="list-style-type: none"> • Minimum legal age for tobacco/nicotine use per local state requirements • Able to read and speak English • Currently a resident of one of the 11 U.S. states where ZYN[®] is available in retail outlets (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY) • Individuals who provide electronic informed consent <p>Respondents who meet any of the following criteria will be excluded from the study:</p> <ul style="list-style-type: none"> • Respond as “don’t know” or “decline to answer” to specific demographics (gender, geographical region, ethnicity, or education) for the purpose of balancing cohorts • Unwilling or unable to provide electronic informed consent • 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 of being screened for qualification to the Retrospective Study
Data sources	<p>Due to the low incidence of ZYN[®] users among the general population, sample for this cohort will be recruited directly from purchasers of ZYN[®]. A third-party vendor will place study invitation stickers on product packaging (i.e. each individual canister of 15 ZYN[®] pouches) for the six core flavors of ZYN[®].</p> <p>When enrollment in the survey for the ZYN[®] user cohort has reached 40%, the (b) (4) fielding team will analyze the demographic characteristics of the data (i.e., age, gender, race/ethnicity, and education). The demographic characteristics of ZYN[®] users will then be used to stratify the sample of ZYN[®] non-users. The demographic characteristics of the ZYN[®] user will be monitored daily and the recruitment of ZYN[®] non-user cohort will be</p>

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	<p>appropriately adjusted in order to have consistency across ZYN[®] user and ZYN[®] non-user cohorts.</p> <p>The ZYN[®] non-user cohort will be recruited through online survey panels, with any shortfall of demographic stratification targeted through a phone-to-web recruit. By recruiting ZYN[®] non-users based on demographic criteria corresponding to enrolled ZYN[®] users, the sample recruitment plan is designed to provide matching populations with regard to socio-demographic characteristics through online panels and telephone recruitment. This approach is designed to avoid sample bias and to obtain ZYN[®] user and ZYN[®] non-user cohorts that are demographically aligned with the populations they are meant to define. Additionally, the ZYN[®] non-user cohort will be sourced from the same 11 states where ZYN[®] is sold.</p> <p>After completion of the retrospective study, respondents will be invited to participate in the prospective study.</p> <p>Consumers sourced through online panels will be recruited by (b) (4)</p> <p>These panels are large commercial consumer opt-in 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.</p> <p>A call center, Directions in Research (DIR), will be commissioned for telephone recruiting to supplement any shortfall in demographic quotas for the non-ZYN[®] group, if not fully recruited through online panel recruitment. Sample will be purchased from the Marketing Systems Group (MSG) to perform telephone recruitment.</p>
Study size	<p>The retrospective study will aim to achieve (b) (4) participants, split evenly across ZYN[®] users and ZYN[®] non-users. The number of respondents completing the prospective study is undetermined and will be dependent upon the rate of both participation and survey completion.</p>
Data analysis	<p>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 survey¹⁴. The results will then be</p>

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	<p>compiled to determine which changes to the survey instrument are necessary for greater content validity.</p> <p>All analyses performed for the ZYN[®] Patterns of Use Study will be descriptive in nature.</p> <p>Descriptive statistics used to understand the distribution of socio-demographic and outcomes variables will be based on the raw data (i.e., prior to any recoding or any aggregation required for the final presentation of results). Respondents with values for variables that are illogical or deemed unreliable, as determined by the underlying distribution, will be considered for removal prior to performing the main analyses. The SAP will provide greater detail on this topic. Numeric variables will be described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables will be described using frequencies, percentages, and the number of missing observations (if applicable).</p> <p>Unless otherwise specified in the SAP, descriptive statistics reported for the main analyses will include the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs), for numeric variables. For categorical variables it will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category.</p>	
Milestones	Start of data collection	November 2017
	End of data collection	February 2018 (Retrospective) / April 2018 (Prospective)

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5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	11/15/2017	Throughout	Amendment	Changes based on initial Center for Tobacco Products (CTP) feedback on a different MRTP protocol
2	5/28/2018	Throughout	Amendment	Changes based on new information and additional background obtained from: <ul style="list-style-type: none"> 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

In 2009, the Family Smoking Prevention and Tobacco Control Act was signed into law, giving the FDA the power to regulate the tobacco industry and establishing the Center for Tobacco Products (CTP) within the FDA. This law gives the CTP authority to regulate the 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).¹

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole, including users and non-users of the tobacco product.¹ In making this evaluation the FDA will assess the product under review and take into account (1) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (2) the increased or decreased likelihood that those who do not use tobacco products will start using such products.¹ This evidence must be submitted for all currently marketed products as part of a premarket tobacco product application (PMTA). 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

Swedish Match North America (SMNA) began selling ZYN[®] in 2014. ZYN[®] delivers nicotine derived from tobacco, but the ZYN[®] product itself does not contain tobacco leaves. It comes in a small pouch that contains nicotine flavoring elements and other ingredients required to ensure shelf stability. SMNA has no current intention of marketing ZYN[®] as a smoking cessation product, but rather as a nicotine-delivery product that requires no spitting, produces no off-putting odors, is smoke-free, and comes in a variety of flavors and nicotine strengths. As a result of the Tobacco Control Act requirements, SMNA must submit a PMTA to continue marketing the ZYN[®] product. The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA.

7. OBJECTIVES AND HYPOTHESES

The overarching research questions within this project can be stated as follows: (i) *How do ZYN[®] users and ZYN[®] non-users use TNP, and (ii) how do they perceive health risks associated with TNP?* These questions will be studied by means of a retrospective assessment of TNP use among both ZYN[®] users and ZYN[®] non-users (the Retrospective Study); all study participants are of legal age to use TNP in their residential geography. Included as part of this project is a 10-week prospective study among ZYN[®] users and ZYN[®] non-users (the Prospective Study); SMNA is including objectives and related findings from the Prospective Study as part of the secondary objectives, since the specific sample size or composition from that study are unknown. No formal hypotheses are specified for the ZYN[®] Patterns of Use study.

7.1. Primary Objectives

Utilizing data from the Retrospective Study:

1. Compare TNP patterns of use between ZYN[®] users and ZYN[®] non-users over the past 30 days.

The study will examine usage patterns among respondents and, in particular, examine how ZYN[®] users utilize other TNP products, compared with ZYN[®] non-users. Of specific interest will be usage patterns of cigarettes, smokeless tobacco, aids to help stop smoking, and ZYN[®] itself.

2. Among ZYN[®] users, compare TNP patterns of use over the last 30 days with TNP patterns of use during the weeks prior to using ZYN[®].

Within the cohort of ZYN[®] users, the study will explore how usage of TNP products might have changed from the period prior to starting ZYN[®] to the last 30 days. Of particular interest will be whether usage of ZYN[®] offsets usage of products such as cigarettes and smokeless tobacco.

3. Evaluate the level of compliance among ZYN[®] users with ZYN[®] usage instruction over the last seven days.

Focusing on the last seven days, the study will explore how ZYN[®] users report using the product. Specifically of interest will be compliance with usage instructions and presence/absence of product misuse.

7.2. Secondary Objective

Utilizing data from the Retrospective Study:

1. Assess perceptions of absolute risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) among ZYN[®] users and ZYN[®] non-users.

The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN[®] daily, smoking only cigarettes daily, and never having used any TNPs. Discussion sections will highlight any observed divergence between ZYN[®] users with ZYN[®] non-users.

2. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with ZYN[®] as compared with using other TNP, aids that help stop smoking, and never having used any TNPs.

The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN[®] daily relative to using only other TNP daily, daily use of aids to help stop smoking, or never having used any TNPs.

3. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with adding ZYN[®] use to existing TNP use.

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The study will measure the perceived relative risk of the aforementioned health conditions attributed to using both ZYN[®] and other TNP compared with using other TNP alone. From there, further analysis will delve into how adding ZYN[®] to existing TNP use alters perceived risk.

4. Assess ZYN[®] users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) to a person who quits use of all TNP compared with a person who quits all TNP except for daily use of ZYN[®].

The study will measure the perceived relative risk of the aforementioned health conditions attributed to quitting all TNP except for the daily use of ZYN[®] compared with quitting all TNP use.

Utilizing data from the Prospective Study:

5. Explore daily TNP patterns of use among ZYN[®] users and ZYN[®] non-users, including reasons for ZYN[®] use, over a prospective 10-week observational period.
6. Compare the tendencies of ZYN[®] users to quit TNP or use the product in an incremental fashion, in a supplemental fashion, or in complete substitution of other TNP.

8. RESEARCH METHODS

The ZYN[®] Patterns of Use Study consists of two separate projects, meant to gain an understanding of how ZYN[®] is and has been used among consumers. Each project includes ZYN[®] users and non-users, to allow for more informed investigation. Each study relies upon its own survey instrument; cognitive interviews inform the retrospective and prospective surveys to ensure clear communication of survey items to respondents. The Retrospective Study utilizes a cross-sectional design to measure recalled TNP usage among ZYN[®] users and ZYN[®] non-users. The Prospective Study longitudinally evaluates TNP patterns of use among ZYN[®] users and ZYN[®] non-users over a 10-week observation period.

8.1. Data Source

8.1.1. ZYN[®] Users Data Source

Due to the low incidence of ZYN[®] users among the general population, sample for this cohort will be recruited directly from purchasers of ZYN[®]. A third-party vendor will place study invitation stickers on product packaging (i.e. each individual canister of 15 ZYN[®] pouches) for the six core flavors of ZYN[®] from November 27 – December 11, 2017.

The sticker initiative will target approximately 4,500 stores across the 11 states where ZYN[®] is sold^a, covering approximately 65 cans per store, for approximately 290,000 ZYN[®] cans in total. Efforts will be made to ensure that stickers are distributed across all locations at the same time and that all ZYN[®]

^a Retail outlets account for 96% of all sales for ZYN[®] based on Swedish Match North America internal data.²

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users will have the same chance to participate in this study (See Attachment for an example of the stickers).

The study invitation sticker was approved by the Sterling Institutional Review Board and includes a statement of getting paid for providing opinions, as well as eligibility requirements, such as being of legal age and older, limiting one study per household, and that eligibility is limited to a set number of respondents. Additionally, the sticker will include a website (www.ZYNOpinions.com) to learn more information and a unique registration code.

ZYNOpinions.com will serve as a landing page, hosted by New Honor Society, the agency of record for ZYN[®]. From ZYNOpinions.com, respondents will be taken to a study welcome screen; that screen and all following survey pages will be hosted on (b) (4) or (b) (4) third-party partner servers.

Users who are interested in participating will visit the website address shown on the ZYN[®] canister invitation sticker. Upon entry, the participant will be shown the study welcome screen and redirected to a secure and unique survey link. The first set of questions will be the survey screener which will be designed to qualify the participant using the study inclusion and exclusion criteria (further described in Section 8.3.2 and 8.3.3 “Inclusion/Exclusion Criteria”). Questions within the survey screener will also enable cross-checks to reduce the likelihood of the same respondent repeating the survey over the study period.

By giving nearly every ZYN[®] user an equal chance to participate in the study, a demographically representative sample of ZYN[®] users will be obtained, for the 11 states it is available through retail outlets, reflecting the marginal distribution of age, gender, race/ethnicity, and education.

8.1.2. ZYN[®] Non-User Data Source

When enrollment in the survey for the ZYN[®] user cohort has reached 40%, the (b) (4) fielding team will analyze the demographic characteristics of the data (i.e., age, gender, race/ethnicity, and education). The demographic characteristics of ZYN[®] users will then be used to stratify the sample of ZYN[®] non-users. The demographic characteristics of the ZYN[®] user will be monitored daily and the recruitment of ZYN[®] non-user cohort will be appropriately adjusted in order to have consistency across ZYN[®] user and ZYN[®] non-user cohorts.

By recruiting ZYN[®] non-users based on demographic criteria corresponding to enrolled ZYN[®] users, the sample recruitment plan is designed to provide matching populations with regard to socio-demographic characteristics through online panels and telephone recruitment. This approach is designed to avoid sample bias and to obtain ZYN[®] user and ZYN[®] non-user cohorts that are demographically aligned with the populations they are meant to define. Additionally, the ZYN[®] non-user cohort will be sourced from the same 11 states where ZYN[®] is sold.

8.1.2.1. Online Panel Recruitment

Online consumer survey panels (b) (4) (b) (4) and (b) (4) will be utilized to recruit the ZYN[®] non-user cohort. These panels are large commercial consumer panels that profile panelists on self-reported characteristics such as age,

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gender, location, income, ethnicity, household size, marital status, presence of young children, and education.

The online panels are opt-in panels where consumers who join make a conscious decision to participate regularly in surveys. 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; and
- 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 identification number to ensure only one respondent per computer can participate in a survey; blocking 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.

In order to construct matching populations, panelists will be selected based on stored background information collected during the registration survey and ongoing profiling. The sample universe size is based on the size of the desired quotas, in combination with estimated response rates, within specified quota targets. Panelists with matching demographic profiles will be randomly selected for inclusion in the sample universe, until the appropriate sample universe size is reached. Sample will be replicated in batches, to be deployed as needed, throughout the data collection process.

Given the use of multiple panels to achieve the quotas required for demographic representativeness, attempts will be made to balance panel source through sample assignments and daily monitoring. However sample distribution across panels is not a critical factor since the ZYN® user cohort is not recruited through panels.

During the fieldwork, sample performance will be monitored daily; additional panelists will be invited to complete the fieldwork within a pre-determined time frame, to ensure a consistent market

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environment for all respondents. Analysis of response and qualifying rates will be done for each demographic quota. As quota targets are achieved, the random sample selection process will be refined to only target panelists matching those demographic characteristics whose quotas have not yet been reached. If required, additional sample will be selected for specific demographic targets, where the desired quota has not been met, using the sample selection process listed above. This approach is designed to avoid sample bias and to obtain cohorts that are demographically aligned with the populations they define.

Prior to fully launching the surveys, data created by test runs of survey completion for each method of recruitment (sticker on ZYN[®] canister, internet panel, and telephone) will be quality checked prior to the release of the survey to respondents. For the ZYN[®] non-user cohort additional quality checks will be performed through a soft launch, where a limited number of respondents will be recruited to initially take the survey prior to a fully launching the study. The primary objective of this 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, the accuracy of the web-based instrument (i.e., survey), redirects per each recruitment method, all of which work to ensure the primary objectives of the research are met. ZYN[®] non-user 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.

Once the accuracy of the web-based instrument is verified, the ZYN[®] non-user 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 to the appropriate consumers, the invitation will specify that the opinions of TNP users 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 be able to participate as long as 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 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.

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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.

8.1.2.2. Telephone Recruitment

(b) (4) will engage a call center, Directions in Research (DIR), for telephone recruiting to supplement any shortfall in demographic quotas for the non-ZYN[®] group, if not fully recruited through online panel recruitment. DIR will purchase sample from the Marketing Systems Group (MSG). The sample purchased will be representative of the 11 states where ZYN[®] is sold and targeted to individuals that meet the required strata, in the following demographic targets: State (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, WY), Race/Ethnicity, Gender, Age and Education. Amount of sample purchased will be determined by the make-up of the ZYN[®] user group, the incidence of product usage by state, estimated response rates by demographics and estimated completion rates. This sample will include a combination of land line and cell phone numbers.

Sample will be stratified based on characteristics of the demographic quotas. DIR will then randomly dial phone numbers, within targeted demographic groups, to recruit for participation in the online research. Respondents who agree to participate, will be emailed a link to the survey. The call center representative will attempt to keep the respondent on the line, while they confirm receipt of the link. Same as the ZYN[®] user cohort, the ZYN[®] non-users who meet inclusion and exclusion criteria (see Section 8.3.2 and Section 8.3.3) in the screener will be invited to complete the survey via the electronic informed consent form (ICF). In addition to the checks conducted within the survey platform to attempt to reduce the chances of duplicate survey entries, the screener will terminate respondents who indicate past participation in tobacco and/or nicotine studies within the past 2 weeks.

Call center staff will receive daily reports identifying which respondents (who have agreed to participate) have, or have not, completed the online Retrospective survey. Based on the report, the call center will schedule reminder emails and reminder calls, to encourage completion. Up to 3 reminders are permitted, per respondent.

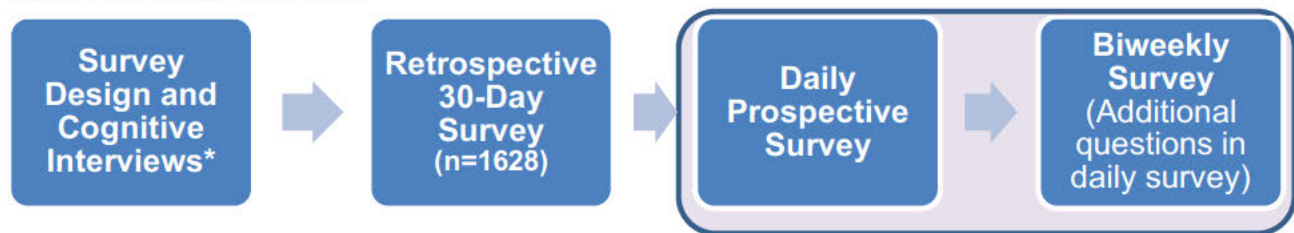
In the end, we will generate an ending sample that will be representative of the ZYN[®] user stratification.

8.2. Study Design

As noted previously, the ZYN[®] Patterns of Use Study seeks to evaluate TNP patterns of use among ZYN[®] users and ZYN[®] non-users through a Retrospective Study focused primarily on 30-day recall, accompanied by a longitudinal Prospective Study comprising of a 10-week self-reported daily e-diary study within the United States (U.S.) adult population.

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 8.2.1 for more details about the cognitive interviews.

Figure 1 below summarizes each phase of research.

Figure 1: Study Flowchart

**Data from respondents who take part in the cognitive interview phase will not be in the final data set.*

8.2.1. Cognitive Interviews

Cognitive interviews will be conducted prior to executing the retrospective or prospective studies. 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.³ Cognitive interviewing is used as a means for applying qualitative research methods to the understanding of the functioning of survey questions.⁴ 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 Prevention⁵. 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. It will also provide input into the clarity, understandability, and interpretation of the patterns of TNP use.

To ensure that the materials are appropriate and sufficiently clear to consumers, the Patterns of Use retrospective and prospective online surveys will be piloted among 10 ZYN® and 10 non-ZYN® users across two rounds of qualitative in-depth, in-person, interviews in two of the 11 states where ZYN® is available in retail outlets. The second round of cognitive interviews will be a week 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 are 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,

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and tobacco/nicotine use behavior. Recruitment will be conducted by Fieldwork Research Denver and Fieldwork Research Seattle at a local level, utilizing their databases of consumers. Panel members will be contacted via email with a link to the screener. The email will 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 8.3.2 and section 8.3.3). 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.

8.2.2. Retrospective Study

All respondents (regardless of recruitment method they originated from) will access a web survey online via a computer, smartphone, or tablet. The Retrospective Study is a 10-20 minute survey where participants are asked to self-report TNP use history within the past 30 days. A 30 day recall period was selected based both upon review of the available tobacco and nicotine peer reviewed literature utilizing 30-day recall for understanding current and recent usage of TNP⁵ as well as applying the PATH methodology of asking consumers to recall specific TNP use in a 30-day period.⁷

Respondents will be able to complete the retrospective online survey via computer, tablet, or smartphone. Following the completion of the retrospective 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 provided as a result of survey completion. Both ZYN[®] users and ZYN[®] non-users recruited via telephone will receive honoraria in the form of a check. Participants from the ZYN[®] non-user cohort recruited via an online survey panel will receive their honoraria in the form of reward points specific to the panel they are a member of and aligned to the fair market value assigned to the survey length.

Additionally, at the completion of the retrospective survey, ZYN[®] users recruited through the sticker program will be asked if they would be interested in being contacted again for follow-up or future research related to nicotine products without tobacco, tobacco, and/or ZYN[®] specific research. If they are interested, they would provide an email address that will be provided to recruiting sources who will log them as interested parties.

8.2.3. Prospective Survey

The Prospective Study is designed as a 5-minute daily survey/e-diary across 10 weeks for a total of 70 daily surveys completed per respondent. Every 14 days, the daily survey is extended by 5 minutes to obtain additional information. A total of 5 of these extended surveys will be administered over the study period of 10 weeks. These extended surveys are referred to as the “bi-weekly e-diary” for the remainder of this protocol. The Prospective Study can also be completed via computer, tablet, or smartphone.

The Prospective Study is designed to have a 10-week observational period after identifying 7-week, 8-week, and 10-week endpoints in the peer reviewed literature regarding smoking cessation studies.^{8,9} The longest observational period of 10 weeks was chosen to provide the most comprehensive dataset.

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The invitation for the prospective 10-week study will follow the debriefing statement at the end of the retrospective survey. The Prospective Study is not required for the participant to receive compensation for their participation in the retrospective survey. If an individual agrees to complete the Prospective Study, their unique link provided for the Retrospective Study will be used to access the e-diary survey. Respondents will be required to provide their informed consent specific to completing the prospective phase of the study.

Each daily e-diary will ask the participant to report their product usage for the prior day. Each participant will be encouraged to complete their daily and bi-weekly survey earlier in the day to improve the accuracy of their recall of their TNP use the day before. At the end of each daily e-diary a reminder to complete the next diary daily will be shown. On the day before the bi-weekly survey, an additional message will be provided reminding the respondents of the longer survey and expressing the importance of completing the next day's survey.

A call center (hotline) with a dedicated toll-free phone number will be established to receive incoming calls from any participant in the prospective 10-week study for questions about the study or to report an adverse event or product complaint (see section 8.4.5). The call center will also make outgoing calls to respondents who fail to complete two consecutive days in their e-diary.

Respondents will receive compensation for each week that they complete the daily e-diary surveys. Successful completion of 1 week requires that participants complete a minimum of 5 of the 7 daily e-diaries, (i.e., missing no more than 2 days out of 7 per week). If a participant misses two days in a week, as agreed to in the ICF, a hotline representative will call and remind the participant to complete the last two days and next survey. If the respondent does not complete the next survey, now missing 3 days of surveys in a single week, they will be excluded from further study participation and compensation. Only respondents completing all 10 weeks in the Prospective Study period will be included in the final analyses. If the participant completes the full 10 weeks of data collection, meeting the criteria for completion each week (i.e., not missing more than 2 surveys in 7 days), they will receive an additional bonus compensation at the end of the 10 weeks.

8.3. Study Population

The study population will include U.S. adult population of legal age for TNP use across the 11 states where ZYN® is currently available for sale at retail; those eleven states are Arizona, California, Oregon, Washington, Idaho, Montana, Nevada, Utah, Colorado, New Mexico, and Wyoming.

To meet the objectives of the Patterns of Use Study for ZYN®, this study will include respondents from the following cohorts:

Current ZYN® users	<p>All ZYN® users will be recruited through the canister sticker-program. Users are then confirmed through the screener to:</p> <ul style="list-style-type: none"> ▪ Currently use ZYN® brand of nicotine pouches; ▪ Have used nicotine pouches fairly regularly; and, ▪ Now using ZYN® pouches every day or some days.
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<p>ZYN[®] non-users who use TNP(s)</p>	<ul style="list-style-type: none"> ▪ Have never used ZYN[®] <u>OR</u> ▪ Have NOT used ZYN[®] regularly AND do NOT currently use ZYN[®] every day or some days <p>AND AT LEAST ONE OF THE FOLLOWING:</p> <ul style="list-style-type: none"> ▪ Have smoked 100 or more cigarettes during lifetime AND currently smoke cigarettes every day or some days <p style="text-align: center;">AND/OR</p> <ul style="list-style-type: none"> ▪ For any of the following products, have been a regular user AND now uses the product every day or some days: <ul style="list-style-type: none"> • 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)
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The definition of users and the product types constituting TNP for this study are adapted from the PATH study, where a threshold of lifetime use is established for cigarette use, which is having smoked 100 or more cigarettes during lifetime. For all other TNP, use is based on the recollection of both ever using TNP fairly regularly and if they now use the product every day or some days.⁷

8.3.1. Sample Size

The ZYN[®] Patterns of Use study will run in conjunction with a Likelihood of Use study¹⁰; these studies in tandem provide the consumer research required to support the PMTA.

While the Patterns of Use study primarily asks questions meant to report behaviors, as opposed to providing opinions, the decision was made to mirror the Likelihood of Use sampling algorithm. Hence, the Patterns of Use study precision analysis was performed under the following assumptions: a confidence interval of 95% ($\alpha=.05$), a standard deviation of 3.74,^b a small interval half-width, and a probability of achieving the desired precision of .99.

The precision analysis suggested a sample size of 814 per cohort in the Retrospective Study would be appropriate. (Note that the Likelihood of Use study and its associated precision analysis, suggested a sample size of n=814 per cohort of interest.) In total, the planned study sample for the Retrospective Study is N=1,628, with n=814 respondents in each cohort. Table 1 presents the sample size for each cohort, while also noting that sample sizes for the Prospective Study will be an undetermined subset of

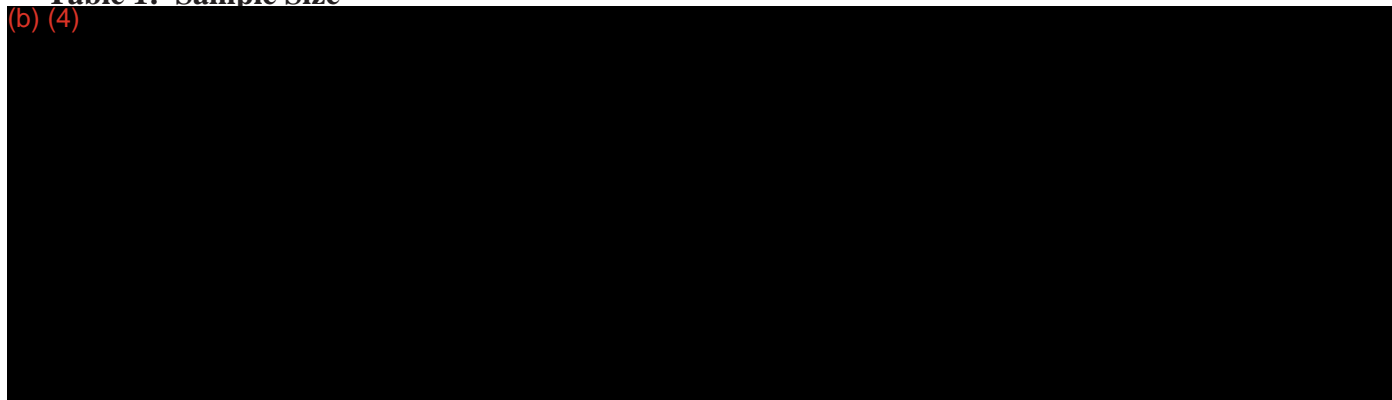
^b The standard deviation used in these power calculations are taken from data provided by Swedish Match, "A market research report (January 2017)" which uses the Juster Scale to measure purchase intentions for moist snuff. The standard deviation is an average of the 3 standard deviations taken from Question #9, 13, and 17.

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those completing the Retrospective Study, and will consist of only participants who complete all 10 weeks of the prospective observational period.

Table 1: Sample Size

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8.3.2. Subject Selection: Inclusion Criteria

In addition to the already mentioned cohort definitions to be included in this study, respondents must meet the following criteria to be included:

- Minimum legal age for tobacco/nicotine use per local state requirements
- Able to read and speak English
- Currently a resident of one of the 11 U.S. states where ZYN® is available in retail outlets (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY)
- Individuals who provide electronic informed consent

8.3.3. Subject Selection: Exclusion Criteria

Respondents who meet any of the following criteria will be excluded from the study:

- Respond as “don’t know” or “decline to answer” to specific demographics (gender, geographical region, ethnicity, or education) for the purpose of balancing cohorts
- Unwilling or unable to provide electronic informed consent
- 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 of being screened for qualification to the Retrospective Study

8.4. Outcomes

8.4.1. Outcomes for Primary Objectives

Outcomes that will be used to evaluate the primary objectives are as follows:

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Reported use in the last 30 days will be assessed by using one item observing frequency of use for each TNP currently used over the last 30 days. The item is based on the approach employed in PATH for observing current TNP use.⁷ Response options for frequency of use include “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.” See Figure 2 for an example.

Figure 2: Reported Use of TNP over Last 30 Days Example

(b) (4)

Intention to quit respective TNP will be assessed using one item for each TNP assessing intention to quit the respective TNP. Intention to quit TNPs will be measured using the Motivation to Stop Scale (MTSS).¹¹ The MTSS consists of one item with seven response options ranging from 1 (lowest) to 7 (highest level of motivation to stop smoking), also including “Don’t know.” Scale developers found that odds of quit attempts increased linearly with increasing levels of motivation. In the current study, we use the MTSS both for assessing intention to quit cigarettes and for other TNPs. Consistent with published research using the MTSS, we will report the mean MTSS score.¹² The MTSS was selected for use in the ZYN® Patterns of Use Study due to its brevity and validation as a strong and accurate predictor of quit attempts.¹¹ See Figure 3 for an example.

Figure 3: Intention to Quit TNP Example

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Reported use in the weeks prior to initiating ZYN[®] usage will be assessed by using one item observing frequency of use for each TNP used by a respondent. The item is based on the approach employed in PATH for observing current TNP use.⁷ Response options for frequency of use include “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.” See Figure 4 for an example.

Figure 4: Reported Use of TNP Prior to Initiating ZYN[®] Example

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Level of compliance with ZYN[®] usage instructions will be assessed using one custom^c item for each of four examples representing proper and improper ZYN[®] use. Items corresponding to proper use include “Placed a ZYN[®] pouch between my gum and upper lip” and “Used one ZYN[®] pouch at a time.” Items corresponding to improper use of ZYN[®] include “Used one ZYN[®] pouch for more than 60 minutes” and “Cut the ZYN[®] pouch open and used the pouch contents.” Response options for each item include “Always,” “Sometimes,” “Never,” “Don’t know” and “Decline to answer.” See Figure 5 for an example.

Figure 5: Compliance with ZYN[®] Usage Instructions Example

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8.4.2. Secondary Objectives

Outcomes that will be used to evaluate the secondary objectives are as follows:

Perceptions of absolute risk 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 four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems). This scale was modified from the risk perception scale in HINTS.¹³ See [Figure 6](#) for an example.

^c Custom items were designed based on product design and features, and respective questions were validated through cognitive interviews, to ensure that the item was appropriate and sufficiently clear to respondents.

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Figure 6: Perceptions of Absolute Risk Example

(b) (4)



Perceptions of relative 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 four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems), contrasting ZYN[®] use with several other risk exposures. The risk exposures to be assessed for each health condition include use of ZYN[®] versus the daily use of other TNP, aids to help stop smoking, and never having used any TNPs; and quitting all TNP relative to quitting all TNP except for ZYN[®]. This scale was modified from the risk perception scale used in HINTS.¹³ See [Figure 7](#) for an example.

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Figure 7: Perceptions of Relative Risk Example

PRODUCT LIST:

1. cigarettes
2. e-cigarettes
3. moist snuff
4. chewing tobacco
5. snus
6. aids to help stop smoking
7. both cigarettes and ZYN®
8. never having used any tobacco or nicotine products

(b) (4)



of causing **[INSERT CONDITION]**

CONDITION LIST:

- a. ADULT TOOTH LOSS
- b. GUM DISEASE
- c. MOUTH CANCER
- d. SERIOUS HEALTH PROBLEMS

(b) (4)

Average daily reported use during the prospective observational period will be assessed based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day of the observational period. Observations of daily TNP use will be used to derive average daily use of each TNP per week in the 10-week observational period. See Figure 8 for an example.

Weekly frequency of use during the prospective observational period will be derived based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day of the observational period. These observations will be used to derive weekly frequency of use for each TNP. For example, respondents participating in the Prospective Study who report using a TNP every day for a given week based on non-missing daily surveys (e.g., usage for 5/5, 6/6, or 7/7 daily surveys) will be considered “Every day” users. Respondents participating in the Prospective Study who report using a TNP at least one day, but not every day, (e.g., usage for 1/5, 1/6, 3/6, 2/7, etc., daily surveys) based on non-missing daily surveys will be considered “Some days” users. Finally, respondents participating in the Prospective Study who do not report any TNP use based on non-missing daily surveys (e.g., usage for 0/5, 0/6, or 0/7 daily surveys) will be considered “Not at all” users. Derived outcomes based on the prospective survey items are based on the approach employed in PATH for observing current TNP use.⁷ See Figure 8 for an example.

Weekly use of ZYN[®] with other TNP will be derived based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day of the observational period. These observations will be used to derive whether respondents used ZYN[®] only, ZYN[®]+cigarettes, ZYN[®]+other TNP (excluding cigarettes), ZYN[®]+smokeless (i.e., moist snuff, chewing tobacco, or snus), ZYN[®]+snus, ZYN[®]+chewing tobacco, or ZYN[®]+moist snuff in each week of the 10-week observational period. See Figure 8 for an example.

Figure 8: Number of Times Each TNP Used Each Day of Observation Period Example

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(b) (4)

Intention to quit each TNP during the prospective observational period will be assessed using the MTSS¹¹ described in detail above. See Figure 9 for an example.

Figure 9: Intention to Quit TNP Example

(b) (4)



Reasons for ZYN[®] use will be assessed using one item in the biweekly survey assessing why respondents had used ZYN[®]. Reasons for using ZYN[®] include:

- To help me reduce my cigarette smoking;
- To help me quit smoking cigarettes;
- To help me reduce my use of tobacco products other than cigarettes;
- To help me quit using tobacco products other than cigarettes;
- To use in environments where other tobacco/nicotine products are not considered appropriate (e.g. church, etc.);
- To use in environments where other tobacco/nicotine products are not allowed (e.g. airplane, etc.);
- Less harmful to my health than cigarettes;
- Less harmful to my health than other tobacco products, excluding cigarettes;
- To avoid spitting as required with other products
- To add variety to the products I use;
- Comes in flavors I like;
- Does not cause me to smell like smoke/tobacco;
- Comes in two different levels of nicotine strength;

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- Less harmful for those around me than cigarettes;
- More acceptable to non-tobacco users;
- No one can tell when I am using it;
- I was just curious to see what it was like;
- Ease of use;
- Recommended by person who works in the store where I buy my TNP;
- None of the above. Additional response options include “Don’t know” and “Decline to answer.”

Percent of days ZYN[®] is used will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the number of ZYN[®] pouches used each day. The average percent of days ZYN[®] is used will be calculated as the percentage of non-missing days in each week where at least one ZYN[®] pouch was used.

Average number of ZYN[®] pouches used per day will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the number of ZYN[®] pouches used each day. The average number of ZYN[®] pouches used per day will be calculated as the average number of ZYN[®] pouches used for non-missing days in each week.

Average number of minutes ZYN[®] was kept in mouth will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the typical duration of time an individual ZYN[®] pouch was used in the given day. The average number of minutes ZYN[®] was kept in the mouth will be calculated based on the duration of time a typical ZYN[®] pouch was kept in the mouth for non-missing days in a given week. See Figure 10 for an example.

Figure 10: Average Number of Minutes Kept in Mouth Example

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Quitting all TNP use will be derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as TNP usage patterns in the last 30 days of the observational period. In particular, respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period.^d Quitting TNP will be determined based on respondents reporting zero TNP use over weeks 9 and 10.

Complete substitution of TNP use will be derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as weeks 9 and 10 of the prospective observational period. In particular, respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period. Similarly, TNP use during weeks 9 and 10 will be used to determine TNP use at the end of the prospective observational period. ZYN[®] users who used other TNP during weeks 1 and 2 of the prospective observational period but only ZYN[®] in weeks 9 and 10 will be considered to have completely substituted ZYN[®] in place of other TNP.^e

8.4.3. Other Variables

Some additional variables will be collected that will not be used to support the primary and secondary objectives. For example baseline characteristics of age, gender, ethnicity, education, and geographical region will be collected to help achieve a representative sample.

8.4.4. Adverse Events and Product Complaints

As this study is observational by design and is conducted in an actual use setting, adverse event (AE) and product complaint reporting will follow a passive surveillance mechanism, recording spontaneously reported events. Participants will be informed that a dedicated toll-free hotline has been established for use during the study so that participants can report product quality complaints and adverse health events associated with the use of ZYN[®]. The hotline staff are trained on the reporting procedures and when receiving spontaneous reports of adverse health events or product complaints, the hotline staff documents these reports on the designated form (Adverse Event Reporting Form or Product Complaint Reporting Form). The participant who reports an AE or product complaint will have the choice to continue or withdraw from the study.

Product complaint forms will be forwarded to the Sponsor's Consumer Contact Line. All reported AEs will be assessed by a Health Care Professional (HCP) for seriousness and causality. All Serious Adverse Events (SAE) will be reported to the IRB.

At the conclusion of the study, all AEs and product complaints will be listed in a summary report and provided to the study Sponsor. A detailed explanation of the reporting and documentation procedures are outlined in the study Adverse Event Management Plan (See Attachment 4).

^d TNP use for the prospective observational period was defined based on TNP use over weeks 1 and 2 in order to capture individuals using TNP at least 2 times per month.

^e Completely substituting ZYN[®] in place of other TNP was defined based on TNP use over weeks 1 and 2 and 9 and 10 in order to capture behavioral change for individuals using TNP at least 2 times per month.

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8.5. Data Management

(b) (4) 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.

(b) (4) 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:

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

8.5.1. Data Quality Control

The data collected for this study will be monitored for adherence with the 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 (b) (4) 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). 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.

(b) (4)

8.5.2. 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.

8.5.3. 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 unlocked, the analytical team will perform further checks prior to conducting data analyses specified in the SAP.

(b) (4) 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.

8.5.4. 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.

8.6. Data Analysis

A formal and more detailed statistical analysis plan (SAP) will be prepared by (b) (4) after finalization of the study protocol and survey.

8.6.1. 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.³ Systematic content analysis will provide the data to be analyzed thus assuring 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 and the product information sheet, 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 whether questions have issues with comprehension, retrieval, decision-judgment, and response across all subjects¹⁴. 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.

8.6.2. Quantitative data analysis

All analyses performed for the ZYN[®] Patterns of Use Study will be descriptive in nature.

(b) (4)

Descriptive statistics used to understand the distribution of socio-demographic and outcomes variables will be based on the raw data (i.e., prior to any recoding or any aggregation required for the final presentation of results). Respondents with values for variables that are illogical or deemed unreliable, as determined by the underlying distribution, will be considered for removal prior to performing the main analyses. The SAP will provide greater detail on this topic. Numeric variables will be described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables will be described using frequencies, percentages, and the number of missing observations (if applicable).

Unless otherwise specified in the SAP, descriptive statistics reported for the main analyses will include the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs), for numeric variables. For categorical variables it will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category.

The study team will format and properly label the data sets (including all responses from respondents and the date that the survey was completed) using SAS[®] software (Statistical Analysis System, version 9.3)¹⁵ so they 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 8.51 “Quality Control”.

8.6.2.1. Statistical Considerations for Primary Objectives

Descriptive statistics for accomplishing primary objectives will be reported for patterns of TNP use (for both ZYN[®] and ZYN[®] non-users) as well as compliance with ZYN[®] usage instructions among ZYN[®] users. Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category for categorical variables.

8.6.2.2. Secondary Objectives

Descriptive statistics for accomplishing secondary objectives utilizing data from the Retrospective Study will be reported for both perceptions of absolute risk and perceptions of relative risk.

Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category, for categorical variables.

Descriptive statistics for accomplishing secondary objectives utilizing data from the Prospective Study will be reported for daily TNP patterns of use as well as incremental use, supplemental use, quitting all TNP excluding ZYN[®], and quitting all TNP including ZYN[®]. Descriptive statistics will include the number of non-missing observations, means, standard deviations, and 95% CIs.

8.6.3. Quality control

There are several aspects to quality control as described below:

Survey Instrument Programming

(b) (4)

- The web-based survey will be created by the (b) (4) programming team using the (b) (4) (b) (4) for web-based survey programming (b) (4)
- Then, the survey will be checked by another programmer independent of the day-to-day project to ensure all programming is correct.
- After the survey has been programmed and tested, the survey link and content will be reviewed by a separate team within (b) (4) fielding operations group from the perspective of the respondent (i.e. the link is reviewed online and not within the (b) (4))
- 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 (b) (4) 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 (b) (4) analytical team to begin study analysis.

Qualitative Study

- As mentioned in Section 8.2.1 “Cognitive Interviews,” a qualitative study will be conducted to assess the online survey instrument in a live setting with 20 total 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.

(b) (4)

- 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.
- Respondents who participate in the Prospective Study are required to complete at least 5 daily surveys in each week in the 10-week observational period. Accordingly, respondents who miss more than 2 daily surveys in a given week will be removed from the final locked data set, but will be retained in a separate complete data set.

8.7. Limitations of the Research Methods

The data collected will be based on responses to a web-based survey. The perceived health risk assessments are intended to simulate possible real world perceptions, 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.

Some respondents will be recruited based on their membership with an online market research panel. As a result, their 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 8.3 “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

(b) (4)

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.

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. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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 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, **(b) (4)** conducts all of 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.

9.2. 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 also 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.

9.3. Respondent information and consent

Prior to beginning the main survey, 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, 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. Contact information for the IRB is also provided if the respondent has any questions or concerns about their rights as a research participant

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

(b) (4)

the electronic informed consent form and any other written information provided to respondents will be obtained prior to the initiation of the study.

Lastly, the statement of informed consent provides potential respondents with a hotline to contact to address any concerns they may have. Contact information is given if the respondent has any specific questions about the survey instrument or incentives for participation. In addition, a hotline will be provided for the participant to report any adverse events experienced. Product-related questions will be referred to SMNA's normal product complaint process.

9.4. Confidentiality

Swedish Match North America, Inc. as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Swedish Match North America, Inc. 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 the sponsor. If the respondent name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. 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.

(b) (4)

10. REFERENCES

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11. ATTACHMENTS

ATTACHMENT 1: RESTROSPECTIVE QUESTIONNAIRE

ATTACHMENT 2: PROSPECTIVE QUESTIONNAIRES

ATTACHMENT 3: STICKER INVITE

ATTACHMENT 4: ADVERSE EVENT MANAGEMENT PLAN

(b) (4)

12. 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):

(b) (4), (b) (6)

Institution:

(b) (4)

Signature:

(b) (6)

Date: 01 June 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 the sponsor; a protocol amendment will not be required.

13. SPONSOR SIGNATURE

Swedish Match North America Signature(s)

The ZYN[®] Patterns of Use Study primarily seeks to understand TNP patterns of use among ZYN[®] users and ZYN[®] non-users through a retrospective 30-day recall study. Secondly, describe behavior over time through a prospective 10-week daily e-diary study. Current residents of one of the 11 U.S. states where Swedish Match actively sells ZYN[®] through retail stores (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY) are eligible to participate.

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

I agree to the terms of this Study protocol.

Name (typed or printed):

(b) (4), (b) (6)

Institution:

Swedish Match North America

Signature:

(b) (6)

Date:

(Day Month Year)

LAST PAGE

Swedish Match North America, Inc.

Protocol for Observational Study

ZYN® Patterns of Use Study

(b) (4)

Status: Approved

Date: 13 November 2017

Prepared by: (b) (4)

Confidentiality Statement

Notice: The Contents of this document and any attachments to it may contain confidential and/or legally privileged information. This information is only for use by the intended recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or taking action based upon the information contained herein is strictly prohibited. If this document was received in error, please notify the sender and delete it thereafter from your system.

Swedish Match North America, its parent and affiliate companies.

(b) (4)

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
AEMP	Adverse Event Management Plan
BRINC	Branded Research Inc.
CA	California
CAPTCHA	Completely Automated Public Turing Test To Tell Computers & Humans Apart
CO	Colorado
CTP	Center for Tobacco Products
DIR	Directions in Research
FDA	Food and Drug Administration
FTP	File Transfer Protocol
ICF	Informed Consent Form
ID	Idaho
IP	Internet Protocol
IRB	Institutional Review Board
LSR	Lightspeed Research
MRTTP	Modified Risk Tobacco Product
MSG	Marketing Systems Group
MT	Montana
MTSS	Motivation To Stop Scale
NCHS	National Center for Health Statistics
NE	Nevada
NM	New Mexico
OMB	Office of Management and Budget
OR	Oregon
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
RDD	Random Digit Dialing
SAE	Serious Adverse Event

(b) (4)

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMNA	Swedish Match North America, Inc.
SSI	Survey Sampling International
TNP	Tobacco/Nicotine Product(s)
U.S.	United States
UT	Utah
WA	Washington
WY	Wyoming
ZYN[®] non-users	ZYN [®] non-users who use tobacco products

(b) (4)

3. RESPONSIBLE PARTIES

3.1. Investigator and Contributors

Investigator:

(b) (4), (b) (6)

(b) (4)

Project Team:

(b) (4), (b) (6)

3.2. Sponsor

Swedish Match North America

(b) (4), (b) (6)

4. SYNOPSIS

Title	ZYN[®] Patterns of Use Study
Protocol version identifier	Version 1, Amendment 1
Date of last version of protocol	August 10, 2017
Protocol number	(b) (4)
Author	(b) (6)

(b) (4)

Rationale and background	<p>Swedish Match North America (SMNA) officially began selling ZYN[®] in 2014. ZYN[®] delivers nicotine derived from tobacco, but the ZYN[®] product itself does not contain tobacco leaves. ZYN[®] comes in a small pouch that contains nicotine flavoring elements, and other ingredients required to ensure shelf stability. SMNA markets ZYN[®] as a nicotine delivery product and not as a smoking cessation product. SMNA will be filing a Premarket Tobacco Product Application (PMTA) for ZYN[®] in 2018.</p> <p>The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA. As primary objectives, the ZYN[®] Patterns of Use Study seeks to understand:</p> <ol style="list-style-type: none"> 1. TNP patterns of use among ZYN[®] users and ZYN[®] non-users; 2. Perceptions of health risks associated with the use of TNP, smoking cessation aids, and never having used any TNP among ZYN[®] users' and ZYN[®] non-users; 3. Perceptions of health risks associated with the use of ZYN[®] and other TNP, smoking cessation aids, and never having used any TNP among ZYN[®] users'; and 4. Compliance with product use instructions among ZYN[®] users' <p>by means of a <u>retrospective</u> study focused primarily on 30-day recall.</p> <p>As a secondary objective, this study will evaluate TNP patterns of use over time among ZYN[®] users and ZYN[®] non-users by means of a <u>prospective</u> 10-week self-reported daily e-diary study.</p>
Research question and objectives	<p>The overarching research questions within this project can be stated as follows: <i>How do ZYN[®] users and ZYN[®] non-users use TNP and how do they perceive health risks associated with TNP?</i> These questions will be studied by means of a retrospective assessment of TNP use among both ZYN[®] users and ZYN[®] non-users (all of whom are of legal age to use TNP in their residential geography). Use and risk perceptions of TNP will be compared across ZYN[®] users and ZYN[®] non-users with independent measures and the use of TNP among ZYN[®] users will be compared with repeated measures.</p> <p>The primary objectives of the Patterns of Use Retrospective study are to:</p> <ol style="list-style-type: none"> 1. Compare TNP patterns of use between ZYN[®] users and ZYN[®] non-users over the past 30 days 2. Among ZYN[®] users, compare TNP patterns of use over the last 30 days to TNP patterns of use during the weeks prior to using ZYN[®]. 3. Compare perceptions of <u>absolute</u> risk associated with: <ul style="list-style-type: none"> • smoking cigarettes every day but using no other tobacco products and • never having used any tobacco or nicotine products between ZYN[®] users and ZYN[®] non-users.

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	<ul style="list-style-type: none"> • The medical conditions under consideration when discussing absolute risk are: <ul style="list-style-type: none"> ▪ Adult tooth loss ▪ Gum disease ▪ Mouth cancer ▪ Serious health problems <p>4. Compare ZYN[®] users' perceptions of absolute risk, associated with using ZYN[®], to smoking cigarettes every day but using no other tobacco products, and to never having used any tobacco or nicotine products.</p> <ul style="list-style-type: none"> • The medical conditions under consideration with ZYN[®], smoking cigarettes every day but using no other tobacco products, and never having used any tobacco or nicotine products are: <ul style="list-style-type: none"> ▪ Adult tooth loss ▪ Gum disease ▪ Mouth cancer ▪ Serious health problems <p>5. Assess ZYN[®] users' perceptions of relative risk associated with ZYN[®] as compared to using other TNP, smoking cessation aids, and never having used any tobacco or nicotine products.</p> <ul style="list-style-type: none"> • The medical conditions under consideration with ZYN[®], other TNP, smoking cessation aids, quitting all TNP, and never having used any tobacco or nicotine products are: <ul style="list-style-type: none"> ▪ Adult tooth loss ▪ Gum disease ▪ Mouth cancer ▪ Serious health problems <p>6. Assess ZYN[®] users' perceptions of relative risk associated with adding ZYN[®] use to existing TNP use.</p> <ul style="list-style-type: none"> ○ The medical conditions under consideration when adding ZYN[®] use to existing TNP use are: <ul style="list-style-type: none"> ▪ Adult tooth loss ▪ Gum disease ▪ Mouth cancer ▪ Serious health problems <p>7. Assess ZYN[®] users' perceptions of relative risk to a person who quits their use of all TNP, compared to a person who quits all TNP except for daily use of ZYN[®].</p>
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	<ul style="list-style-type: none"> ○ The medical conditions under consideration with ZYN[®], smoking cigarettes, and never having used any tobacco or nicotine products are: <ul style="list-style-type: none"> ▪ Adult tooth loss ▪ Gum disease ▪ Mouth cancer ▪ Serious health problems <p>8. Evaluate level of compliance among ZYN[®] users with ZYN[®] usage instruction over the last 7 days.</p> <p>The secondary objective of this study is to describe and compare daily TNP patterns of use among ZYN[®] users and ZYN[®] non-users over a prospective 10-week observational period.</p>
Study design	<p>The retrospective portion of the research will be conducted via web-based surveys to capture self-reported tobacco/nicotine patterns of use over the last 30 days.</p> <p>Additionally, a subset of the participants who agree to participate, will utilize web-based surveys for self-reporting daily usage of TNP over a 10-week period, comprising the prospective portion of the research.</p> <p>The study will be designed to enable univariate assessment and bivariate comparison between ZYN[®] users and ZYN[®] non-users' patterns of use and perceptions of health risk in the absolute, relative to other TNP, and in combination with ZYN[®].</p> <p>Cognitive interviews will be conducted prior to launching the web-based surveys to 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.</p>
Population	<p>The study will include respondents of legal age for TNP use across the 11 U.S. states where ZYN[®] is currently available for retail sale, listed below.</p> <p>Respondents must meet all of the following inclusion criteria to be included in the study:</p> <ul style="list-style-type: none"> • Minimum legal age for tobacco/nicotine use per local state requirements • Current TNP users • Able to read and speak English • Currently a resident of one of the 11 U.S. states where Swedish Match actively sells ZYN[®] through retail stores¹⁵ (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY) • Provide electronic informed consent

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	<p>Respondents who meet any of the following criteria will be excluded from the study:</p> <ul style="list-style-type: none"> • Respond as “don’t know” or “decline to answer” to specific demographics (gender, geographical region, ethnicity, or education) for the purpose of balancing cohorts. • Unwilling or unable to provide electronic informed consent • Employed in any of the following fields or professions: market research, marketing, advertising, manufacturers of TNP, or physicians • Taken part in a consumer research study on tobacco in the past 2 weeks <p>Please see Data Sources below for more detail about where the sample is sourced.</p>
Data sources	<p>Due to the low incidence of ZYN[®] users among the general population, sample for the ZYN[®] user cohort will be recruited directly from purchasers of ZYN[®] via the use of study invitation stickers placed directly on ZYN[®] canisters (referred to as the sticker-program in this protocol). The ZYN[®] non-user cohort will be recruited through online survey panels, with any shortfall of demographic stratification targeted through a phone-to-web recruit. After completion of the retrospective study, respondents will be invited to participate in the prospective study.</p> <p>Consumers sourced through online panels will be recruited by Lightspeed Research Panel (LSR), Survey Sampling International (SSI), and Branded Research Inc. (BRINC). These panels are large commercial consumer opt-in 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.</p> <p>A call center, Directions in Research (DIR), will be commissioned for telephone recruiting to supplement any shortfall in demographic quotas for the non-ZYN[®] group, if not fully recruited through online panel recruitment. Sample will be purchased from the Marketing Systems Group (MSG) to perform telephone recruitment.</p>
Study size	<p>The retrospective study will aim to achieve 1,628 participants, split evenly across ZYN[®] users and ZYN[®] non-users. The number of respondents completing the prospective study is undetermined and will be dependent upon the rate of both participation and survey completion.</p>
Data analysis	<p>The series of individual comments obtained in the cognitive interviews, across multiple interviews will be compiled into a coherent set of summary findings that transcend the individual interview level. Results from the cognitive interviews will be used to finalize the survey design.</p> <p>In the quantitative phase, the analysis will focus on test versus control (ZYN[®] users compared to ZYN[®] non-users) using independent measures and pre- / post-tests utilizing repeated measures for those questions asked only</p>

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	<p>among ZYN[®] users. Additionally, the entire study sample as well as each cohort separately, will be described with respect to demographics and tobacco/nicotine variables (e.g., current TNP used, frequency of TNP used, etc.) using frequencies and percentages for categorical variables and counts, means, medians, standard deviation, minimum, and maximum for continuous variables.</p> <p>Each of the study cohorts will be compared in bivariate analyses (correlations, chi-square tests and t-tests) to ascertain if there are differences between groups (e.g., current TNP used, perceptions of relative risk, etc.).</p>	
Milestones	Start of data collection	November 2017
	End of data collection	February 2018 (Retrospective) / April 2018 (Prospective)

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	11/15/2017	Throughout	Amendment	Changes based on initial Center for Tobacco Products (CTP) feedback on a different MRTP protocol
2				
...				

6. BACKGROUND AND RATIONALE

In 2009, the Family Smoking Prevention and Tobacco Control Act, was signed in to law, giving the FDA the power to regulate the tobacco industry and established the Center for Tobacco Products (CTP) within the FDA. This law gives the CTP authority to regulate the marketing/advertising content and sale of TNP. The FDA requires that the marketing of a new tobacco product is appropriate for the protection of the public health as determined “on the basis of well-controlled investigations” (section 910).¹

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole, including users and non-users of the tobacco product.^{1,2} In making this evaluation the FDA will assess whether the product under review and take into account (1) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (2) the increased or decreased likelihood that those who do not use tobacco products will start using such products.¹ This evidence must be submitted for all currently marketed products as part of a premarket tobacco product application (PMTA). Products marketed in the U.S. after February 15, 2007 must obtain a marketing authorization through a PMTA application or they can no longer be sold in the U.S.¹

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Swedish Match North America (SMNA) began selling ZYN[®] in 2014. ZYN[®] delivers nicotine derived from tobacco, but the ZYN[®] product itself does not contain tobacco leaves. It comes in a small pouch that contains nicotine flavoring elements, and other ingredients required to ensure shelf stability. SMNA has no current intention of marketing ZYN[®] as a smoking cessation product, but rather as a nicotine-delivery product that requires no spitting, produces no off-putting odors, is smoke-free, and comes in a variety of flavors and nicotine strengths. As a result of the Tobacco Control Act requirements, SMNA must submit a PMTA application to continue marketing the ZYN[®] product.

The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA. For this purpose, the primary objective of the Patterns of Use Study is to evaluate TNP patterns of use among ZYN[®] users and ZYN[®] non-users historically, and secondarily, describe behavior over time, under real world conditions.

7. OBJECTIVES AND HYPOTHESES

The overarching research questions within this project can be stated as follows: *How do ZYN[®] users and ZYN[®] non-users use TNP and how do they perceive health risks associated with TNP?* These questions will be studied by means of a retrospective assessment of TNP use among both ZYN[®] users and ZYN[®] non-users (all of whom are of legal age to use TNP in their residential geography). Use and risk perceptions of TNP will be compared across ZYN[®] users and ZYN[®] non-users with independent measures and the use of TNP among ZYN[®] users will be compared with repeated measures.

7.1. Primary Objectives

The primary objectives of the Patterns of Use Retrospective study are to:

1. Compare TNP patterns of use between ZYN[®] users and ZYN[®] non-users over the past 30 days
2. Among ZYN[®] users, compare TNP patterns of use over the last 30 days to TNP patterns of use during the weeks prior to starting ZYN[®].
3. Compare perceptions of absolute risk associated with:
 - smoking cigarettes every day but using no other tobacco products and
 - never having used any tobacco or nicotine products
 between ZYN[®] users and ZYN[®] non-users.
 - The medical conditions under consideration when discussing absolute risk are:
 - Adult tooth loss
 - Gum disease
 - Mouth cancer
 - Serious health problems
4. Compare ZYN[®] users' perceptions of absolute risk, associated with using ZYN[®], to smoking cigarettes every day but using no other tobacco products, and to never having used any tobacco or nicotine products.
 - The medical conditions under consideration with ZYN[®], smoking cigarettes every day but using no other tobacco products, and never having used any tobacco or nicotine products are:
 - Adult tooth loss
 - Gum disease

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- Mouth cancer
 - Serious health problems
- 5. Assess ZYN[®] users' perceptions of relative risk associated with ZYN[®] as compared to using other TNP, smoking cessation aids, and never having used any tobacco or nicotine products.
 - The medical conditions under consideration with ZYN[®], other TNP, smoking cessation aids, quitting all TNP, and never having used any tobacco or nicotine products are:
 - Adult tooth loss
 - Gum disease
 - Mouth cancer
 - Serious health problems
- 6. Assess ZYN[®] users' perceptions of relative risk associated with adding ZYN[®] use to existing TNP use.
 - The medical conditions under consideration when adding ZYN[®] use to existing TNP use are:
 - Adult tooth loss
 - Gum disease
 - Mouth cancer
 - Serious health problems
- 7. Assess ZYN[®] users' perceptions of relative risk to a person who quits their use of all TNP, compared to a person who quits all TNP except for daily use of ZYN[®].
 - The medical conditions under consideration with ZYN[®], smoking cigarettes, and never having used any tobacco or nicotine products are:
 - Adult tooth loss
 - Gum disease
 - Mouth cancer
 - Serious health problems
- 8. Evaluate level of compliance among ZYN[®] users with ZYN[®] usage instruction over the last 7 days.

7.2. Secondary Objective

The secondary objective of this study is to describe and compare daily TNP patterns of use among ZYN[®] users and ZYN[®] non-users over a prospective 10-week observational period.

7.3. Hypotheses

Specifically, this study aims to test the following hypotheses:

1. Considering the past 30 days, ZYN[®] users will report lower usage of other TNP than ZYN[®] non-users.
2. Considering the past 30 days, usage of smoking cessation aids among ZYN[®] users and ZYN[®] non-users will be equivalent.

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3. ZYN® users will report an equal or greater likelihood to quit using other TNP compared to ZYN® non-users.
4. ZYN® users will report lower use of TNP over their past 30 days than the weeks before they started using ZYN®.
5. ZYN® users' and ZYN® non-users will have equivalent perceptions of the absolute risks of certain medical conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems) to a person who
 - smoking cigarettes every day but using no other tobacco products; and
 - has never used any tobacco or nicotine products
6. ZYN® users' perceptions of the absolute risks of adverse effects (adult tooth loss, gum disease, mouth cancer, and serious health problems) due to the daily use of only ZYN®:
 - will be lower than smoking cigarettes every day but using no other tobacco products; and
 - will be higher than never having used any TNP.
7. ZYN® users' perceptions of the relative risks of certain medical conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems) due to the daily use of only ZYN® usage:
 - **will be lower** than the daily use of only **cigarettes**
 - **will be lower** than the daily use of **both ZYN® and cigarettes**
 - **will be lower** than the daily use of only **moist snuff**
 - **will be lower** than the daily use of only **chewing tobacco**
 - **will be lower** than the daily use of only **snus**
 - **will be equivalent to** the daily use of only **e-cigarettes**
 - **will be higher** than the daily use of only **smoking cessation aids**
 - **will be higher** than **never having used any TNP**
8. ZYN® users' perceptions of the relative risks of certain medical conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems) to a person who quits their use of all TNP will be lower compared to a person who quits all TNP except for daily use of ZYN®.
9. ZYN® users' perception of the relative risks of certain medical conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems) **will be higher** for all of the following scenarios:
 - both ZYN® and cigarettes v. cigarettes alone;
 - both ZYN® and e-cigarettes v. e-cigarettes;
 - both ZYN® and moist snuff v. moist snuff alone;
 - both ZYN® and chewing tobacco v. chewing tobacco alone;
 - both ZYN® and snus v. snus alone; and
 - both ZYN® and smoking cessation aids v. smoking cessation aids alone.

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10. Considering ZYN[®] use during the past 7 days, more ZYN[®] users will correctly select “always” or “sometimes” rather than “never” for each of the following:
 - “Placed a ZYN[®] pouch between my gum and upper lip”
 - “Used one ZYN[®] pouch at a time”
11. Considering ZYN[®] use during the past 7 days, more ZYN[®] users will correctly select “never” rather than “always” or “sometimes” for each of the following:
 - “Used one ZYN[®] pouch for more than 60 minutes”
 - “Cut the ZYN[®] pouch open and used the pouch contents”

8. RESEARCH METHODS

8.1. Data Source

8.1.1. ZYN[®] Users Data Source

Due to the low incidence of ZYN[®] users among the general population, sample for this cohort will be recruited directly from purchasers of ZYN[®]. A third-party vendor will place study invitation stickers on product packaging (i.e. each individual package of 15 ZYN[®] pouches) for the six core flavors of ZYN[®] from November 27 – December 11, 2017.

The sticker initiative will target approximately 4,500 stores across the 11 states where ZYN[®] is sold, covering approximately 65 cans per store, for approximately 290,000 ZYN[®] cans in total. Efforts will be made to ensure that stickers are distributed across all locations at the same time and that all ZYN[®] users will have the same chance to participate in this study (See Attachment for an example of the stickers).

The study invitation sticker was approved by the Sterling Institutional Review Board and includes a statement of getting paid for providing opinions, as well as eligibility requirements, such as being of legal age and older, limiting one study per household, and that eligibility is limited to a set number of respondents. Additionally, the sticker will include a website (www.ZYNOpinions.com) to learn more information and a unique registration code.

ZYNOpinions.com will serve as a landing page, hosted by New Honor Society, the agency of record for ZYN[®]. From ZYNOpinions.com, respondents will be taken to a study welcome screen; that screen and all following survey pages will be hosted on (b) (4) or (b) (4) third-party partner servers.

Users who are interested in participating will visit the website address shown on the ZYN[®] canister invitation sticker. Upon entry, the participant will be shown the study welcome screen and redirected to a secure and unique survey link. The first set of questions will be the survey screener which will be designed to qualify the participant using the study inclusion and exclusion criteria (further described in Section 8.3.2 and 8.3.3 “Inclusion/Exclusion Criteria”). Questions within the survey screener will also enable cross-checks to reduce the likelihood of the same respondent repeating the survey over the study period.

By giving nearly every ZYN[®] user an equal chance to participate in the study, a demographically representative sample of ZYN[®] users will be obtained., for the 11 states it is available through retail outlets¹⁵, reflecting the marginal distribution of age, gender, race/ethnicity, and education.

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8.1.2. ZYN[®] Non-User Data Source

When enrollment in the survey for the ZYN[®] user cohort has reached 40%, (b) (4) will analyze the demographic characteristics of the data (i.e., age, gender, race/ethnicity, and education). The demographic characteristics of ZYN[®] users will then be used to stratify the sample of the ZYN[®] non-user. The demographic characteristics of the ZYN[®] user will be monitored daily and the recruitment of ZYN[®] non-user cohort will be appropriately adjusted in order to have consistency across ZYN[®] user and ZYN[®] non-user cohorts.

By recruiting ZYN[®] non-users based on demographic criteria corresponding to enrolled ZYN[®] users, the sample recruitment plan is designed to provide matching populations with regard to socio-demographic characteristics through online panels and telephone recruitment. This approach is designed to avoid sample bias and to obtain ZYN[®] user and ZYN[®] non-user cohorts that are demographically aligned with the populations they are meant to define. Additionally, the ZYN[®] non-user cohort will be sourced from the same 11 states where ZYN[®] is sold.

8.1.2.1. Online Panel Recruitment

Online consumer survey panels Lightspeed Research Panel (LSR), Survey Sampling International (SSI), and Branded Research Inc. (BRINC), will be utilized to recruit the ZYN[®] non-user cohort. These panels 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.

The online panels are opt-in panels where consumers who join make a conscious decision to participate regularly in surveys. 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; and
- 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 identification number to ensure only one respondent per computer can participate in a survey; blocking 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.

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In order to construct matching populations, panelists will be selected based on stored background information collected during the registration survey and ongoing profiling. The sample universe size is based on the size of the desired quotas, in combination with estimated response rates, within specified quota targets. Panelists with matching demographic profiles will be randomly selected for inclusion in the sample universe, until the appropriate sample universe size is reached. Sample will be replicated in batches, to be deployed as needed, throughout the data collection process.

Given the use of multiple panels to achieve the quotas required for demographic representativeness, attempts will be made to balance panel source through sample assignments and daily monitoring. However sample distribution across panels is not a critical factor since the ZYN[®] user cohort is not recruited through panels. The use of differing recruitment methodologies will be discussed further in the Potential Confounders section (8.4.3)

During the fieldwork, sample performance will be monitored daily; additional panelists will be invited to complete the fieldwork within a pre-determined time frame, to ensure a consistent market environment for all respondents. Analysis of response and qualifying rates will be done for each demographic quota. As quota targets are achieved, the random sample selection process will be refined to only target panelists matching those demographic characteristics whose quotas have not yet been reached. If required, additional sample will be selected for specific demographic targets, where the desired quota has not been met, using the sample selection process listed above. This approach is designed to avoid sample bias and to obtain cohorts that are demographically aligned with the populations they define.

Prior to fully launching the surveys, data created by test runs of survey completion for each method of recruitment (sticker on ZYN[®] canister, internet panel, and telephone) will be quality checked prior to the release of the survey to respondents. For the ZYN[®] non-user cohort additional quality checks will be performed through a soft launch, where a limited number of respondents will be recruited to initially take the survey prior to a fully launching the study. The primary objective of this 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, the accuracy of the web-based instrument (i.e., survey), redirects per each recruitment method, all of which work to ensure the primary objectives of the research are met. ZYN[®] non-user 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.

Once the accuracy of the web-based instrument is verified, the ZYN[®] non-user 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 to the appropriate consumers, the invitation will specify that the opinions of TNP users 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 be able to participate as long as 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 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

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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 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.

8.1.2.2. Telephone Recruitment

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will engage a call center, Directions in Research (DIR), for telephone recruiting to supplement any shortfall in demographic quotas for the non-ZYN[®] group, if not fully recruited through online panel recruitment. DIR will purchase sample from the Marketing Systems Group (MSG). The sample purchased will be representative of the 11 states where ZYN[®] is sold and targeted to individuals that meet the required strata, in the following demographic targets: State (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, WY), Race/Ethnicity, Gender, Age and Education. Amount of sample purchased will be determined by the make-up of the ZYN[®] user group, the incidence of product usage by state, estimated response rates by demographics and estimated completion rates. This sample will include a combination of land line and cell phone numbers.

Sample will be stratified based on characteristics of the demographic quotas. DIR will then randomly dial phone numbers, within targeted demographic groups, to recruit for participation in the online research. Respondents who agree to participate, will be emailed a link to the survey. The call center representative will attempt to keep the respondent on the line, while they confirm receipt of the link. Same as the ZYN[®] user cohort, the ZYN[®] non-users who meet inclusion and exclusion criteria (see Section 8.3.2 and Section 8.3.3) in the screener will be invited to complete the survey via the electronic informed consent form (ICF). In addition to the checks conducted within the survey platform to attempt to reduce the chances of duplicate survey entries, the screener will terminate respondents who indicate past participation in tobacco and/or nicotine studies within the past 2 weeks.

Call center staff will receive daily reports identifying which respondents (who have agreed to participate) have, or have not, completed the online Retrospective survey. Based on the report, the call center will schedule reminder emails and reminder calls, to encourage completion. Up to 3 reminders are permitted, per respondent.

In the end, we will generate an ending sample that will be representative of the ZYN[®] user stratification.

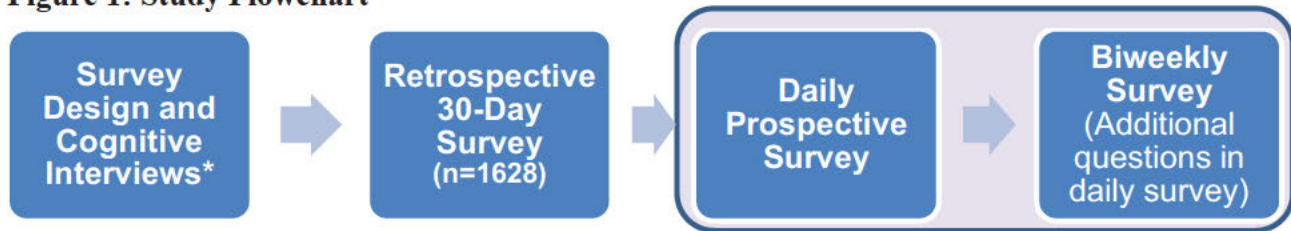
8.2. Study Design

As noted previously, the ZYN[®] Patterns of Use Study seeks to evaluate TNP patterns of use among ZYN[®] users and ZYN[®] non-users through a retrospective study focused primarily on 30-day recall, accompanied by a longitudinal prospective 10-week self-reported daily e-diary study within the United States (U.S.) adult population.

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 8.2.1 for more details about the cognitive interviews.

Figure 1 below summarizes each phase of research.

Figure 1: Study Flowchart



**Data from respondents who take part in the cognitive interview phase will not be in the final data set.*

8.2.1. Cognitive Interviews

Cognitive interviews will be conducted prior to executing the retrospective or prospective studies. 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.⁸ Cognitive interviewing is used as a means for applying qualitative research methods to the understanding of the functioning of survey questions.^{10,11} 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 Prevention⁹. 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. It will also provide input into the clarity, understandability, and interpretation of the patterns of tobacco/nicotine use.

To ensure that the materials are appropriate and sufficiently clear to consumers, the Patterns of Use retrospective and prospective online surveys will be piloted among 10 ZYN® and 10 non-ZYN® users across two rounds of qualitative in-depth, in-person, cognitive interviews in two of the 11 states where ZYN® is available in retail outlets. The second round of cognitive interviews will be a week 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 are 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 conducted by Fieldwork Research Denver and Fieldwork Research Seattle at a local level, utilizing their databases of consumers. Panel members will be contacted via email with a link to the screener. The email will include a general introduction to the

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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 8.3.2 and section 8.3.3). 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.

8.2.2. Retrospective Study

All respondents (regardless of recruitment method they originated from) will access a web survey online via a computer, smartphone, or tablet. The retrospective study is a 10-20 minute survey where participants are asked to provide TNP use history within the past 30 days. A 30 day recall period was selected based both upon review of the available tobacco and nicotine peer reviewed literature utilizing 30-day recall for understanding current and recent usage of TNP² as well as applying the PATH methodology of asking consumers to recall specific TNP use in a 30-day period¹².

Respondents will be able to complete the retrospective online survey via computer, tablet, or smartphone. Following the completion of the retrospective 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 provided as a result of survey completion. Both ZYN[®] users and ZYN[®] non-users recruited via telephone will receive honoraria in the form of a check. Participants from the ZYN[®] non-user cohort recruited via an online survey panel will receive their honoraria in the form of reward points specific to the panel they are a member of and aligned to the fair market value assigned to the survey length.

Additionally, at the completion of the retrospective survey, ZYN[®] users recruited through the sticker program will be asked if they would be interested in being contacted again for follow-up or future research related to nicotine products without tobacco, tobacco, and/or ZYN[®] specific research. If they are interested, they would provide an email address that will be provided to recruiting sources who will log them as interested parties.

8.2.3. Prospective Survey

The prospective study is designed as a 5-minute daily survey/e-diary across 10 weeks for a total of 70 daily surveys completed per respondent. Every 14 days, the daily survey is extended by 5 minutes to obtain additional information. A total of 5 of these extended surveys will be administered over the study period of 10 weeks. These extended surveys are referred to as the “bi-weekly e-diary” for the remainder of this protocol. The prospective study can also be completed via computer, tablet, or smartphone.

The prospective study is designed to have a 10-week observational period after identifying 7-week, 8-week, and 10-week endpoints in the peer reviewed literature regarding smoking cessation studies.^{4,56,7} The longest observational period of 10 weeks was chosen to provide the most comprehensive dataset.

The invitation for the prospective 10-week study will follow the debriefing statement at the end of the retrospective survey. The prospective study is not required for the participant to receive compensation for their participation in the retrospective survey. If an individual agrees to complete the prospective study, their unique link provided for the retrospective study will be used to access the e-diary survey. Respondents will be required to provide their informed consent specific to completing the prospective phase of the study.

Each daily e-diary will ask the participant to report their product usage for the prior day. Each participant will be encouraged to complete their daily and bi-weekly survey earlier in the day to improve the accuracy of their recall of their TNP use the day before. At the end of each daily e-diary a reminder to

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complete the next diary daily will be shown. On the day before the bi-weekly survey, an additional message will be provided reminding the respondents of the longer survey and expressing the importance of completing the next day's survey.

A call center (hotline) with a dedicated toll-free phone number will be established to receive incoming calls from any participant in the prospective 10-week study for questions about the study or to report an adverse event or product complaint (see section 8.4.5.). The call center will also make outgoing calls to respondents who fail to complete two consecutive days in their e-dairy.

Respondents will receive compensation for each week that they complete the daily e-diary surveys. Successful completion of 1 week requires that participants complete a minimum of 5 of the 7 daily e-diaries, (i.e., missing no more than 2 days out of 7 per week). If a participant misses two days in a week, as agreed to in the ICF, a hotline representative will call and remind the participant to complete the last two days and next survey. If the respondent does not complete the next survey, now missing 3 days of surveys in a single week, they will be excluded from further study participation and compensation. If the participant completes the full 10 weeks of data collection, meeting the criteria for completion each week (i.e., not missing more than 2 surveys in 7 days), they will receive an additional bonus compensation at the end of the 10 weeks.

8.3. Study Population

The study population will include U.S. adult population of legal age for TNP use across the 11 states where ZYN® is currently available for sale at retail; those eleven states are Arizona, California, Oregon, Washington, Idaho, Montana, Nevada, Utah, Colorado, New Mexico, and Wyoming.

To meet the objectives of the Patterns of Use Study for ZYN®, this study will include respondents from the following cohorts:

Current ZYN® users	<p>All ZYN® users will be recruited through the canister sticker-program. Users are then confirmed through the screener to:</p> <ul style="list-style-type: none"> ▪ Currently use ZYN® brand of nicotine pouches; ▪ Have used nicotine pouches fairly regularly; and, ▪ Now using ZYN® pouches every day or some days.
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<p>ZYN[®] non-users who use TNP(s)</p>	<ul style="list-style-type: none"> ▪ Have never used ZYN[®] <u>OR</u> ▪ Have NOT used ZYN[®] regularly AND do NOT currently use ZYN[®] every day or some days <p>AND <u>AT LEAST ONE OF THE FOLLOWING:</u></p> <ul style="list-style-type: none"> ▪ Have smoked 100 or more cigarettes during lifetime AND currently smoke cigarettes every day or some days <p style="text-align: center;">AND/OR</p> <ul style="list-style-type: none"> ▪ For any of the following products, have been a regular user AND now uses the product every day or some days: <ul style="list-style-type: none"> • 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)
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The definition of users and the product types constituting TNP for this study are adapted from the PATH study, where a threshold of lifetime use is established for cigarette use and for all other TNP it is based on recollection of ever using TNP fairly regularly and if they now use the product every day or some days.¹²

8.3.1. Sample Size

To compare TNP patterns of use among ZYN[®] users versus ZYN[®] non-users retrospectively over the past 30 days an *a priori* power analysis was conducted to determine appropriate sample sizes. Sample sizes were determined using the following assumptions; a small effect size of .01 (when variability is considered), a continuous outcome (using Chi-squared statistic [z test] with continuity correction), a power level of .80, and a Type 1 error rate of .05. This power analysis suggested a sample size of 814 per cohort would conservatively detect such an effect.

Additional power analysis was performed to confirm the sample size of 814 offered sufficient power ($1-\beta \geq 0.8$) for McNemar's tests, which will be used to analyze paired dichotomous outcomes. Sample sizes were determined using the following assumptions; an odds ratio among discordant respondents of 2 (i.e., 2 times the number of respondents fall in cell *c* versus *b*, or vice versa), an alpha of 0.0025, which accounts for 20 multiple comparisons under a Bonferroni correction, and that 20% of the sample would be discordant pairs. Under these assumptions a total sample of 600 respondents would be required to reach a power of 0.8, which implies sufficient power under the n=814 sample size.

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Table 1: Sample Size

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8.3.2. Subject Selection: Inclusion Criteria

In addition to the already mentioned cohort definitions to be included in this study, respondents must meet the following criteria to be included:

- Minimum legal age for tobacco/nicotine use per local state requirements
- Able to read and speak English
- Currently a resident of one of the 11 U.S. states where ZYN® is available in retail outlets¹⁵ (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY)
- Individuals who provide electronic informed consent

8.3.3. Subject Selection: Exclusion Criteria

Respondents who meet any of the following criteria will be excluded from study:

- Respond as “don’t know” or “decline to answer” to specific demographics (gender, geographical region, ethnicity, or education) for the purpose of 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 of being screened for qualification to the retrospective study

8.4. Outcomes**8.4.1. Outcomes for Primary Objectives**

Outcome variables supporting attainment of the primary objectives include those variables collected to evaluate patterns of TNP use over the past 30 days and variables collected to evaluate risk perceptions. Figure 2 presents example outcome variables related to the primary objectives of the retrospective study.

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Figure 2: Examples of Variables Supporting the Primary Objectives

A 30-day recall of use was selected to represent a duration of time where TNP use patterns are more stable, yet easy to remember. Additionally, utilizing the 30-day recall of TNP use is consistent the methodology employed in the PATH study. Further, the use of responses “every day” / “some days” / “not at all” are also consistent with the scales used in PATH to capture TNP use¹².

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The products for the relative risk questions are those that are considered the competitive set for ZYN®, as well as the use of ZYN® in combination and the complete avoidance of TNP.

PRODUCT LIST:

1. cigarettes
2. e-cigarettes
3. moist snuff
4. chewing tobacco
5. snus
6. aids to help stop smoking
7. both cigarettes and ZYN®
8. never having used any tobacco or nicotine products

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A 7-day time frame for understanding compliance with product instructions was based on ease of recalling most recent ways of using the product.

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8.4.2. Outcomes for Secondary Objective

Figure 4 presents example outcome variables for the secondary objective, specifically, objectives related to patterns of TNP use over the 10-week observational period in the prospective study. Patterns of use includes volume, frequency of use, and change in tobacco/nicotine use status (i.e., a change from active use to quitting) and change in intention to quit (i.e., a change from no intent to quit to having an intent to quit based on MTSS¹⁶).

Figure 3: Example of Variables Supporting the Secondary Objectives

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8.4.3. Potential Confounders

As stated previously, the fielding will begin with ZYN[®] users and upon 40% being complete, the ZYN[®] non-user fielding will commence. This element of the recruitment plan has both benefits and limitations. First, the benefit is the ability to align socio-demographic variables between sample cohorts in a circumstance where, *a priori*, ZYN[®] users socio-demographic variables are not known. The primary disadvantage is the potential risk that the separated periods of fielding may introduce confounding factors. Accordingly, the recruitment plan prioritizes a known confounding factor over a potential confounding factor.

Since the ZYN[®] non-user cohort will be sampled such that it reflects the basic socio-demographic characteristics (e.g., age, gender, race/ethnicity, and education) of the ZYN[®] user cohort. This sampling approach will be utilized to mitigate potential confounding factors. Nevertheless, confounding variables may include respondent demographics (age, gender, ethnicity, education, and geographic region), frequency of tobacco use, and current TNP used. 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 based on ZYN[®] user group

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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, the potential introduction of confounding factors could arise from differing sample recruitment methodologies: 1) ZYN® users through stickers on product canisters in retail stores and 2) ZYN® non-user from panels. A description of the 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.

8.4.4. Other Variables

Some additional variables will be collected that will not be used to support the primary and secondary objectives. For example baseline characteristics of age, gender, ethnicity, education, and geographical region will be collected to help achieve a representative sample.

8.4.5. Adverse Events and Product Complaints

As this study is observational by design and is conducted in an actual use setting, adverse event (AE) and product complaint reporting will follow a passive surveillance mechanism, recording spontaneously reported events. Participants will be informed that a dedicated toll-free hotline has been established for use during the study so that participants can report product quality complaints and adverse health events associated with the use of ZYN®. The hotline staff are trained on the reporting procedures and when receiving spontaneous reports of adverse health events or product complaints, the hotline staff documents these reports on the designated form (Adverse Event Reporting Form or Product Complaint Reporting Form). The participant who reports an AE or product complaint will have the choice to continue or withdraw from the study.

Product complaint forms will be forwarded to the Sponsor's Consumer Contact Line. All reported AEs will be assessed by a Health Care Professional (HCP) for seriousness and causality. All Serious Adverse Events (SAE) will be reported to the IRB.

At the conclusion of the study, all AEs and product complaints will be listed in a summary report and provided to the study Sponsor.

A detailed explanation of the reporting and documentation procedures are outlined in the study Adverse Event Management Plan (See Attachment 4).

8.5. Data Management

(b) (4) 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.

(b) (4) 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;

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

8.5.1. Data Quality Control

The data collected for this study will be monitored for adherence with the study protocol. All data will be collected using a programmed web survey. Prior to initiating the study, appropriate edit programming will be conducted to assure 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 **(b) (4)** 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 respondents that will be utilized for the analysis. 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.

8.5.2. 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.

8.5.3. Data Transfer

(b) (4) will transfer final data files to SMNA in a zipped file via a secure FTP site at the conclusion of the study. SMNA will confirm receipt of these files. File name will include the study name and date of transfer.

8.5.4. 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.

8.6. Data Analysis

A formal and more detailed statistical analysis plan (SAP) will be prepared by **(b) (4)** after finalization of the study protocol and survey.

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8.6.1. Qualitative 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.⁸ Systematic content analysis will provide the data to be analyzed thus assuring 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 and the product information sheet, 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 whether questions have issues with comprehension, retrieval, decision-judgment, and response across all subjects¹². 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.

8.6.2. Quantitative data analysis

The main analyses for the study will consist of descriptive, bivariate, and multivariable statistical analysis. 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.

Variables will be categorized based on pre-determined threshold or logic required to form the cohort of interest. Quality control of the data will also be performed, this will focus on identifying potential outliers that exist in the dataset. Identification of potential 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.

The main analyses for the study will consist of descriptive, bivariate, and multivariable statistical analysis.

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 (SAS 9.4), transform the data (if appropriate) so they are suitable for analysis, and produce a data codebook that describes the variables in the data sets. 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 8.51 “Quality Control”.

8.6.3. Statistical Considerations

The analysis will focus on test versus control (ZYN® users compared to ZYN® non-users) using independent measures and pre- / post-tests utilizing repeated measures for those questions asked only among ZYN® users. Statistical considerations for both Primary and Secondary Objectives are described below.

8.6.3.1. Statistical Considerations for Primary Objectives

8.6.3.1.1. Descriptive analysis

Descriptive analysis will provide summary statistics for all variables collected in both the retrospective and prospective studies. Summary statistics will include counts and proportions for categorical variables and means, standard deviations, medians, minimums and maximums for ordinal and continuous variables. Descriptive statistics will be used to describe the sample as well as verify the quality of the data.

8.6.3.1.2. Bivariate analysis

Bivariate analysis will be provided, broken out by the ZYN[®] users and ZYN[®] non-users as described in the Study Population section of this protocol (Section 8.3). Each potentially confounding variable (e.g., socio-demographics, etc.) along with each outcome variable supporting the primary objectives (see Outcomes for Primary Objectives 8.4.1) will be included in the bivariate analysis. The only exception to this being those variables collected that are ZYN[®] specific, and therefore do not have a corresponding variable collected for the ZYN[®] non-user cohort.

Bivariate comparisons will be conducted to test statistical differences between ZYN[®] users and ZYN[®] non-user cohorts, as well as repeated measures testing in ZYN[®] users cohort on the outcomes supporting the primary objectives listed in the Outcomes section (8.4.1) above.

Specifically, chi-square tests will be conducted for categorical variables and one-way t-tests will be conducted for continuous variables. All results will be presented in tables organized by primary objectives, and statistical significance will be determined at $\alpha=.05$ significance level.

8.6.3.1.3. Multivariable analysis

The proposed sampling plan is intended to generate study cohorts balanced based on key demographics. However, balance on key demographics cannot be guaranteed due to limitations in fielding. If balance is not attained, as revealed by bivariate analysis, multivariable analysis will be conducted to adjust for the differences. Multivariable analysis will include generalized linear models (GLMs) where key demographics will be included as covariates. The distribution selected for the GLMs will be determined by the distribution of the dependent variable. Results will include parameter estimates and p-values for the primary independent variables, with adjusted means to help facilitate interpretation.

8.6.3.2. Secondary Objectives

8.6.3.2.1. Descriptive analysis

Descriptive analysis for the secondary objectives will consist of summary statistics for some outcomes and graphical presentation of others. Descriptive statistics (counts and proportions) will be presented for outcomes supporting the patterns of use objectives to characterize TNP patterns of use, cessation, and changes to intent to quit over the 10-week observational period. Outcomes supporting the patterns of use objective to characterize changes in the ratio, volume, and frequency of TNP use over the 10-week observational period will be presented in graphically, comparing the ZYN[®] users and ZYN[®] non-users.

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8.6.3.2.2. Bivariate analysis

Bivariate analysis will be provided, broken out by ZYN[®] users and ZYN[®] non-users as described in the Study Population section of this protocol (Section 8.3). Outcomes supporting the patterns of use objective to characterize TNP patterns of use, cessation, and intention to quit (based on MTSS¹⁶) over the 10-week observational period will be compared using chi-square tests for categorical variables and t-tests for continuous variables. Results will be presented in tables where statistical significance will be determined at $\alpha=.05$ significance level.

8.6.3.2.3. Multivariable analysis

Multivariable analysis will be performed to compare the rate of change in the ratio, volume, and frequency of TNP use for the ZYN[®] users and ZYN[®] non-user cohorts over the 10-week observational period. Weekly reporting of data will be considered valid if a minimum of 5 out of 7 days in a single week are complete. To ascertain whether the ZYN[®] cohort exhibits a rate of change on these outcomes significantly greater than 0, or significantly different from the ZYN[®] non-user cohort, a series of generalized linear mixed models (GLMMs) will be used. GLMMs will account for the longitudinal nature of the data (i.e., violation of the independence assumption within the data). The dependent variables will be the total volume, ratio, and frequency of TNP used over the week.

When testing whether the rate of change in volume, ratio, and frequency of use is significantly different than 0, the primary independent variable will be time (as a continuous measure) and the model will be fit using data from only the ZYN[®] user cohort. When testing whether the rate of change in volume, ratio, and frequency of use in the ZYN[®] user cohort is significantly different than the ZYN[®] non-user cohort, the primary independent variable will be the interaction of time (as a continuous measure) with the cohort identifier. Confounding variables will be selected based on results generated in the bivariate analysis of potential confounders outlined in support of the primary and objectives (section 8.43).

Results from the multivariable analysis will be reported for each model separately, and included relevant parameter estimates, confidence intervals, and p-values.

8.6.4. Quality control

There are several aspects to quality control as described below:

Survey Instrument Programming

- The web-based survey will be created by one programmer using the Decipher[®] software for web-based survey programming (v117, Fresno, CA).
- Then, the survey will be checked by another programmer independent of the day-to-day project to ensure all programming is correct.
- After the survey has been programmed, the survey link and content will be reviewed by a separate team within the operations group from the perspective of the respondent (i.e. the link is reviewed online and not within the Decipher[®] software).
- All logic, ranges, termination points, “other specify” and open ends are checked to ensure they match the intentions of the questionnaire

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Qualitative Study

- As mentioned in section 8.2.1 “Cognitive Interviews” a qualitative study will be conducted to validate the online survey instrument in a live setting with 20 respondents who meet 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

- Respondents who lack variability in their responses to a battery of questions (“straight liners”) will be identified using standard deviation customized for each battery found in the survey. Those people whose responses have a standard deviation of zero, a very low standard deviation or a discernable pattern in their answers inconsistent with any coherent understanding of the question will be flagged and examined individually. Respondents who are straight lining or giving patterned responses consistently throughout the survey will be individually scrutinized, and potentially removed from the analysis.
- Those data points which appear to be unattainable in real life (e.g., respondent who indicates they smoke 5,000 cigarettes in one day) will be removed from the analysis.
- Preliminary outliers will be identified using 3x standard deviations from the mean or those beyond the 5th and 95th percentiles. Each data point will be examined individually to determine whether the response represents realistic data. More specific details on handling of outliers will be provided in the SAP. Outliers will be identified and 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.
- All statistical analyses and results output will be checked by another researcher for quality control.

8.7. Limitations of the Research Methods

The data collected will be based on responses to a web-based survey. The perceived health risk assessments are intended to simulate possible real world perceptions, 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.

Some respondents will be recruited based on their membership with an online market research panel. As a result, their 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

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consumers), the recruitment plan is designed to mirror the underlying populations (see Section 8.3 “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. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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 in accordance with CTP guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole¹⁴. Additionally, **(b) (4)** conducts all of 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.

9.2. 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 also 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.

9.3. Respondent information and consent

Prior to beginning the main survey, 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, 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. Contact information for the IRB is also provided if the respondent has any questions or concerns about their rights as a research participant

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

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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.

Lastly, the statement of informed consent provides potential respondents with a hotline to contact to address any concerns they may have. Contact information is given if the respondent has any specific questions about the survey instrument or incentives for participation. In addition, a hotline will be provided for the participant to report any adverse events experienced. Product-related questions will be referred to SMNA’s normal product complaint process.

9.4. Confidentiality

Swedish Match North America, Inc. as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Swedish Match North America, Inc. 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 the sponsor. If the respondent name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. 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.

10. REFERENCES

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11. ATTACHMENTS

ATTACHMENT 1: RESTROSPECTIVE QUESTIONNAIRE

ATTACHMENT 2: PROSPECTIVE QUESTIONNAIRES

ATTACHMENT 3: STICKER INVITE

ATTACHMENT 4: ADVERSE EVENT MANAGEMENT PLAN

(b) (4)

12. 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):

(b) (4), (b) (6)

Institution:

(b) (4)

Signature:

(b) (6)

Date: 13 November 2017

(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 the sponsor; a protocol amendment will not be required.

13. SPONSOR SIGNATURE

Swedish Match North America Signature(s)

The ZYN[®] Patterns of Use Study primarily seeks to understand TNP patterns of use among ZYN[®] users and ZYN[®] non-users through a retrospective 30-day recall study. Secondly, describe behavior over time through a prospective 10-week daily e-diary study. Current residents of one of the 11 U.S. states where Swedish Match actively sells ZYN[®] through retail stores (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY) are eligible to participate.

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

I agree to the terms of this Study protocol.

Name (typed or printed):

(b) (4), (b) (6)

Institution:

Swedish Match North America

Signature:

(b) (6)

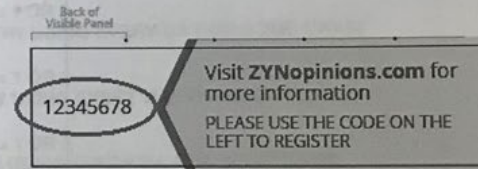
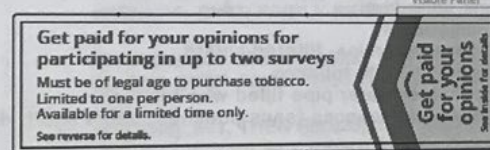
Date: 13 November 2017

(Day Month Year)

LAST PAGE

FOR ZYN SAMPLE ONLY:

To access the survey, in the box below please enter the registration code found on the survey invitation sticker present on the can of ZYN®. See below for example of where to find the registration code.



ENTER THE REGISTRATION CODE HERE:

_____ [PROGRAMMERS: USE ZYN STICKER CODE LIST. DO NOT ALLOW MORE THAN ONE ENTRY OF THE SAME CODE ONCE THE SCREENER HAS BEEN ANSWERED]

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