Methodological Considerations for Actual Use Study Designs

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Altria

Acknowledgements

CORESTA NWIP #351 Group

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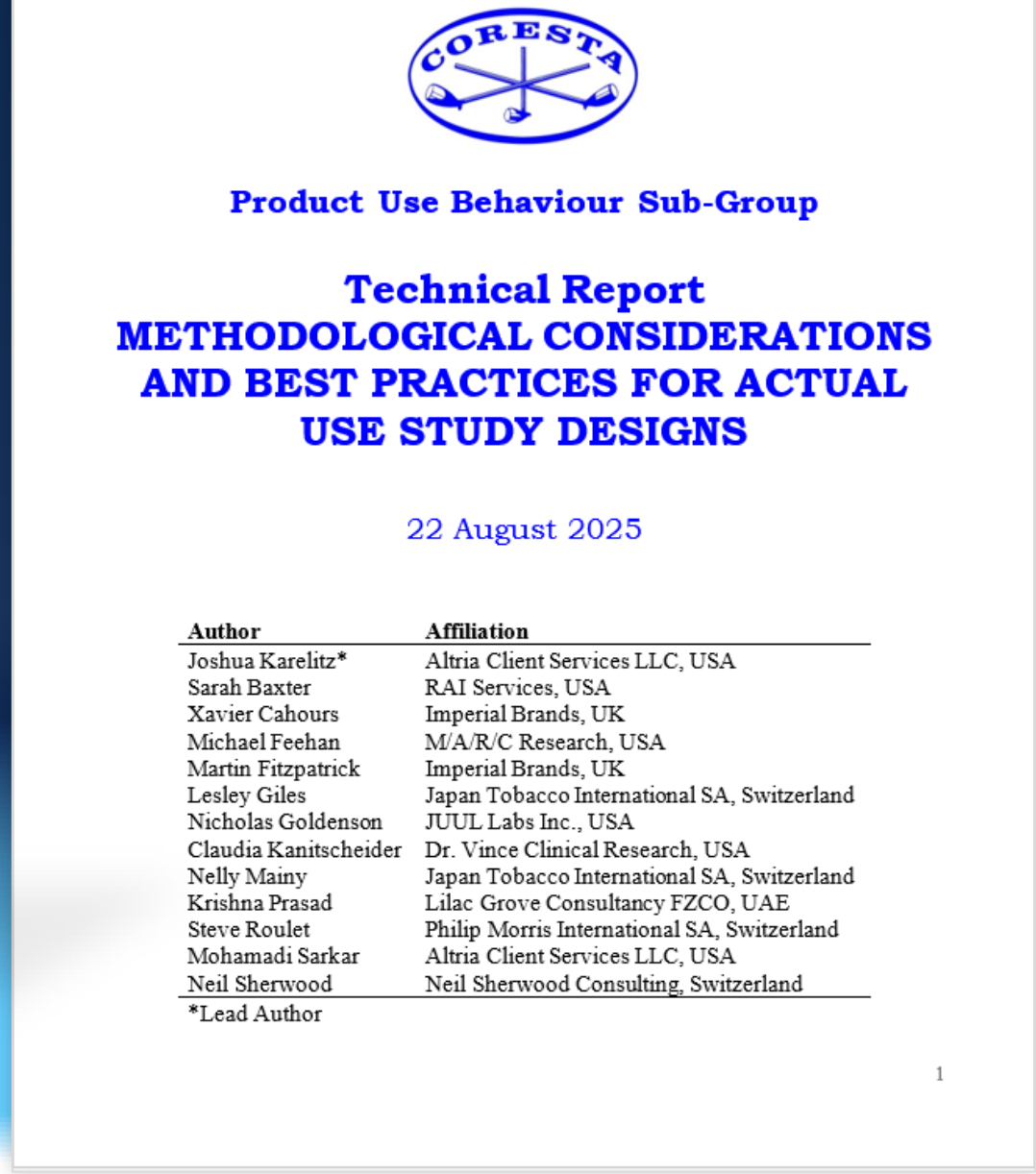

CORESTA

Product Use Behaviour Sub-Group

Technical Report
METHODOLOGICAL CONSIDERATIONS AND BEST PRACTICES FOR ACTUAL USE STUDY DESIGNS

22 August 2025

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Objectives

PROVIDE
foundational information
on regulatory rules/guidance in context of an AUS

CONDUCT
a literature review
of published AUS supplemented with methodology from publicly available presentations and FDA documents

IDENTIFY
practical recommendations
for conducting and reporting AUS based on themes emerging from the literature review

AUS=Actual Use Studies; FDA=Food and Drug Administration.

Agenda

Introduction to AUS

Regulatory Framework

Literature Review

Recommendations for AUS

Introduction to AUS

PURPOSE

AUS assess use of premarket tobacco products by adults to gather ecologically valid data

REGULATORY IMPORTANCE

AUS data inform regulatory decisions on new tobacco products

Provides information on how current tobacco consumers would use the premarket product and its impact on the use of other tobacco products

LACK OF FORMAL GUIDANCE

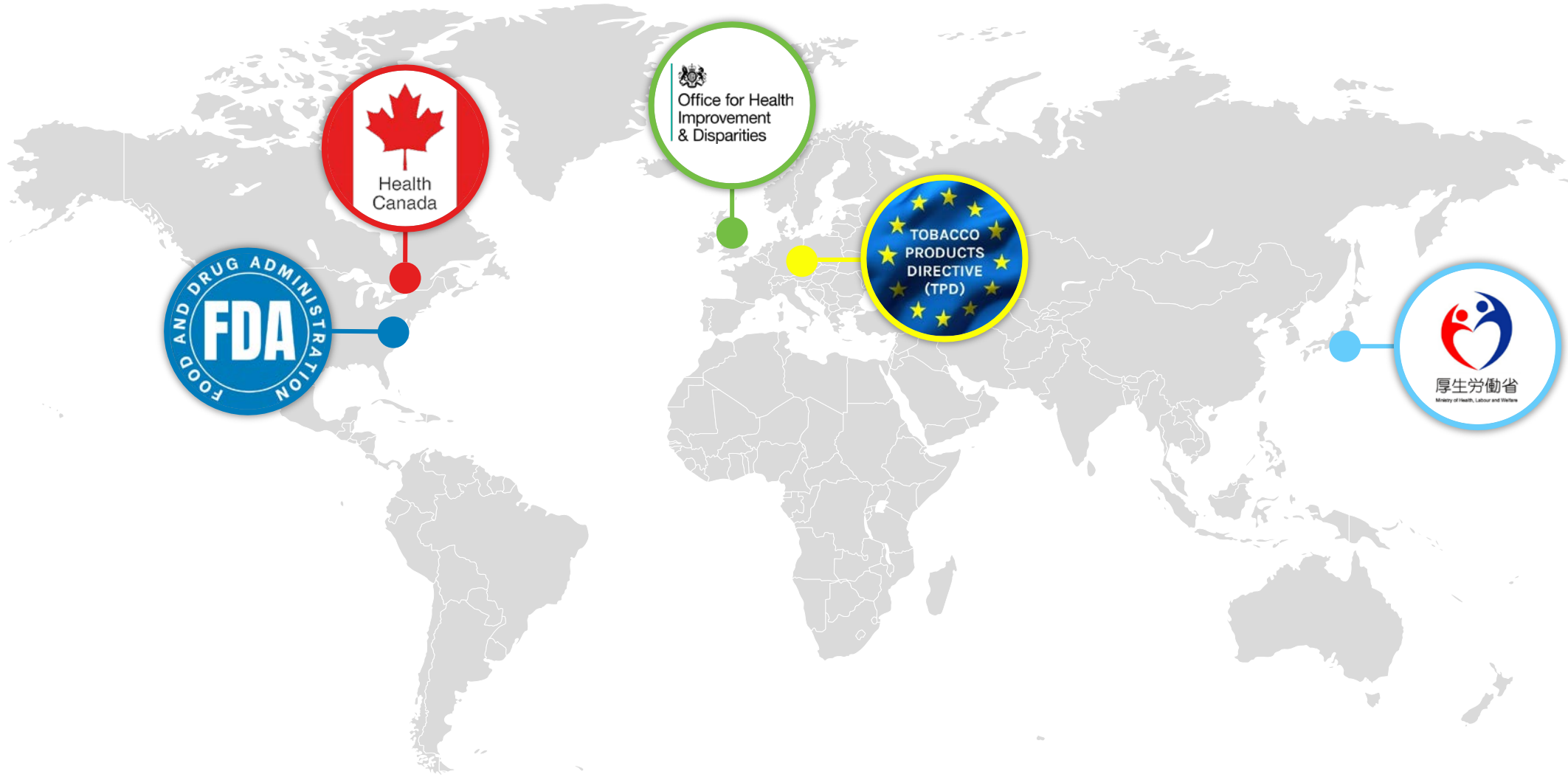
No published guidelines on the design and conduct of AUS within the tobacco regulatory domain

METHODOLOGY ADAPTED FROM PHARMACEUTICAL INDUSTRY

Initially developed to provide data to support regulatory decisions of whether prescription drugs could be switched to over-the-counter sale

"premarket" refers to tobacco/nicotine products that have not received marketing authorization from the respective regulatory body.

Regulatory Framework



AUS Working Definitions

Criteria	Determinants
Population	Adult tobacco consumers
Intervention	Premarket tobacco/nicotine product provision
Comparison	N/A (uncontrolled)
Outcome	Longitudinal ad libitum premarket tobacco/nicotine product use behavior
Study Setting	Near real world setting (i.e., participants' natural environments)

"Premarket" refers to tobacco/nicotine products that have not received marketing authorization from the respective regulatory body.

Literature Search

PRIMARY LITERATURE SEARCH

Conducted:
September 2023 and December 2024

PubMed keywords/terms:

(“actual use” OR “home use” OR "real world evidence" OR "real world data" OR "real world condition" OR "real world setting")

AND (“tobacco” OR “nicotine”)

AND ("over time" OR "longitudinal" OR "prospective" OR "weeks" OR "months" OR "daily")

SUPPLEMENTAL SEARCH

POSTERS
PRESENTATIONS
STUDY RECORDS

- MRTP application materials available via the FDA Center for Tobacco Products’ website
- Tobacco manufacturers’ online repositories of scientific publications
- Abstracts on the CORESTA website
- US Clinical Trials website
- Pre-print repositories: Research Square and Qeios

Study Inclusion Criteria

Longitudinal assessment of ad libitum premarket tobacco product use behavior among adults

Did not include randomization or control condition

Provided premarket product to participants at no cost

Published in peer-reviewed journals no earlier than 2009

"Premarket" refers to tobacco/nicotine products that have not received marketing authorization from the respective regulatory body.

Results

Characteristics of Included Studies

Search Results

Primary Literature Search

68 PubMed Results

9 Full Texts Screened

4 Eligible Articles

Supplemental Search

67 Relevant Records

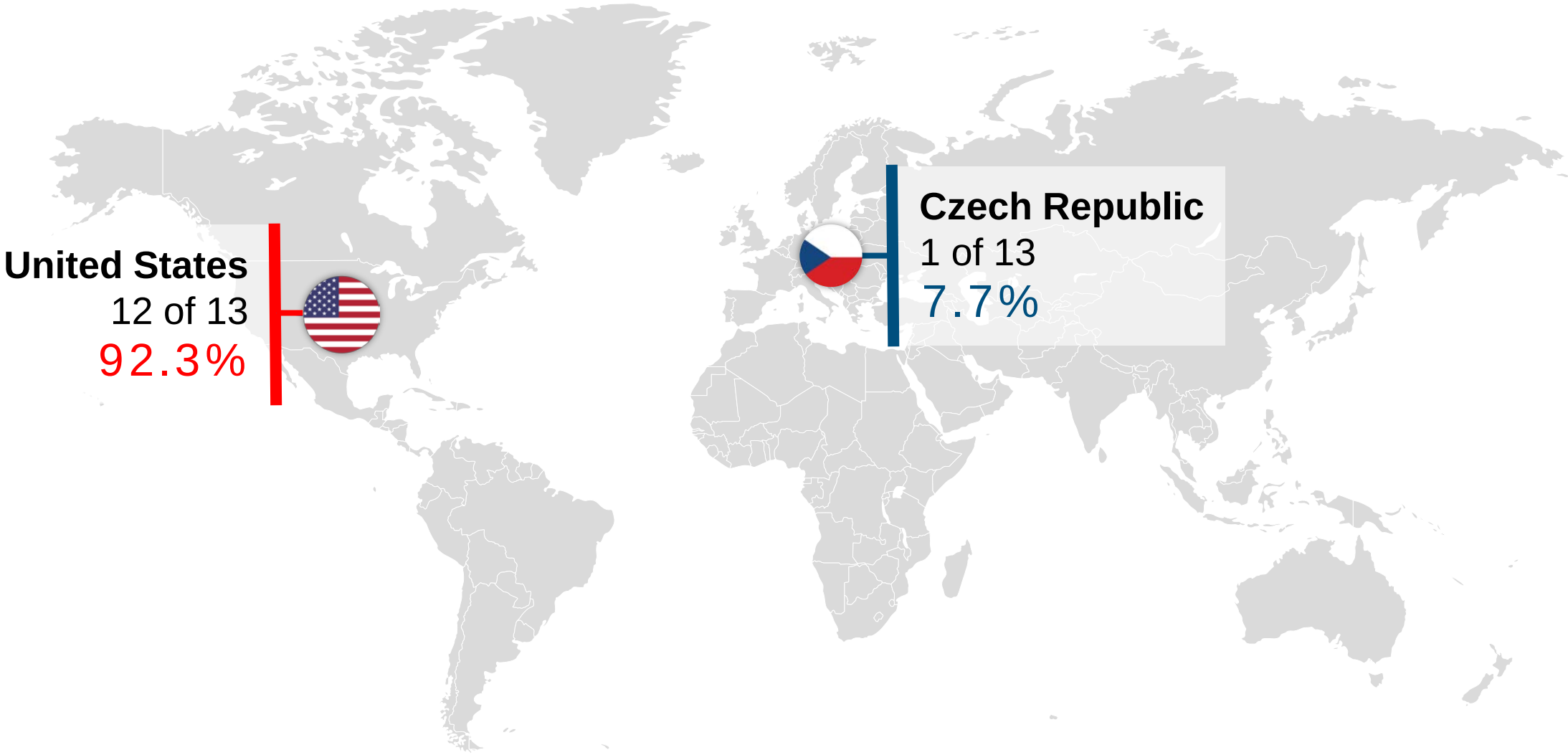
13 Records Screened

9 Eligible Records

13 Unique Studies

Publication/Presentation Years

Study Locations

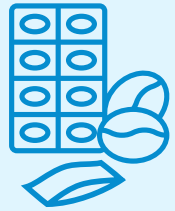


Research Products

5 STUDIES
heated tobacco products

4 STUDIES
nicotine pouch products

3 STUDIES
ENDS



1 STUDY
gum, lozenges, and pouches

Emergent Themes

- Study Objectives
- Study Design
- Population and Sample
- Study Procedures
- Ethical Considerations and Safety Monitoring
- Measures
- Data Collection Methods
- Endpoints
- Data Analysis
- Synthesis

Emergent Themes: Study Objectives

ASSESSMENT OF

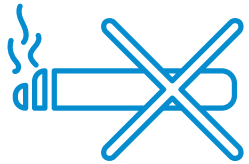
Continuous Use

Evaluate whether use of the research product becomes continuous following a trial period

Reduction in Use

OF PRIOR TOBACCO PRODUCTS

Assess whether there is a ≥50% reduction in consumption of the prior tobacco product compared to baseline levels by the end of study



Switching or Abstinence

FROM PRIOR TOBACCO PRODUCTS

Determine whether participants fully switch to the research product or achieve abstinence from the prior product regardless of subsequent nicotine use

EMERGENT THEMES:
Study Design

PHASES

Enrollment
4 of 13 studies
30.8%

Baseline
7 of 13 studies
53.8%

Product Trial
6 of 13 studies
46.2%

Actual Use/Observation
13 of 13 studies
100%

DURATION

Overall ranged from six weeks to six months

Most tended to be six to eight weeks
10 of 13 studies
76.9%

Actual Use/Observation Phase ranged from four weeks to six months

Most tended to be five to six weeks
11 of 13 studies
84.6%

EMERGENT THEMES:

Population and Sample

STUDY POPULATIONS

Adult tobacco consumers of legal purchasing age
(based on lifetime and current use)

Ten studies reported additional criteria:

Most recruited those not intending to quit current product
9 of 13 studies
69.2%

Intention/openness to try/use the research product
9 of 13 studies
69.2%

SAMPLE SIZE

Sample sizes included in analyses ranged 99 to 1160

- One study reported an a priori sample size calculation
- Two reported demographic quotas for sample recruitment

EMERGENT THEMES:

Study Procedures

RECRUITMENT

Many studies reported used third-party commercial databases

6 of 13 studies

46.2%

Typically, two-stage screening:

1. Online/phone
2. In-person

INITIAL RESEARCH PRODUCT INTRODUCTION

Product information only

4 of 13 studies

30.8%

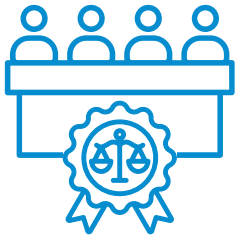
Physical product examples available for interaction (without product trial)

ACTUAL USE/OBSERVATION PERIOD

- Free choice among the available research product variants within study-specific limits
- Products provided at no cost; one study required purchase via provided pre-paid cards
- Participants could use research and other tobacco products ad libitum (or not at all)
- Unused products returned at end of each week or end of actual use period

EMERGENT THEMES:

Ethical Considerations and Safety Monitoring



ETHICAL REVIEW & INFORMED CONSENT

All studies approved by an
Institutional Review Board or Ethics Committee

Informed consent obtained

SAFETY MONITORING

All had some level of safety monitoring for adverse experiences
(not all reported their monitoring process)

Reported methods included surveys or a phone number for reporting adverse experiences, product issues, or procedural difficulties

CLOSE-OUT PERIOD

Six studies included a post-use period for passive safety monitoring and study-end activities

EMERGENT THEMES: Measures

PRODUCT USAGE DATA

All studies tracked research and other tobacco product use (frequency and quantity)

Category-specific usage for studies of **OTP**

- Measures included placement in mouth and simultaneous product use

SUBJECTIVE MEASURES

Many studies assessed **liking, sensory experience, or ease of use**
7 of 13 studies
53.8%

BEHAVIORAL INTENTIONS

Intentions to use, switch, or purchase evaluated at study end
7 of 13 studies
53.8%

ADDITIONAL MEASURES

Nicotine dependence
2 of 13 studies
15.4%

Motivation to quit smoking
2 of 13 studies
15.4%

Respiratory symptoms
1 of 13 studies
7.7%

Unintended Use
4 of 13 studies
30.8%

EMERGENT THEMES:

Data Collection Methods

RESEARCH AND/OR TOBACCO PRODUCT USAGE TRACKING

Nearly all studies required participants to log research and other product use in an electronic or online database

12 of 13 studies

92.3%

REPORTING FREQUENCY

Most studies recorded previous-day usage

10 of 13 studies

76.9%

Others recorded on:

30-day	7-day	Stick-by-stick basis
1 of 13	1 of 13	1 of 13
7.7%	7.7%	7.7%

ADDITIONAL DATA COLLECTION METHODS REPORTED

- Surveys at study sites
- Follow-up phone calls
- In-person interviews

EMERGENT THEMES:
Endpoints

RESEARCH PRODUCT USE

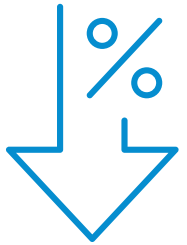
Usage measured by amount, frequency, and variant (flavor or nicotine level)

Some studies reported if participants met specific usage threshold (“established use” or “started using”)
5 of 13 studies
38.5%

IMPACT ON PREVIOUS TOBACCO PRODUCT USED

All studies reported change in use of previous tobacco product (either absolute or relative to baseline)

Many studies reported proportions of participants who reduced previous tobacco product consumption by ≥50%
9 of 13 studies
69.2%



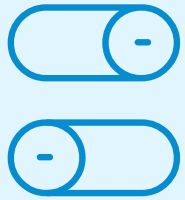
USE PATTERNS

All reported on use of:

other tobacco products

dual use

complete switching



EMERGENT THEMES:
Data Analysis

ANALYSIS APPROACH

All studies used descriptive methods; three included inferential analyses

Characterized patterns of research product and other tobacco product use

REPORTED METRICS

- Absolute/relative frequency
- Mean
- Median
- SD
- 95% CI
- Missing data

USAGE REPORTING

Frequency and quantity:

- Per day
- Per week
- Per month
- Across the entire observational period

SD=Standard Deviation; CI=Confidence Interval

Synthesis

SIMILARITIES

1. Study objectives
2. Study duration
3. Ethical considerations
4. Product provision methods
5. Actual use period procedures
6. Assessment of research product and incoming tobacco product use

DIFFERENCES

1. **Reporting of additional measures**
2. **Threshold for established use of research product**
3. **Endpoint definitions**
4. **Reporting of initial product introduction**

Best Practice Recommendations

Best Practice Recommendations

PUBLISH

Publishing results openly supports credibility and informs regulators, public health, and the public

Some studies presented at conferences, but lack of indexing (e.g., PubMed, Google Scholar) and peer review limit reach

MEASUREMENT QUALITY

Use robust data capture and validated self-report instruments per **CORESTA** CROM guidance

STANDARDIZATION NEEDED

Inconsistent outcome definitions (e.g., switching/transition/partial replacement) hinder cross-study comparisons —adopt CORESTA CROM best practices: **https://www.coresta.org/crom**

REGULATORY CONTEXT

Best practices should come from the regulator

There's no one-size-fits-all— METHODS NEED TO BE TAILORED TO PRODUCT CATEGORY

Emerging Methodologies for Consideration

ADAPTIVE STUDY DESIGNS

Hybrid designs (e.g., Sequential Multiple Assignment Randomized Trial) enable adaptive testing of variables to increase study flexibility and precision

REMOTE PRODUCT DISTRIBUTION AND DATA COLLECTION

Broaden geographic reach and increase diverse participant inclusion

CONNECTED DEVICES AND WEARABLES

Integration of wearable devices tracks physical activity and well-being to complement self-reported data

HOLISTIC ENDPOINTS AND STANDARDS

Expanded endpoints such as emotional and social health

cdisc standards improve data management and regulatory alignment

THANK YOU!