Statistical Analysis Plan

Reduce tobacco use in people living with HIV in Switzerland: A pragmatic randomized trial within the Swiss HIV Cohort Study (RETUNE)

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorization:	Risk category A according to ClinO, Art. 61
Study Registration:	NCT06789692
Sponsor Investigator:	Prof. Matthias Briel, MD PhD Division of Clinical Epidemiology, University Hospital Basel Totengässlein 3, 4051 Basel +41 61 265 38 15 Matthias.Briel@usb.ch
Investigated Intervention:	Offer of a menu of different tobacco smoking substitution products (nicotine pouches, electronic nicotine delivery systems, and nicotine patches)
Protocol ID BASEC:	2024-02417, Version 1.2 (dated 08.08.2025)
Version and Date:	Version 1.0 (dated 27.05.2026)

LIST OF PROJECT LEADERS AND OTHER KEY PERSONS INVOLVED IN THE TRIAL

Title	Names	Institution	Role and Function/Responsibility in the project
MD PhD	Matthias Briel	Division of Clinical Epidemiology, University Hospital Basel, University of Basel	Sponsor Investigator; Responsible for the overall trial implementation
MD PhD	Alain Amstutz	Division of Clinical Epidemiology, University Hospital Basel, University of Basel	Co-Principal Investigator; Responsible for the overall trial implementation Supervises the conduct of the statistical analysis
MD PhD	Christof Manuel Schönenberger	Division of Clinical Epidemiology, University of Basel, University Hospital Basel	Co-Principal Investigator; Coordinating all aspects of the trial Conducts the statistical analysis
PhD	Frédérique Chammartin	Division of Clinical Epidemiology, University Hospital Basel, University of Basel	Trial Statistician; Input on the data analysis Supervises the conduct of the statistical analysis

SAP SIGNATURE FORM

Study Title	Reduce tobacco use in people living with HIV in Switzerland: A pragmatic randomized trial within the Swiss HIV Cohort Study
Study ID	NCT06789692

The Sponsor-investigator, the other principal investigators, and all people involved in the statistical analysis of the trial have approved the statistical analysis plan version 1.0 (dated 07/04/2026) and confirm hereby to conduct the analysis according to the statistical analysis plan.

Co-Principal investigators:

Name: Prof. Matthias Briel, MD PhD

Date: 27.05.2026 | 21:45 MESZ Signature: DocuSigned by: Dr Matthias Briel DEABFE19BDFC46B...

Name: Alain Amstutz, MD PhD

Date: 27.05.2026 | 11:59 MESZ Signature: DocuSigned by: 38D181CBE57F4F7...

Name: Christof Manuel Schönenberger, MD PhD

Date: 27.05.2026 | 11:59 MESZ Signature: DocuSigned by: C.Schönenberger 2F6855B0A45A447...

Statistician:

Name: Frédérique Chammartin, PhD

Date: 27.05.2026 | 13:04 CEST Signature: DocuSigned by: F.Chammartin 0E09BF2613A14B1...

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GLOSSARY OF ABBREVIATIONS

ATE	*Average treatment effect*
AESI	*Adverse event of special interest*
BASEC	*Business administration system for ethical committees*
CACE	*Complier average causal effect*
DAG	*Directed acyclic graph*
RETUNE	*Reduce tobacco use in people living with HIV*
SAE	*Serious adverse event*
SHCS	*Swiss HIV cohort study*
TwiCs	*Trial within cohorts*
PLWH	*People living with HIV*

1 Introduction

This statistical analysis plan provides a detailed description of the methodology we will follow when analyzing and reporting results from the *Reduce tobacco use in people living with HIV in Switzerland* (RETUNE) trial. The reporting follows the *guidelines for the content of statistical analysis plans in clinical trials*.[1]

1.1 Background and rationale

In high income settings, cardiovascular diseases and cancer have become the leading cause of death among people living with HIV (PLWH).[2,3] Tobacco smoking is a major etiological factor for both diseases. High smoking prevalence among PLWH indicates a lack of effective smoking cessation interventions.[4]

Evidence suggests that nicotine substitute products improve quitting tobacco smoking and therefore reduce associated health burden.[5] However, previous smoking cessation trials predominantly included people who are motivated to quit smoking and focused on testing a single nicotine substitution product.[6,7] Both limits the clinical applicability of the results.

The RETUNE trial tests the effectiveness of offering a menu of nicotine substitute products, including e-cigarettes, nicotine pouches, and nicotine patches, to PLWH who smoke tobacco cigarettes regardless of their willingness to quit smoking ("opt-out" approach).

We refer to the trial protocol for more details (www.retune-trial.com).

1.2 Objectives

Primary objective: The purpose of this trial is to test the effectiveness of offering a menu of different nicotine substitute products (e-cigarettes, nicotine pouches, nicotine patches in addition to usual care) for tobacco smokers in the Swiss HIV Cohort Study (SHCS) in achieving self-reported 7-day tobacco cigarette abstinence at 6 months.

Secondary objectives:

- To assess the effect of offering the preference-based smoking cessation intervention on tobacco smoking cessation (defined as 7-day tobacco cigarette abstinence) at 12 and 24 months.
- To assess the effect of offering the preference-based smoking cessation intervention on (i) reduction of smoked tobacco cigarettes per day; (ii) reduction of cardiovascular risk and (iii) occurrence of cardiovascular events or death.

2 RETUNE methods

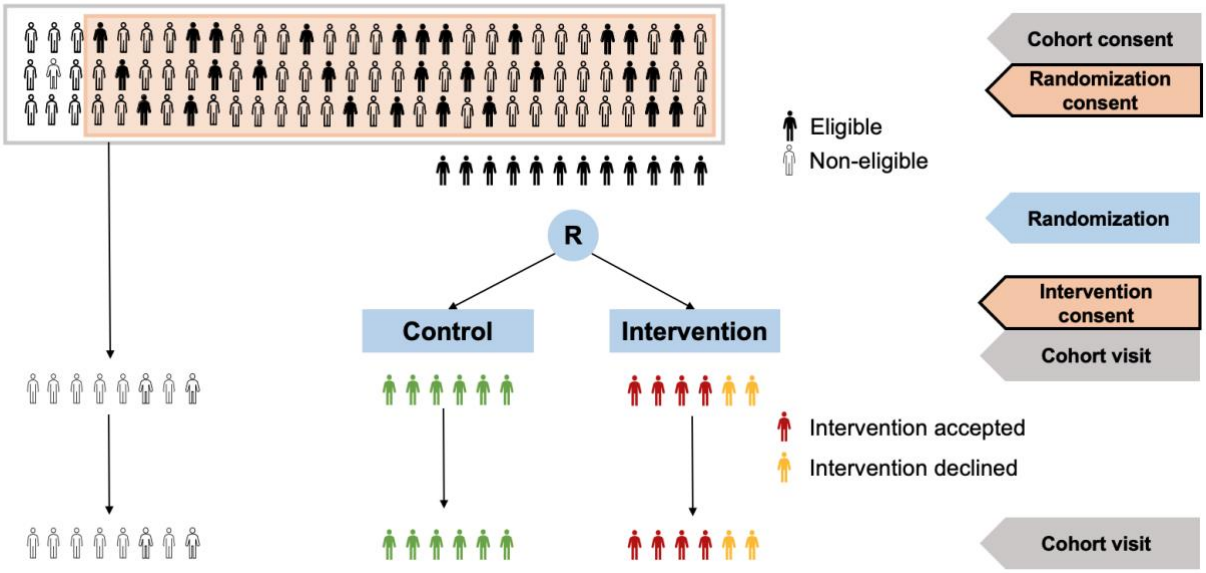
2.1 Trial design

RETUNE is a multicenter, pragmatic, 1:1 randomized, superiority clinical trial using the Trials within Cohorts (TwiCs) design.[8] In the TwiCs design, participants first consent to the longitudinal data collection (*cohort consent*) and, second, to be randomized into future trials (*randomization consent*). Participants who meet eligibility criteria of a specific trial are then randomized. People in the control group are not informed about their allocation. People in the intervention group can accept or decline the offered intervention. If they accept the intervention, they sign an additional consent form (*intervention consent*).

RETUNE is integrated in the SHCS. The SHCS, established in 1988, is a multicenter, prospective, observational, nationwide, cohort study.[9] PLWH are recruited at all university hospitals in Switzerland and at various other clinics and regular follow-up visits are conducted every 6 months. The cohort currently includes about 9'500 active participants.[10] In June 2024, the SHCS amended their protocol to enable the conduct of trials using the TwiCs design. RETUNE recruits participants at the SHCS centers in Basel, Bern, Geneva, Lausanne, St. Gallen, Aarau and Zurich (up to date information regarding the participating sites at the time of analysis are available in the trial registry and the trial webpage). The trial protocol was approved by all involved ethics committees and is available in the trial registry (NCT06789692) and on the RETUNE website

(https://retune-trial.com). The trial was designed and conducted without any involvement by the funder or companies.

Figure 1: Trials within Cohorts (TwiCs) design



To be part of the SHCS, all participants need to sign the "cohort consent". Since the amendment of the SHCS protocol in August 2024 participants are also routinely asked for an additional "randomization consent". Smokers who signed the "randomization consent" and without exclusion criteria become eligible for the RETUNE trial. They are randomized in a 1:1 ratio. Participants in the intervention group may accept or decline the offered intervention. If they accept the intervention, they sign an "intervention consent". The primary analysis will be conducted using an intention-to-treat analysis set. All trial outcomes are collected within the routine cohort visits.

2.2 Trial population

RETUNE recruits PLWH from the SHCS who smoke tobacco cigarettes. The specific eligibility criteria are:

Inclusion criteria:

- Signed informed consent for the data collection and participation in the SHCS (Cohort consent).
- Signed informed consent to be randomized to future interventions (Randomization consent).
- Age 18 years or older.

- Smokes one or more tobacco cigarettes per day (smoking status = yes) at the time of enrolment.

Exclusion criteria:

- Currently using e-cigarettes or nicotine pouches or nicotine patches.
- Pregnant women.

2.3 Trial procedures

RETUNE is embedded in the regular SHCS visits. The cohort visits take place approximately every 6 months and involve laboratory and clinical monitoring of the person living with HIV, their medication as well as the management of any concomitant conditions and their treatment.

During routine cohort visits, the treating physicians collect follow-up data using the SHCS data collection tool (Django). Simultaneously, cohort participants are assessed for RETUNE eligibility by an in-built algorithm based on the routine data from the current visit. If eligible, the physician is prompted to hit a randomization button. If allocated to the intervention, the physician offers the intervention and collects consent (intervention consent) of accepting participants. If the person is allocated to the control group, the physician continues the visit without offering the intervention.

2.4 Trial arms

The intervention consists of *offering* a menu of different nicotine substitute products. Available are e-cigarettes with e-liquids (menthol and tobacco flavor; nicotine concentrations 3 mg/ml, 6 mg/ml, 16 mg/ml), nicotine pouches (menthol and mountain herbs flavor), and nicotine patches (nicotine concentration 21 mg/24h, 14 mg/24h, 7 mg/24h). The participant can choose one of the products during the baseline visit and can switch the product after 8 and 16 weeks. The e-cigarettes and the nicotine pouches are provided free of charge for 24 weeks, the nicotine patches are provided free of charge for 12 weeks. Standard smoking cessation counselling as currently done in the SHCS is permitted, including referral to special consultations as per

smokers' request. In the control group, only standard smoking cessation counselling is offered. Of note, no interventional products from the trial are dispensed to the control group. Also, participants are not directed to use e-cigarettes or nicotine pouches at their own costs. Standardization of the control group with a rigid protocol is not intended. After the intervention period, the participants remain in the SHCS and have access to usual smoking cessation services

2.5 Outcomes

Following the TwiCs design, all trial outcomes are routinely collected data, measured at the SHCS visit. The time windows for the outcome collection are described in section 2.11. Additionally, we will collect information on the safety and usage of the interventional products in the intervention group via retrospective surveys.

Primary outcome:

- Tobacco smoking status (yes/no) measured as self-reported abstinence in the last 7 days at 6 months (window: 120 - 270 days)

Secondary outcome:

- Tobacco smoking status (yes/no) measured as self-reported abstinence in the last 7 days at 12 months (window: 271 - 450 days) and 24 months (window: 630 - 810 days).
- Self-reported number of tobacco cigarettes smoked per day at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.
- Self-reported use of any nicotine containing product other than tobacco cigarettes (yes/no): If yes, self-reported use of e-cigarettes (yes/no) or nicotine pouches (yes/no) or patches (yes/no) or other (yes/no) at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days) and 24 (window: 630 - 810 days) months.
- Self-reported abstinence of any nicotine containing product (yes/no) after 6 (window: 120 - 270 days),12 (window: 271-450 days) and 24 (window: 630-810 days) months.

- High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) Cholesterol (mmol/l) at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.
- Systolic and diastolic blood pressure (mmHg) at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.
- Body weight (kg) at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.
- SCORE2[11]-risk prediction algorithm at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.
- Occurrence of cardiovascular events (myocardial infarction, coronary angioplasty/stenting, coronary artery by-pass grafting, carotid endarterectomy, stroke, deep vein thrombosis, pulmonary embolism, heart transplantation) and all-cause death at 6 (window: 120 - 270 days), 12 (window: 271 - 450 days), and 24 (window: 630 - 810 days) months.

Safety endpoint:

- Serious Adverse events (SAEs) are collected after 6, 12, and 24 months. SAEs include death, life-threatening medical occurrence, hospitalization or prolongation of existing hospitalization, medical occurrence that result in disability, or causes anomaly or birth defect.

2.6 Randomization and allocation concealment

For the randomization, we used a python-based stochastic treatment allocation algorithm based on the variance method to minimize imbalances simultaneously for region (Non-German vs German speaking part of Switzerland), men having sex with men (yes/no), current injectable drug user (yes/no), and number of cigarettes smoked per day.[12] A probability of 80% was set to assign the preferred treatment and avoid deterministic allocation. These key variables were selected

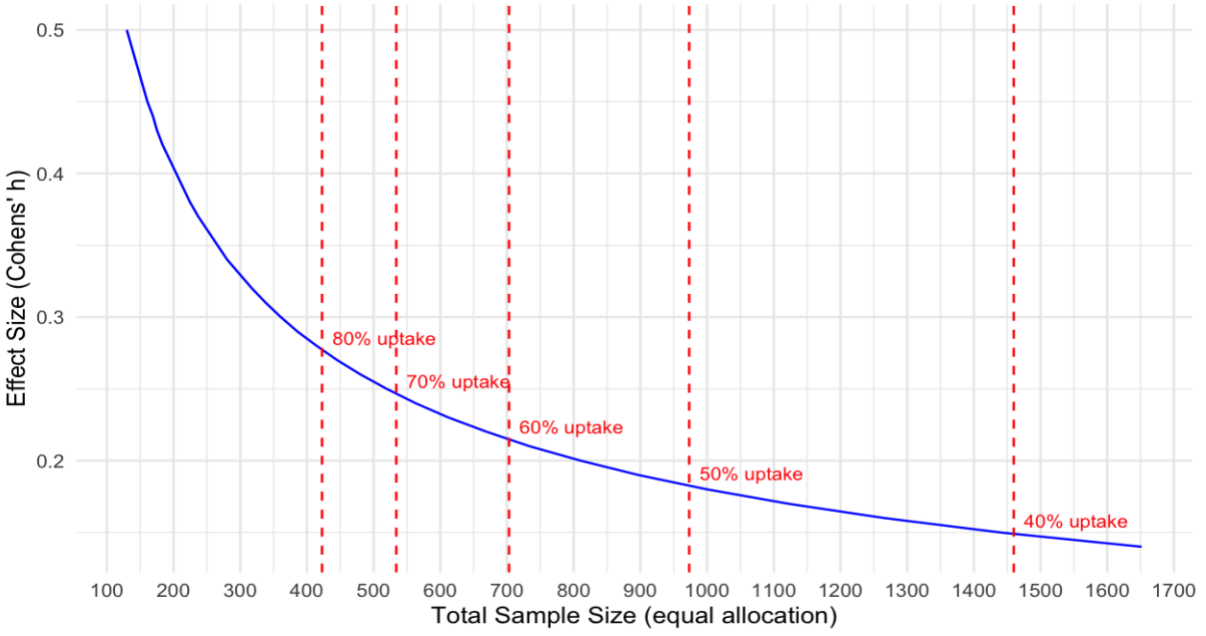
based on routine cohort data availability, prior evidence from the literature indicating association to our outcome, and expert knowledge.

The random allocation sequence was generated centrally, and the randomization module is integrated in the SHCS data collection tool. The SHCS physicians who performed the randomization had no access to the random allocation sequence and cannot see the allocation probabilities prior to assignment. The physicians who offered the intervention and collected the outcomes are aware of the group assignment. Participants in the control group were not aware of the trial (as per TwiCs design).

2.7 Sample size

We assume a smoking cessation rate of 8.5% in the control arm (based on current SHCS data), a 20% cessation rate in the intervention arm (based on external evidence of similar trials[13-15]), and an attrition rate of 3% (based on SHCS data).[9] Anticipating a low uptake of 50% in the intervention and thus dilution of the intervention effect, we aim at enrolling a total 972 participants (486 in each arm) to achieve 80% power with a two-sided alpha level of 5%. End of 2022, the SHCS had about 1600 smokers treated in a RETUNE center. Following recommendations from the literature and approaches used in other TwiCs, we will reassess our uptake assumption at pre-specified timepoints (after 100, 200, and 300 randomized participants).[16,17] If the uptake is higher than expected, we will reduce the target total sample size (Figure 2). We will not analyze outcomes at the sample size re-evaluation time points; thus, these do not constitute formal interim analyses with alpha spending and no correction for multiplicity is required. If uptake falls below 45%, we will consider adding more sites or discontinuing the trial, depending on available budget and operational resources. The full R code for the sample size calculation is available on GitHub (https://github.com/alainamstutz/TwiCs_samplesize/blob/main/TwiCs_samplesize.md).

Figure 2: Influence of the effect size on target sample size (adjusted for 3% attrition; power 80%; alpha 5%)



2.8 Framework

For all analysis, we use a frequentist approach. We hypothesize that the intervention is superior to the control.

2.9 Timing of the final analysis

We will analyze the outcomes after the follow-ups for the respective time point are complete. The primary outcome is assessed at 6 months; secondary outcomes are assessed also at 12 and 24 months. The analysis of the 6-month outcome can be conducted after all participants completed the 6-month follow-up, i.e., latest 270 days after last enrolment. The analysis of the 12-month outcome can be conducted after all participants completed the 12-month follow-up, i.e., latest 450 days after last enrolment. The analysis of the 24-month outcome can be conducted after all participants completed the 24-month follow-up, i.e., 810 days after last enrolment.

2.10 Timing of the outcome assessments

The RETUNE efficacy outcomes are collected within the SHCS routine data collection. Therefore, the RETUNE data collection is linked to the SHCS visits which take place approximately twice a year.

The baseline is defined as the date of randomization. The date of randomization corresponds to a routine SHCS visit. For the outcome assessments at six months (180 days), a range of 120 to 270 days applies. For the outcomes assessments at twelve months (360 days), a range of 271 to 450 days after enrolment applies. For the outcomes assessments at twenty-four months (720 days), a range of 630 to 810 days after enrolment applies. If several measurements within the time window are available, the one closest to 6 months will be used.

Table 1: Nominal visits and permitted outcome collection windows

Nominal visit month	Nominal visit day	Window for outcome collection as defined in the protocol in days
0 (Baseline)	0 (Baseline)	0
6	180	[120, 270]
12	360	[271, 450]
24	720	[630, 810]

3 Statistical principles

3.1 Confidence intervals and p-values

For all analysis, we will use two-sided tests and confidence intervals. All point estimates will be presented with 95% confidence intervals. The significance level is 0.05. P-values will be presented when appropriate. None of the planned analysis will be adjusted for multiplicity.

3.2 Adherence and protocol deviation

Adherence to the intervention is not systematically captured and not included in the analysis. This means, we do not assess whether and how the participants are using the interventional products. However, we plan a complier analysis of all participants, who accepted the offered

intervention (i.e., one of the three offered products) and signed the intervention consent. This complier analysis is described in section 5.4.1 in more detail.

Any protocol deviations as reported by the trial team or detected at the time of data cleaning or analysis will be reported. Possible anticipated protocol deviations are:

- A participant randomized to the control group receives the offer of the intervention.
- A participant randomized to the intervention group does not receive the offer of the intervention.
- A participant receives the intervention (the products free of charge) for longer than 24 weeks.
- The delivery of the intervention failed e.g., because the provided address of the participant was wrong and it was not possible to contact the participant.

3.3 Analysis population

The primary outcome is analyzed as per intention-to-treat reflecting a treatment policy estimand. The groups are compared as randomized, regardless of the uptake of the offered intervention, regardless of the adherence to the intervention (in case of uptake), and regardless of any product use outside of the trial (crossover).

The estimand of interest is described following current recommendations.[18,19] Table 2 describes the estimand for the primary outcome. The description of the population and the treatment condition as well as the handling of intercurrent events is identical for all secondary outcomes (the outcomes are listed in section 2.5). The summary measures for the secondary outcomes are described in section 5.2.2.

Table 2: Description of the primary estimand and handling of intercurrent events

Attribute	Definition
Population	Adults living with HIV in Switzerland, smoking one or more tobacco cigarettes per day.
Treatment condition	
Intervention	Offer of different nicotine substitute products (e-cigarettes, nicotine pouches or nicotine patches) free of charge for 6 months.
Control	Usual smoking cessation care in the SHCS.
Endpoint	Self-reported abstinence from tobacco smoking in the past 7 days at 6 months.
Summary measure	Odds ratio, risk ratio, and absolute risk difference between groups, adjusted for key prognostic baseline covariates.
Handling of intercurrent events	
Death (truncating event)	While-alive strategy: Only outcomes before the occurrence of the death are considered.
Non-uptake of any smoking cessation product in the intervention group and uptake of an intervention smoking cessation product in the control group (treatment-modifying event)	Treatment policy strategy: The occurrence of these intercurrent events is part of the treatment condition. Participants stay in the intention-to-treat analysis set as randomized at baseline regardless of (non-)uptake thereafter.
Stop or switch of use of a smoking cessation product at any time during the intervention due to any reason (treatment-modifying event)	Treatment policy strategy: The occurrence of the intercurrent event is part of the treatment condition. Participants stay in the intention-to-treat analysis set, regardless of their adherence to the intervention.
Attrition from SHCS (truncating event)	Principal stratum strategy: Participants dropping out of the SHCS are excluded from the analysis set, assuming missing at random, occurring at similar frequency across both groups and considered as such in the power calculation.

4 Trial population

4.1 Screening data

We did not capture specific screening data. The screening was performed using the routine SHCS data collection. However, we will provide information on how many participants would have been eligible to be randomized over the course of the trial but have not (see section 7.1).

4.2 Flow-chart

The participant flow during the trial will be visualized using a CONSORT flow-chart. Following the TwiCs design, the screening is performed automatically based on the data collected in the routine visits (see section 2.2 for eligibility criteria). Therefore, we will not present numbers how many participants were screened and we will not display reasons for screening failures. The flow-chart will show how many participants have accepted the offered intervention. The follow-up and potential reasons for lost to follow-up will be presented in the flow-chart. A template for the flow-chart is provided in section 7.1.

4.3 Recruitment

The enrolment over time is available as a regularly updated figure on the RETUNE website (www.retune-trial.com).

4.4 Baseline participant characteristics

We will summarize baseline characteristics by randomized groups. We will use medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. We will not statistically test for “imbalance” between the groups. A shell baseline table is provided in section 7.2.

5 Analysis

The analysis will be performed by CMS under supervision of AA and FC. AA will check the analysis code. All involved people are aware of the group allocation.

Percentages will be reported to zero decimal places, unless <0.5% when they will be given to one decimal place.

5.1 Outcome definition

Following the TwiCs design, all outcomes are collected within the SHCS routine data collection.

5.1.1 Self-reported tobacco smoking abstinence

The primary outcome was chosen based on a smoking cessation core outcome set,[20,21] previous smoking cessation trials,[22] discussions with the Participant Advisory Board, and the availability of routinely collected data in the SHCS. Results from large scale randomized trials indicate that relative estimates from 7-day self-reported abstinence rates are similar to biochemically verified abstinence rates.[14,23,24] Moreover, the self-reported primary outcome will minimize missing and incomplete outcome data, because biochemical validation additionally requires urine or blood samples and a biobanking consent from participants.

Importantly, ongoing nicotine consumption, for example by consumption of one of the intervention products, does not interfere with the outcome of tobacco smoking abstinence. The corresponding question in the SHCS data collection tool is:

- “Does the patient smoke cigarettes? (if less than 1 cigarette per day = no)”; Possible responses: 0=No,1=Yes
- If no: “Has the person smoked any cigarette (even just one) in the last 7 days?”; Possible responses: 0=No,1=Yes

For the primary outcome, someone is counted as non-smoker if the person has not smoked for the last 7 days.

5.1.2 Self-reported number of tobacco cigarettes per day

The number of cigarettes smoked per day is asked as follows:

- “Does the patient smoke cigarettes? (if less than 1 cigarette per day = no)”; Possible responses: 0=No,1=Yes
- If yes: “Number of cigarettes per day? (If a range is given, compute the average)”; Possible responses: Number value 1-99

5.1.3 Self-reported use of any nicotine containing products other than tobacco cigarettes

This question captures nicotine consumption via different sources than tobacco cigarettes. This is important to differentiate between ongoing nicotine consumption and nicotine cessation in RETUNE participants and to identify double use of tobacco cigarettes and alternative nicotine products. The corresponding question in the SHCS data collection tool is:

- "Did you use other nicotine containing products?"; Possible responses: 0=No,1=Yes
- If yes: "Which one?"; Possible responses: 1=Nicotine patches, 2=Chewing gums, 3=Snus, 4=Nicotine pouches, 5=Pipe, 6=Snuff, 7=IQOS
- "Does the patient smoke e-cigarette?"; Possible responses: 0=No,1=Yes

For this secondary outcome, someone is counted as nicotine patch user if the first question is answered with "Yes" and the "Nicotine patches" are reported in the second question. The same applies for nicotine pouches. E-cigarette users are defined if the third question is answered with "Yes".

5.1.4 Self-reported abstinence of any nicotine containing product

Abstinence from any nicotine consumption is a combined information from the following questions:

- "Does the patient smoke cigarettes? (if less than 1 cigarette per day = no)"; Possible responses: 0=No,1=Yes
- "Did you use other nicotine containing products?"; Possible responses: 0=No,1=Yes

For this secondary outcome, complete abstinence of any nicotine containing products is defined if both questions are answered with "No".

5.1.5 Cholesterol levels

We investigate the difference between the groups in mean High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), and total cholesterol in (mmol/l). The samples are collected during the cohort visits and analyzed at the laboratory of the respective hospital.

5.1.6 Blood pressure

We investigate the difference between the groups in mean systolic and diastolic blood pressure measured in mmHg by nurses using automated devices during the cohort visits.

5.1.7 Body weight

We investigate the difference in mean body weight between the groups measured in kilogram during the cohort visits by nurses or doctors.

5.1.8 SCORE2 risk prediction

As a secondary outcome, we will estimate the calibrated 10-year risk of fatal and non-fatal cardiovascular disease through the SCORE2[11] risk prediction algorithm using the "RiskScorecvd" package in R. SCORE2 will be calculated for each participant using the published sex-specific model coefficients and baseline survival, together with the calibration corresponding to the study country/risk region (Switzerland: low-risk region). The individual 10-year cardiovascular disease risk will be expressed as a percentage. Model coefficients, baseline survival and calibration factor are given in Table 3 and Table 4.

SCORE2 is applicable to individuals aged 40–69 years without previous cardiovascular disease or diabetes. Therefore, SCORE2 will only be calculated for participants meeting these criteria. Participants with a history of cardiovascular disease or diabetes will be considered not applicable for this secondary outcome and will be excluded from its analyses.

The calibrated 10-year risk of cardiovascular disease is calculated as follows:

Calibrated 10-year risk, % =

$$[1 - \exp(-\exp(scale1 + scale2 \times \ln(-\ln(1 - (1 - baseline\ survival^{\exp(x)})))))] \times 100$$

$$\text{where } x = \sum(\beta \times (transformed\ variables))$$

Table 3: Model coefficients and baseline survival SCORE2 risk prediction algorithm

Risk factor (Variable)	**Transformed variable**	**B coefficient for Male**	**B coefficient for Female**
Age, years	cage = (age – 60)/5	0.3742	0.4648
Smoking	current = 1, other = 0	0.6012	0.7744
Systolic blood pressure, mmHg	csbp = (sbp – 120)/20	0.2777	0.3131
Total cholesterol mmol/L	ctchol = tchol – 6	0.1458	0.1002
HDL cholesterol mmol/L	chdl = (hdl – 1.3)/0.5	-0.2698	-0.2606
Smoking*age interaction	smoking*cage	-0.0755	-0.1088
Systolic blood pressure*age interaction	csbp*cage	-0.0255	-0.0277
Total cholesterol*age interaction	ctchol*cage	-0.0281	-0.0226
HDL cholesterol*age interaction	chdl*cage	0.0426	0.0613
Baseline survival		**0.9605**	**0.9776**

Table 4: Published region- and sex-specific recalibration factors

	Male		Female	
Risk region	Scale 1	Scale 2	Scale 1	Scale 2
Low (Switzerland)	-0.5699	0.7476	-0.7380	0.7019

5.1.9 Occurrence of cardiovascular events and all-cause deaths

Deaths and cardiovascular events as well as their dates are captured in the routine SHCS data collection. The following questionnaire items are used:

- Reason for drop-out: 0=Patient died, 1=Patient moved to foreign country and cannot continue, 2=Patient wanted to discontinue, 3= Patient did not respond to several written invitations, 4=Patient changed address without notice, 5=Other (please specify)
    - Date of death: dd/mm/yyyy

- Code of disease or procedure: PUL=Pulmonary embolism, AMI=Myocardial infarction, BYP=Coronary artery by-pass grafting, CEI=Cerebral infarction, DVT=Deep vein thrombosis, END=Carotid endarterectomy, HTR=Heart transplantation
    - Date of diagnosis: dd/mm/yyyy

5.1.10 Safety endpoints – Serious Adverse Events (SAEs)

The definition and handling of Serious Adverse Events (SAEs) are given in section 5.8.1.

5.2 Analysis method

5.2.1 Analysis method – primary outcome

For the primary analysis, we will model the primary outcome using a fixed effect logistic regression with treatment group as the main explanatory variable and adjusted for region (binary: Non-German vs. German speaking part of Switzerland), men having sex with men (binary: yes/no), current injectable drug user (binary: yes/no), and number of cigarettes per day at baseline (continuous). The model will estimate the odds of reported non-smoking.[25-27] The treatment effect will be presented as an adjusted odds ratio derived from the model coefficient for the treatment group ($\exp(\beta_1)$) with 95% Wald confidence interval. The model is specified as follows:

$$logit\{Pr(Y_i = 1)\} = log\left(\frac{\Pr(Y_i = 1)}{\Pr(Y_i = 0)}\right)$$
$$= \beta_0 + \beta_1 \times Treatment_i + \beta_2 \times Region_i + \beta_3 \times MSM_i + \beta_4 \times Drug_i + \beta_5 \times Cigarettes\_day_i$$

- $Y_i = 1$: reported **no smoking**, $Y_i = 0$ reported smoking
- $Treatment_i = 1$: intervention group, $Treatment_i = 0$: control group,
- $Region_i = 1$: German-speaking region, $Region_i = 0$: **Non**-German-speaking region

- $MSM_i = 1$: risk group is Men having sex with men, $MSM_i = 0$: risk group **is not** Men having sex with men
- $Drug_i = 1$: current injectable drug user, $Drug_i = 0$: no current injectable drug user
- $Cigarettes\_day_i$ = number of cigarettes per day (continuous)

From the same model, we will derive standardized risk ratio and absolute risk difference. To do so, we will compute averaged risks under intervention and under control across all participants included in the primary analysis. 95% confidence intervals will be computed using bootstrapping using 2,000 bootstrap samples with resampling of participants. The steps of this marginal standardization are outlined below:

Predicted probability *under the intervention* (Treatment=1):

$$\hat{p}_{1i} = \Pr(Y_i = 1 \mid Treatment_i = 1, MSM_i, Drug_i, Cigarettes\_day_i, Region_i)$$
$$= logit^{-1}\left(\hat{\beta}_0 + \hat{\beta}_1 \times 1 + \hat{\beta}_2 \times MSM_i + \hat{\beta}_3 \times Drug_i + \hat{\beta}_4 \times Cigarettes\_day_i + \hat{\beta}_5 \times Region_i\right)$$

Predicted probability *under the control* (Treatment=0):

$$\hat{p}_{0i} = \Pr(Y_i = 1 \mid Treatment_i = 0, MSM_i, Drug_i, Cigarettes\_day_i, Region_i)$$
$$= logit^{-1}\left(\hat{\beta}_0 + \hat{\beta}_1 \times 0 + \hat{\beta}_2 \times MSM_i + \hat{\beta}_3 \times Drug_i + \hat{\beta}_4 \times Cigarettes\_day_i + \hat{\beta}_5 \times Region_i\right)$$

By averaging over all participants, we get the adjusted risks of non-smoking under intervention and control:

$$\hat{p}_1 = \frac{1}{N}\sum_{i=1}^{N} \hat{p}_{1i}$$

$$\hat{p}_0 = \frac{1}{N}\sum_{i=1}^{N} \hat{p}_{0i}$$

The effect measures are defined as:

- Risk difference = $\hat{p}_1 - \hat{p}_0$
- Relative risk = $\frac{\hat{p}_1}{\hat{p}_0}$

5.2.2 Analysis method – secondary outcomes

Most secondary outcomes will follow the procedure for the primary outcome, using fixed effect logistic regression or fixed effect linear regression depending on the nature of the outcome. Table 5 provides an overview of the corresponding analysis methods. Hypothesis testing will only be conducted for the primary outcome. The reporting of 95% confidence intervals for secondary outcomes intends to support descriptive interpretation and are of exploratory nature.

Table 5: Methods summary for the secondary outcomes

Outcome	Endpoint variable	Efficacy parameter	Method	Comment
Tobacco smoking status (yes/no) measured as self-reported abstinence in the last 7 days at 12 and 24 months.	Tobacco smoking yes/no (binary)	Odds ratio	Fixed effect logistic regression model[1]	Adjusted effect with 95% confidence intervals
Self-reported number of tobacco-based cigarettes smoked per day at 6,12, and 24 months.	Number of cigarettes (continuous)	Mean	Fixed effect linear regression model[1]	Adjusted effect with 95% confidence intervals
Self-reported use of any nicotine containing product other than tobacco cigarettes (yes/no). If yes, self-reported use of e-cigarettes (yes/no) or nicotine pouches (yes/no) or patches (yes/no) or other (yes/no) at 6, 12, and 24 months.	Nicotine containing products yes/no (binary) Use of e-cigarettes yes/no (binary)	Odds ratio	Fixed effect logistic regression model[1]	Adjusted effect with 95% confidence intervals

	Use of nicotine pouches yes/no (binary) Use of nicotine patches yes/no (binary) Use of other nicotine containing products yes/no (binary)			
Self-reported abstinence of any nicotine containing product (yes/no) at 12 and 24 months.	Nicotine containing products yes/no (binary)	Odds ratio	Fixed effect logistic regression model[1]	Adjusted effect with 95% confidence intervals
High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) Cholesterol (mmol/l) at 6,12, and 24 months.	HDL (continuous) LDL (continuous)	Mean	Fixed effect linear regression model[2]	Adjusted effect with 95% confidence intervals
Systolic and diastolic blood pressure (mmHg) between the groups at 6,12, and 24 months.	Systolic blood pressure (continuous) Diastolic blood pressure (continuous)	Mean	Fixed effect linear regression model[3]	Adjusted effect with 95% confidence intervals
Body weight (kg) at 6,12 and 24 months.	Kilogram (continuous)	Mean	Fixed effect linear regression model[4]	Adjusted effect with 95% confidence intervals
SCORE2-risk score at 6, 12, and 24 months.	SCORE2-risk score	Mean	Fixed effect linear regression model[5]	Adjusted effect with 95% confidence intervals
Occurrence of cardiovascular events (myocardial infarction, coronary angioplasty/stenting, coronary artery by-pass grafting,	Number of events	-	Purely descriptive by treatment arm and	Frequency of counts and percentages

carotid endarterectomy, stroke, deep vein thrombosis, pulmonary embolism, heart transplantation) and all-cause death at 6,12, and 24 months.			overall	

[1] Adjusted for region [Non-German vs. German speaking part of Switzerland], men having sex with men [yes/no], current injectable drug user [yes/no], number of cigarettes per day

[2] Adjusted for region [Non-German vs. German speaking part of Switzerland], men having sex with men [yes/no], current injectable drug user [yes/no], number of cigarettes per day, baseline LDL/HDL cholesterol level

[3] Adjusted for region [Non-German vs. German speaking part of Switzerland], men having sex with men [yes/no], current injectable drug user [yes/no], number of cigarettes per day, baseline systolic/diastolic blood pressure

[4] Adjusted for region [Non-German vs. German speaking part of Switzerland], men having sex with men [yes/no], current injectable drug user [yes/no], number of cigarettes per day, baseline body weight

[5] Adjusted for region [Non-German vs. German speaking part of Switzerland], men having sex with men [yes/no], current injectable drug user [yes/no], number of cigarettes per day, baseline SCORE2-risk score

5.3 Missing data

RETUNE relies on routine SHCS data for all trial efficacy endpoints. Missing data may arise if information was not captured by the treating physician, the participant declined to answer, or the participant has no data available within the endpoint window (see section 2.11). We assume missingness at random. We will summarize the extent and patterns of missing baseline covariates and outcomes by randomized arm (and by center).

Death and attrition from SHCS are handled as intercurrent events per section 3.3. Outcome after these intercurrent events will not be imputed for the primary analysis (i.e., while-alive strategy for death and principal stratum strategy for discontinuation from SHCS).

5.3.1 Multiple imputation for the primary outcome

As our primary analysis approach, we will do multiple imputation for missing data for the primary outcome. The primary outcome consists of 2 questions (see section 5.1.1). A missing primary outcome is defined as missing only if the first question (tobacco smoking yes/no) is missing. If only the second question (has the person smoked any cigarette in the last 7 days yes/no) is missing, the primary outcome will be defined solely according to the first question. Since the second question is dependent on the first, scenarios where only the answer to the second question is available but not to the first are unlikely.

We will use multiple imputation by chained equations with m=50 imputations and 20 iterations per imputation.[28,29] The imputation will be performed separately by randomized arm to preserve arm-specific associations.[30] The imputation models will be compatible with the analysis models by having the same structure as the analysis model.

The imputation set will include all variables from the model for the primary endpoint and auxiliary variables expected to predict missingness and/or outcomes. All included variables are listed in table 6.

Each imputed dataset will be analyzed with the prespecified model (see section 5.2.1). We will combine estimates and standard errors using Rubin's rules.[31] We will use a fixed random seed for reproducibility. For all secondary outcomes, we will use a complete case approach.

Table 6: Variables to be included in multiple imputation

Variable	Timepoints	Model specification
Primary endpoint variable		
Tobacco smoking status	6 months[1]	1=No, 0=Yes (logit)
Covariates for the primary endpoint model		
Number of smoked cigarettes per day	Baseline	Continuous (predictive mean matching)

Men having sex with men	Baseline	0=No, 1=Yes (logit)
Injectable drug use	Baseline	0=No, 1=Yes (logit)
Region (assumption: centers LS and GE are Non-German speaking, centers BS, ZH, BE, SG, AA are German speaking)	Baseline[1]	1=German speaking part, 0=Non-German speaking part (logit)
Auxiliary variables		
Age	Baseline	Continuous (predictive mean matching)
Sex at birth	Baseline	1=Male, 2=Female (logit)
Education	Baseline	1=No completed school or professional education, 2=Mandatory school (9 years in Switzerland), 3=Finished apprenticeship, 4=Bachelor, 5=Higher professional education,6=Higher technical or commercial school, 7=University, 0=Other, 9=NA (mlogit)
Alcohol use (at least once a week during the last 6 months)	Baseline	0=No, 1=Yes (logit)
Cannabis use (at least once a week)	Baseline	0=No, 1=Yes (logit)
Packyears of tobacco smoking	Baseline	Continuous (predictive mean matching)
Ethnicity	Baseline	1=White, 2=Black, 3=Hispano-American, 4=Asian, 0=Other (mlogit)
Immigration to Switzerland	Baseline	0=No, 1=Yes (logit)

Hospitalization during the last 6 months	Baseline	0=No, 1=Yes (logit)
Steady partnership during the last 6 months	Baseline	0=No, 1=Yes (logit)
Depression	Baseline	0=No, 1=Yes (logit)

[1] This variable is not possible to missing at baseline because it was required to assess trial eligibility.

5.4 Per protocol analyses for the primary outcome

Per-protocol analyses will be defined in several ways, e.g. accounting for the non-uptake of the intervention among the intervention group.

We will estimate a) the "Effect of the intervention for participants who complied with the treatment assigned to" (Complier Average Causal Effect (CACE)) and b) the "Effect of everyone had taken up a product at baseline vs no-one had taken up a product at baseline" (Average Causal Effect (ACE)). For all per-protocol analysis, we will use a complete case analysis set (see section 5.5.2) and not the multiply imputed data set used for the primary analysis to reduce complexity.

5.4.1 Per protocol analysis – Complier Average Causal Effect (CACE)

Because uptake of the intervention products at baseline is expected to be incomplete (currently estimated at approximately 50%), the treatment policy estimand using an intention-to-treat analysis approach provides an unbiased estimate of the effect of *offering* the intervention to all eligible participants. While this estimand is of primary relevance for policy makers, it may be less informative for patients and treating physicians interested in the effect of *actual intervention uptake*.[32]

To address this, we will estimate per-protocol effects using observational causal inference methods. In a first per-protocol analysis, we will estimate the CACE, defined as the causal effect of intervention uptake at baseline on the primary outcome among participants who comply with their randomized assignment. In this context, compliers are participants who would take up at

least one intervention product if offered the intervention and would not take up any intervention product if not offered the intervention.

We will estimate the CACE using an instrumental variable approach, with randomized assignment serving as the instrument for intervention uptake. Unlike standard observational methods, instrumental variable analyses do not rely on the assumption of no unmeasured confounding between uptake and outcome but instead require a different set of assumptions:

i) **Relevance**: Randomized assignment is associated with intervention uptake at baseline. This assumption is expected to hold because only participants randomized to the intervention arm are offered the intervention. The strength of this association will be assessed empirically in the first-stage model.

ii) **Independence**: Randomized assignment is independent of counterfactual outcomes and potential uptake, which is ensured by design.

iii) **Exclusion restriction**: Randomized assignment affects the primary outcome (self-reported tobacco smoking after 6 months) only through its effect on intervention uptake. This assumption cannot be tested empirically but is considered plausible in RETUNE, as both groups receive standard counseling and similar background care, consistent with previous studies in comparable settings.[33,34]

iv) **Monotonicity**: There are no defiers. That is, no participant would take up the intervention if not offered it but fail to take it up if offered. This assumption is considered plausible in the TwiCs design, because participants in the control arm are not offered the intervention through the study.[35-38]

We will estimate the CACE using a two-stage least squares instrumental variable approach, with randomized assignment serving as the instrument for intervention uptake at baseline. The CACE is defined as:

$$\text{CACE} = \mathbb{E}[Y_i^{(1)} - Y_i^{(0)} \mid A_i(1) = 1, A_i(0) = 0]$$

- $A_i \in \{0,1\}$: uptake at baseline (1 = uptake, 0 = non uptake)
- Y_i: outcome (e.g., smoking yes/no)

The two-stage least square estimator is defined as:

$$\widehat{\text{CACE}} = \frac{\mathbb{E}(Y \mid Z = 1) - \mathbb{E}(Y \mid Z = 0)}{\mathbb{E}(A \mid Z = 1) - \mathbb{E}(A \mid Z = 0)} = \frac{ITT\ effect\ of\ assignment\ on\ outcome}{Effect\ of\ assignment\ on\ uptake\ (first\ stage)}$$

- $Z_i \in \{0,1\}$: randomized assignment (1 = offered intervention, 0 = control)
- $A_i \in \{0,1\}$: uptake at baseline (1 = uptake, 0 = non uptake)

In the first stage, baseline uptake of at least one intervention product (yes/no) will be regressed on randomized assignment. The first stage model is defined as:

$$A_i = \pi_0 + \pi_1 Z_i + \boldsymbol{\pi}_2^{\top} \boldsymbol{L_i} + \varepsilon_i$$

- A_i is the observed uptake
- $Z_i \in \{0,1\}$: randomized assignment (1 = offered intervention, 0 = control)
- π_0 Intercept of the first stage regression
- π_1 Effect of the randomized assignment on uptake
- π_2 Vector of coefficients for baseline covariates in the first stage model
- L_i Vector of prespecified baseline covariates (education, cannabis use, being in a stable partnership, immigration, alcohol use, cigarettes smoked per day, pack years, depression, trial center, i.v. drug use, age, sex, men having sex with men, ethnicity)
- ε_i Error term

In the second stage, the outcome will be regressed on the predicted values of uptake obtained from the first-stage model. The resulting coefficient for predicted uptake estimates the CACE, corresponding to the causal effect of intervention uptake among compliers. The second stage model is defined as:

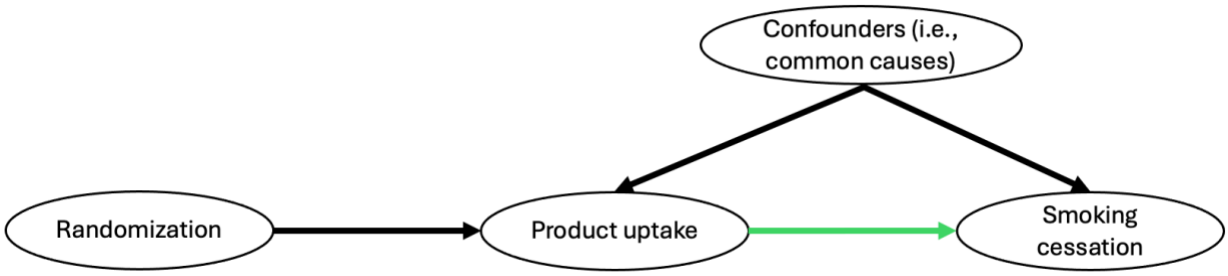
$$Y_i = \alpha_0 + \alpha_1 \hat{A}_i + \boldsymbol{\alpha_2^\top L_i} + \eta_i$$

- $\hat{A}_i$ are the fitted values from the first stage
- α_0 Intercept of the second stage regression
- α_1 Two-stage least squares estimate of the CACE
- α_2 Vector of coefficients for baseline covariates in the second stage model
- L_i Vector of baseline covariates used for adjustment (e.g., region, men having sex with men, current drug use, baseline number of cigarettes per day)
- η_i Error term

Because both uptake and the primary outcome are binary, this analysis corresponds to a linear instrumental-variable model and estimates the CACE on the absolute risk difference scale. As with other linear probability models, fitted values may fall outside the 0 to 1 range; however, the parameter of interest is the average causal effect among compliers rather than individual predicted probabilities.[39] We will calculate standard errors using heteroskedasticity-robust variance estimators. Adjustment covariates are prespecified baseline variables and included in both stages to improve precision.

As a sensitivity analysis, we will calculate the CACE effect without modelling to examine the robustness of conclusions to the linear probability specification.

Figure 4: DAG– Randomization as instrumental variable



Notes: Confounding of the Product uptake on smoking cessation may exist, but randomization serves as instrumental variable.

Green arrow: Complier Average Causal Effect to be estimated.

5.4.2 Per protocol analysis – Average Treatment Effect among the treated (ATT)

In a sensitivity per-protocol analysis, we will estimate the average causal effect of intervention among treated using a propensity score matching. This analysis aims to estimate the effect of the intervention among participants who accepted the intervention and those who would have accepted it if it was offered.

$Z_i \in \{0,1\}$ denotes for the randomized assignment (1 = intervention offered, 0 = control) and $A_i \in \{0,1\}$ denotes for uptake of at least one intervention product at baseline (1 = uptake, 0 = no uptake). Among participants randomized to the intervention group ($Z_i = 1$), we will estimate the probability of uptake conditional on baseline covariates $\boldsymbol{L_i}$ using logistic regression:

$$\Pr(A_i = 1 \mid L_i) = \text{logit}^{-1}(\alpha_0 + \boldsymbol{\alpha}^{\top}\boldsymbol{L_i}),$$

$\boldsymbol{L_i}$ includes baseline variables associated with both uptake and outcome (education, cannabis use, being in a stable partnership, immigration, alcohol use, cigarettes smoked per day, pack years, depression, trial center, i.v. drug use, age, sex, ethnicity, men having sex with men).

This model will be used to derive propensity scores among adherers in intervention and control as $\hat{e}_i = \Pr(A_i = 1 \mid L_i)$ which represents the probability that participant i would accept the

intervention if offered. We will use these propensity scores to match intervention accepters ($Z_i = 1, A_i = 1$) to control participants ($Z_i = 0$) with similar predicted probabilities of uptake, thereby identifying control participants with similar probability of receiving the treatment, given observed baseline covariates. We will use 1:1 nearest-neighbor matching without replacement. We will perform the matching on the logit of the propensity score using a caliper width equal to 0.2 times the standard deviation of the logit-transformed propensity score:

$$\text{caliper} = 0.2 \times \text{SD}(\log\left(\frac{\hat{e}_i}{1-\hat{e}_i}\right))$$

The matching will be performed using 1:1 nearest-neighbor matching without replacement on the propensity score scale. In the matched sample, we will assess covariate balance using standardized mean differences, with values below 0.1 indicating adequate balance.

In the matched sample, we will estimate the intervention effect as the absolute risk difference:

$$\text{RD} = \Pr(\text{Y}=1|\text{T}=1, \text{matched}) - \Pr(\text{Y}=1|\text{T}=0, \text{matched})$$

Y=1 indicates smoking cessation. T_i indicates treatment status, with Ti=1 denoting individuals that receive intervention (uptake) and Ti=0 denoting matched control individuals selected from the untreated population. We will derive 95% confidence interval for using nonparametric bootstrapping.

5.5 Sensitivity analyses for the primary outcome

5.5.1 Sensitivity analysis 1: Different definition of missingness for the primary outcome

For this sensitivity analysis, we define the primary outcome differently. The primary outcome consists of 2 questions (see section 5.1.1). For the primary analysis, we treat the primary outcome as missing if the first question (tobacco smoking yes/no) is missing. If only the second question (has the person smoked any cigarette in the last 7 days yes/no) is missing, the variable is not treated as missing. In this sensitivity analysis, we will treat the primary outcome as missing, if only

the second question is missing. We will impute missing primary outcomes as described in section 5.3.1. Since the second question is dependent on the first, scenarios where only the answer to the second question is available but not to the first are unlikely.

5.5.2 Sensitivity analysis 2: Complete case analysis

We will perform a sensitivity analysis where participants with missing primary outcomes (i.e., all participants who remain in the SHCS but have missing primary outcome data) will be excluded from the analysis.

5.5.3 Sensitivity analysis 3: Multiple imputation for participants dropping out of the SHCS

Our primary approach to deal with the intercurrent event "attrition from SHCS" is a principal stratum strategy, i.e. excluding everyone experiencing this event (see section 3.3). In this sensitivity analysis, we will impute missing primary outcome, including those due to drop out from the SHCS. Multiple imputation will follow the same approach as described in section 5.3.1.

5.5.4 Sensitivity analysis 4: Alternative model with centers instead of regions (centers as fixed effects)

In this sensitivity analysis, we will model the primary endpoint using a logistic regression with treatment group as the main explanatory variable and adjusted for center (BS [reference], ZH, SG, BE, LS, GE, AA), men having sex with men (yes/no), current drug user (yes/no), and number of cigarettes per day at baseline (continuous). The model will estimate the conditional odds of reported non-smoking. We will use the same data set as for the primary analysis model including multiple imputed primary outcome data. The treatment effect will be presented as an adjusted odds ratio derived from the model coefficient for the treatment group ($\exp(\beta_1)$) with 95% Wald confidence interval.

$$logit\{Pr(Y_i = 1)\} = log\left(\frac{\Pr(Y_i = 1)}{\Pr(Y_i = 0)}\right)$$

$$= \beta_0 + \beta_1 \times Treatment_i + \beta_2 \times MSM_i + \beta_3 \times Drug_i + \beta_4 \times Cigarettes\_day_i$$

$$+ \gamma ZH \times Z_i^{ZH} + \gamma SG \times Z_i^{SG} + \gamma BE \times Z_i^{BE} + \gamma LS \times Z_i^{LS} + \gamma GE \times Z_i^{GE} + \gamma AA \times Z_i^{AA}$$

- $Y_i = 1$: reported **no smoking**, $Y_i = 0$: reported smoking
- $Treatment_i = 1$: intervention group, $Treatment_i = 0$: control group,
- $MSM_i = 1$: risk group is Men having sex with men, $MSM_i = 0$: risk group **is not** Men having sex with men
- $Drug_i = 1$: current drug user, $Drug_i = 0$: no current drug user
- $Cigarettes\_day_i$ = number of cigarettes per day (continuous)
- $Center$ (categorical, 7 levels): BS=reference center; ZH, BE, SG, LS, GE, AA=dummy-coded
    - $Z_i^{ZH} = 1$ if center is Zurich, $Z_i^{ZH} = 0$ if if center **is not** Zurich
    - $Z_i^{SG} = 1$ if center is St. Gallen, $Z_i^{SG} = 0$ if if center **is not** St. Gallen
    - $Z_i^{BE} = 1$ if center is Bern, $Z_i^{BE} = 0$ if if center **is not** Bern
    - $Z_i^{LS} = 1$ if center is Lausanne, $Z_i^{LS} = 0$ if if center **is not** Lausanne
    - $Z_i^{GE} = 1$ if center is Geneva, $Z_i^{GE} = 0$ if if center **is not** Geneva
    - $Z_i^{AA} = 1$ if center is Aarau, $Z_i^{AA} = 0$ if if center **is not** Aarau

5.5.5 Sensitivity analysis 6 or 7: Pilot study interference

The first 200 randomized participants were part of the internal pilot study. Some of these participants allocated to the intervention group received an additional phone call within the first 4 weeks that allowed discussion and potential change of the offered products. To assess whether this additional contact influenced the primary endpoint, we will perform a sensitivity analysis on the primary outcome. We will fit a logistic regression model including the pilot indicator and a treatment-by-pilot interaction term:

$$logit\{Pr(Y_i = 1)\} = log\left(\frac{\Pr(Y_i = 1)}{\Pr(Y_i = 0)}\right)$$

$$= \beta_0 + \beta_1 \times Treatment_i + \boldsymbol{\beta_1^T} \times \boldsymbol{X_i} + \beta_3 \times Pilot_i + \beta_4 \times (Treatment_i \times Pilot_i)$$

- $Y_i = 1$: reported **no** smoking, $Y_i = 0$ reported smoking
- $Treatment_i = 1$: intervention group, $Treatment_i = 0$: control group,

- X_i: Usual adjustment variables (region, MSM, drug use, baseline number of cigarettes per day)
- $Pilot_i = 1$: participant was part of the internal pilot study, $Pilot_i = 0$: participant was **not** part of the internal pilot study

5.6. Subgroup analysis on the primary outcome

We will assess effect modification of treatment effect on the primary outcome for seven pre-defined subgroups. We plan an exploratory subgroup analysis (no pre-specified hypothesis) for the number of cigarettes smoked per day at baseline (continuous), age in years (continuous), and sex (binary), higher educational degree (binary), weekly cannabis use (binary), HIV viral load ≤50 copies/ml (binary). We will include corresponding interaction terms – one at a time – in the adjusted logistic regression model. If a p-value of an interaction term turns out to be smaller than 0.1, we will assess the credibility of the effect using the ICEMAN tool.[40]

5.7 Interim analysis

There are no prespecified interim analyses and no formal stopping rules.

5.8 Harms

5.8.1 Serious Adverse Event (SAE)

SAEs are a trial outcome as defined in section 2.5. and will be reported and compared across groups. We define SAEs in accordance with ClinO, Art. 63[41] , as any untoward medical occurrence that:

1. Results in death or is life-threatening,
2. Requires in-patient hospitalization or prolongation of existing hospitalization,
3. Results in persistent or significant disability or incapacity, or
4. Causes a congenital anomaly or birth defect

SAEs are collected in the routine SHCS data. The following questions will be used to collect the required information:

1. Reason for dop out: 0=Participant died
    a. Date of death: dd/mm/yyyy
2. Was the patient hospitalized within the last six months? 1=yes, 0=no, 9=unkown
    a. Date of hospitalization? dd/mm/yyyy
    b. Date of discharge? dd/mm/yyyy
3. Code of disease or procedure: PUL=Pulmonary embolism, AMI=Myocardial infarction, BYP=Coronary artery by-pass grafting, CEI=Cerebral infarction, DVT=Deep vein thrombosis, END=Carotid endarterectomy, HTR=Heart transplantation
    a. Date of diagnosis? dd/mm/yyyy

The information on congenital anomaly and birth defects is captured in the Swiss Mother and Child HIV Cohort Study, a sub-study of the SHCS. However, we anticipate no such cases since pregnancy is an exclusion criterion. However, in case we register a pregnancy among RETUNE participants, we will check for this SAE.

An independent physician will perform a causality assessment of all SAEs. The independent physician will provide a statement whether the SAE is definitely related, probably related, possibly related, unlikely related, or unrelated to the offered intervention.

Table 7: Causality assessment SAEs

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible

Unlikely	Any assessable reaction that does not fulfill the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Further, the independent physician makes a severity assessment of the event as mild, moderate, or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

5.8.2 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) are adverse events probably related to the tested nicotine substitute products. We pre-defined the following AESI:

- New or increased nausea after use of the investigational product
- New or increased emesis after use of the investigational product
- New or increased headache after the use of the investigational product
- New or increased dizziness after the use of the investigational product
- New or increased respiratory symptoms: cough, phlegm, wheezing, sore throat after the use of the investigational product (only asked for e-cigarette and nicotine pouch users)
- New or increased gingival pain after use of the investigational product (only asked for nicotine pouch users)
- New or increased gingival bleeding after use of the investigational product (only asked for nicotine pouch users)
- New or increased mouth ulcers after use of the investigational product (only asked for e-cigarette and nicotine pouch users)
- New or increased eczema / allergic skin reactions after use of the investigational product
- New or increased mouth and tongue irritation / change of the oral mucosa after use of the investigational product (only asked for e-cigarette and nicotine pouch users)

AESI information is collected via a retrospective survey (online or telephone based) amongst participants in the intervention group who accepted the offered intervention and provided intervention consent. For all AESIs we asked if they appeared after every use, after some use, only at the initiation of the product, or only once overall. Since this information is not collected in the control group, this is not considered a trial outcome. AESI will be presented using descriptive summery measures.

5.9 Statistical software

We will use R for all described analysis. The used packages will be listed in the final report.

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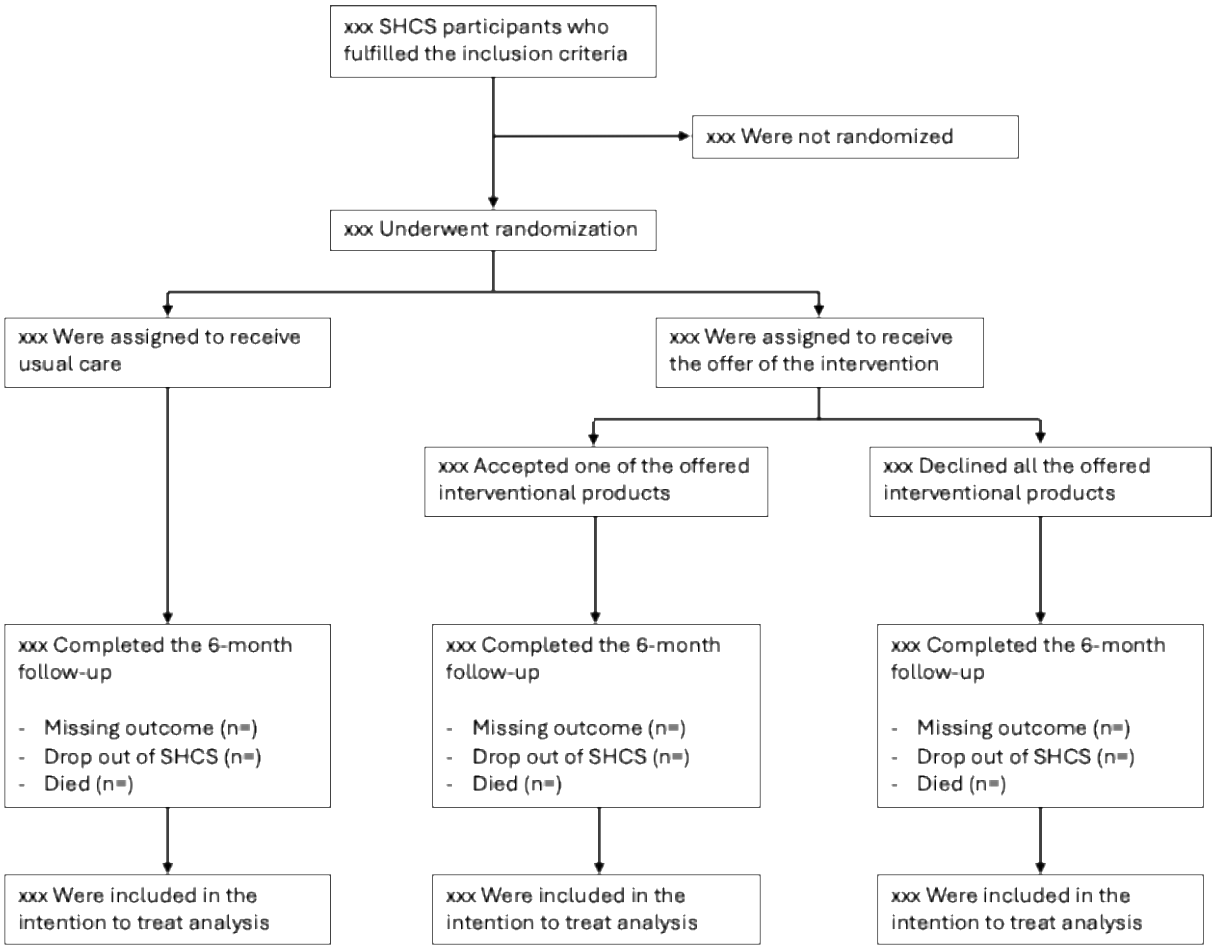
7 Appendix

7.1 Shell flowchart



7.2 Shell baseline table

Characteristic	Usual care group	Intervention group	Intervention group Uptake	Intervention group Non-uptake
Age in years – median (interquartile range)				
Female sex assigned at birth - no. (%)				
Higher educational degree - no. (%)[1]				
Ethnicity - no. (%)				
White				
Black				
Hispano-American				
Asian				
Other				
Immigration to Switzerland - no. (%)				
Origin - no. (%)				
Europe				
Outside Europe				
Median number of cigarettes per day (interquartile range)				
Median years of tobacco smoking (interquartile range)				
Center – no. (%)				
center 1				
center 2				
center 3				
center 4				
center 5				
center 6				
Missed antiretroviral therapy in the last 4 weeks – no. (%)				
>1/month				
1/month				
Never				
Not applicable				
Most likely mode of HIV acquisition – no. (%)				
Men who have sex with men				
Heterosexual contact				
People who inject substances				
Other/unknown				
Perinatal				
Blood products				
Viral load – no. (%)				
<50 copies/ml				
50-399 copies/ml				
≥400 copies/ml				
Median CD4 count (interquartile range)				
Diagnosis of depression – no. (%)[2]				
Any substance use – no. (%)				
Injectable substances[3]				
Cannabis[4]				
Other substances[5,6]				
In a substance program				

Excessive alcohol use – no. (%)[7]				

[1]Higher educational degree: defined as completed higher professional education or university degree above mandatory school (9 years in Switzerland) and finished apprenticeship
[2]Assessed by a SHCS physician or a psychiatrist
[3] Frequency injectable substance use: weekly (n=x), monthly (n=x), less frequently (n=x)
[4] Frequency cannabis use: daily (n=x), weekly (n=x), monthly (n=x), less frequently (n=x), missing (n=x)
[5]Other substances: amphetamine/speed, cannabis, cannabidiol (CBD), cocaine, crack cocaine, crystal meth/tina, ecstasy, Gamma-hydroxybutyrate (GHB)/Gamma-butyrilactone (GBL), Ketamine, Lysergic acid
[6] Frequency other substances: daily (n=x), weekly (n=x), monthly (n=x), less frequently (n=x), missing (n=x)
[7]Excessive alcohol consumption: defined as an AUDIT-C (Alcohol Use Disorder Identification Test Consumption) score ≥3 in female or ≥4 in male