Efficacy and Safety of Electronic Cigarettes for Smoking Cessation: Keeping a Trial on a Polarizing Topic Running Under Regulatory and Epidemic Changes.

Reto Auer, MD, MAS

Associate Professor, Head of Substance Use Unit, Institute of Primary Health Care (BIHAM), University of Bern
Adjunct physician, Unisanté, Lausanne
Primary care physician, GemeinschaftspraxisBrunnmatt (GPB), Bern

reto.auer@unibe.ch

Study disclosure

No co-author has a relationship with the tobacco, vaping, or pharmaceutical industries that would create a conflict of interest in these analyses.

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Trial Registration: ClinicalTrials.gov NCT03589989

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Study team:

- **Bern: Anna Schoeni,** Stéphanie Baggio, Julian Jakob, Kali Tal, Mirah J. Stuber, Moa Lina Haller, Martin Feller, Nicolas Rodondi, Sven Trelle, Sheila Appadoo, Andreas Limacher, Mattia Branca, Jean-Benoît Rossel, Maria Schüpbach, Lukas Ehrsam, Rylana Wenger, Tanja Flückiger, Dijana Andrijanic, Nathalie Schwab
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-> Study participants and further stakeholders!

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krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

LUNGE ZÜRICH
Hilft. Informiert. Wirkt.

«Hate the smoke, love the smokers»

Steven A. Schroeder, MD

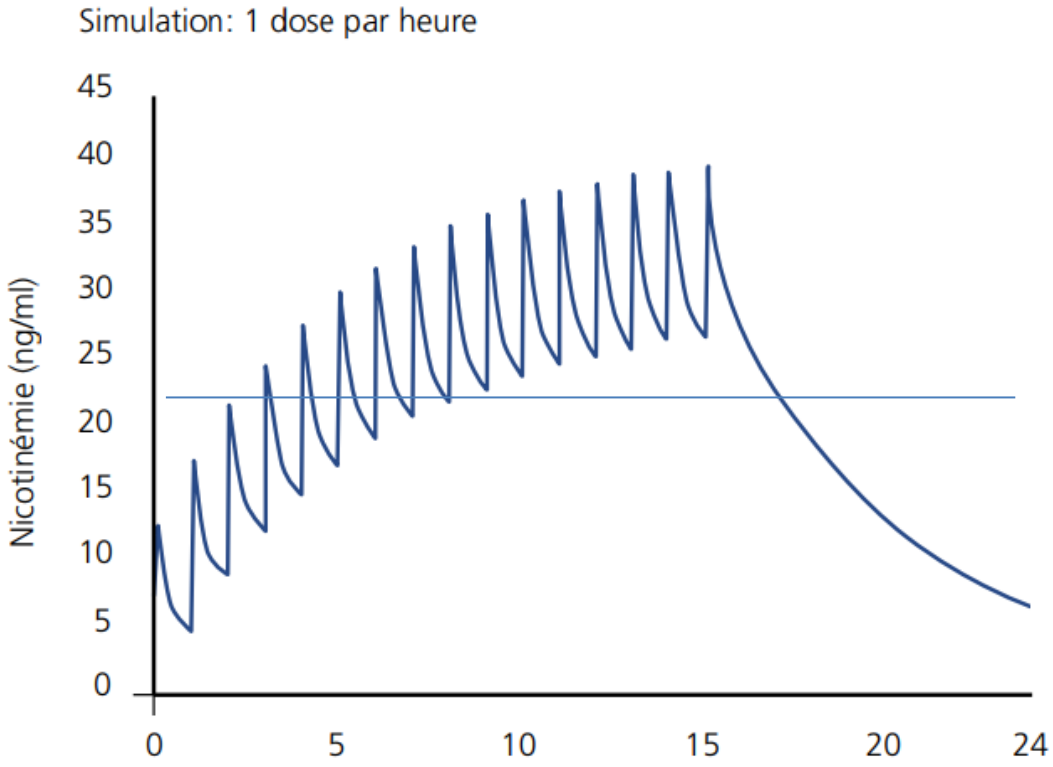
«There is no harm of being sometimes wrong – especially if someone is promptly found out».

John Meynard Keynes, CB, FBA

Nicotine

- "*People smoke for the nicotine, but they die from the tar*" M. Russell

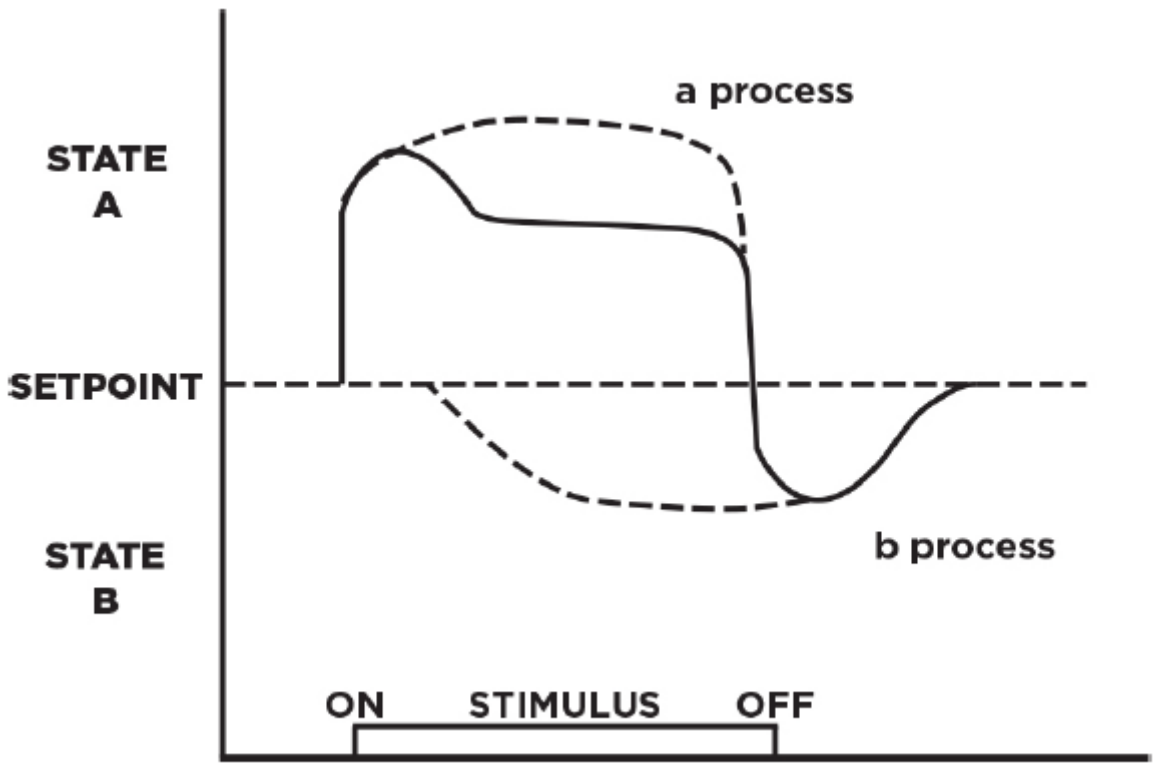
- Nicotine can induce addictive behaviour.
- Health risk:
  - NOT listed as a carcinogen by the International Agency for Research on Cancer (IARC).
  - In randomized trials of nicotine replacement therapy for smoking cessation, no increased risk of myocardial infarction or stroke with nicotine replacement therapy
  - Acute effect on sympathetic nervous system:
    - Possible trigger heart attacks due to acute increase blood pressure and heart rhythm
    - Risk atherosclerosis by nicotine not settled
  - Other effects:
    - Potential beneficial effect: Alzheimers, Parkinson's disease, Sarcoïdosis, Rectocolitis Ulcerosa.
    - Potential negative effect: Crohn's disease



Nicotine - a weak stimulant

- Individual set-point for ideal nicotine level
- No clear tachyphylaxis
- Half-life in blood: 1.6-2.8 hours
- If too much nicotine - pause in intake
  - If too little - urge to smoke
  - First cigarette usually the best (nicotine level lowest)

-> If more effective ncotine replacement therapy, more effective smoking cessation!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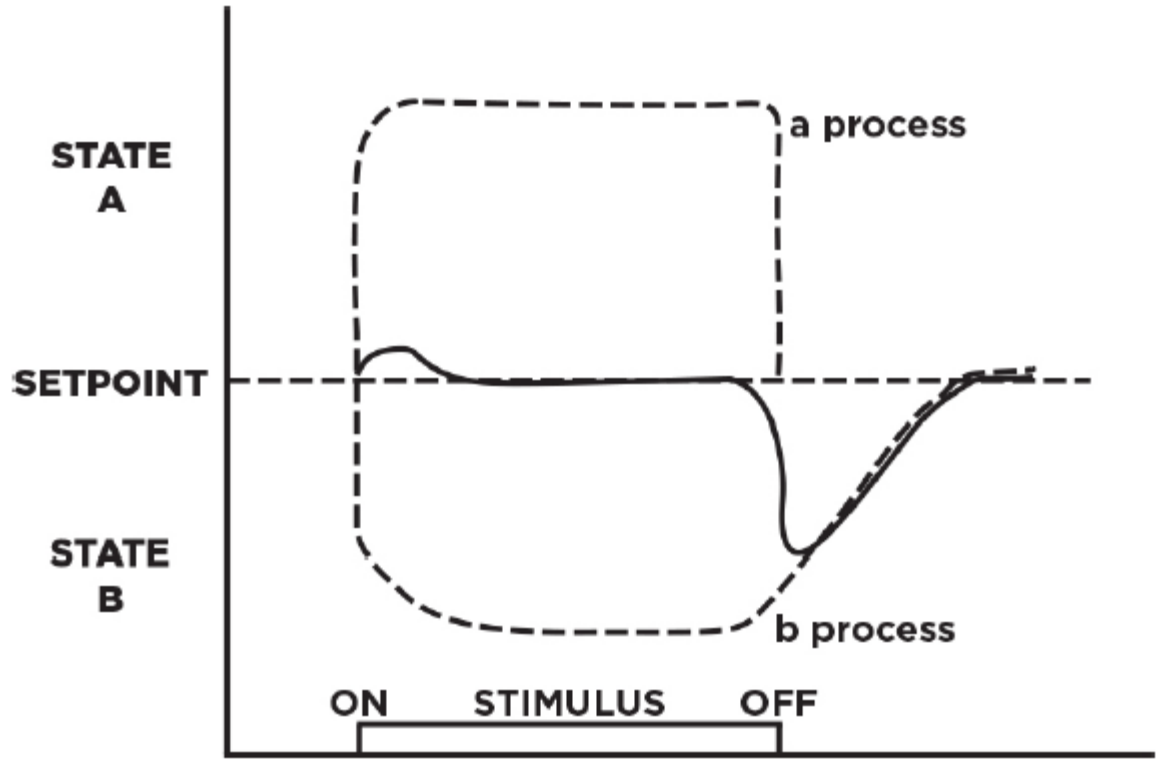
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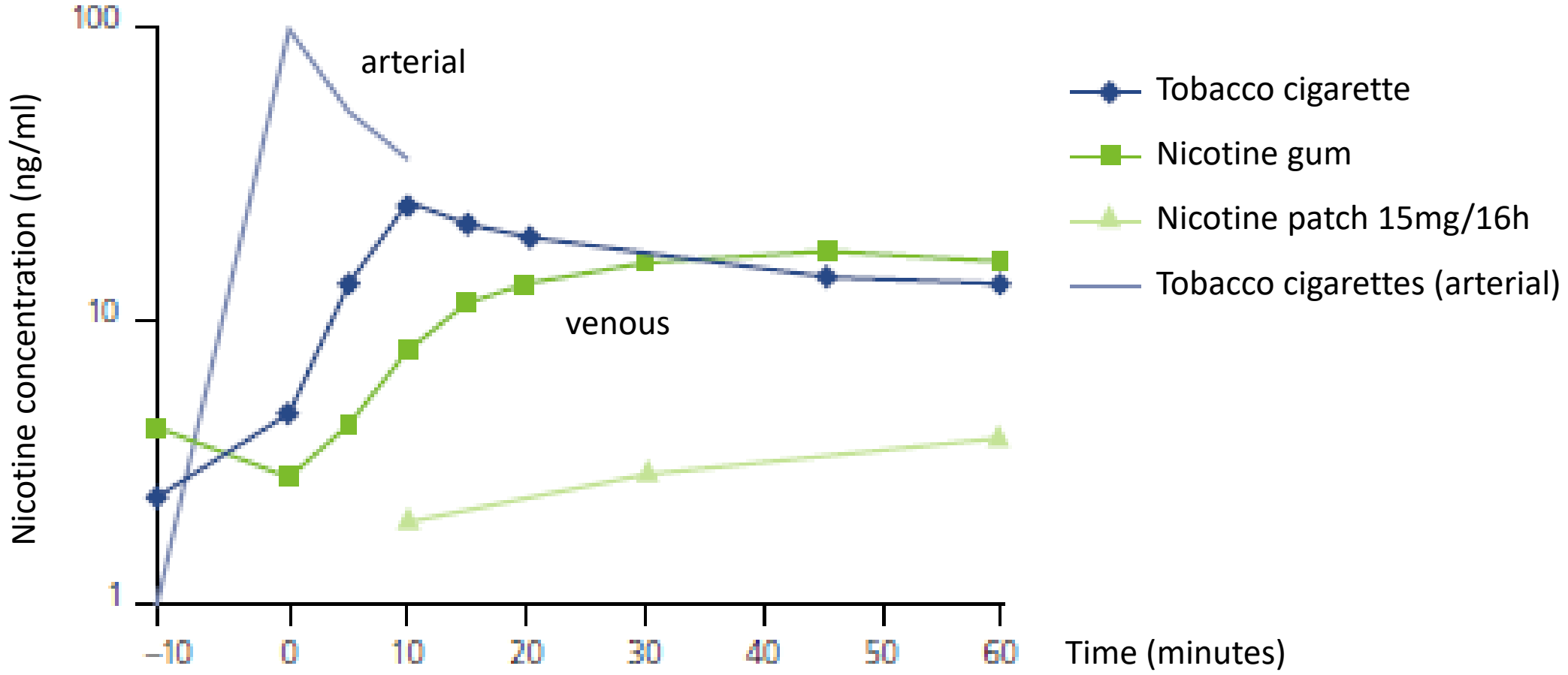
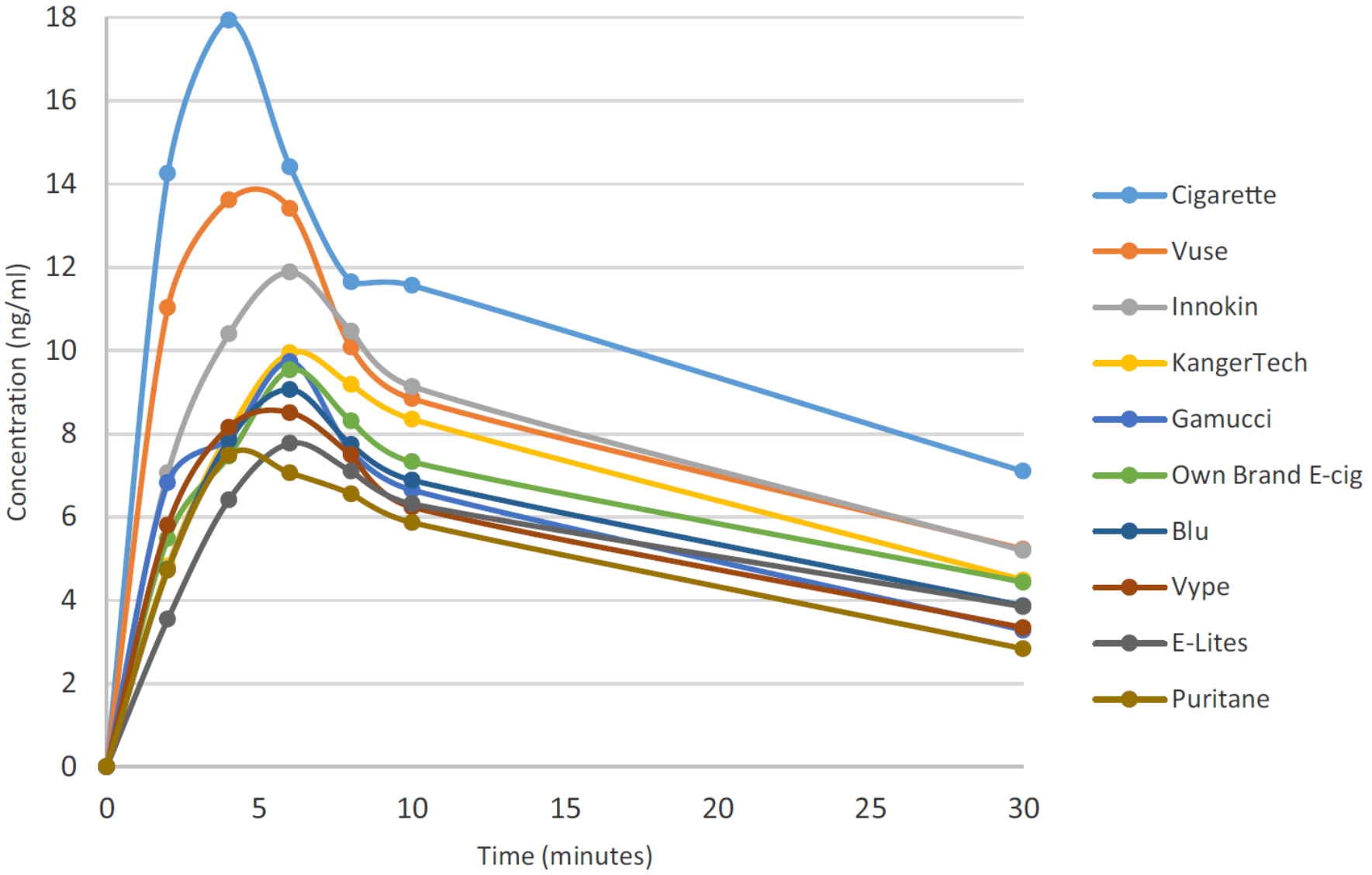
Potential for development of nicotine dependence based on delivery form





Hajek et al. Psychopharmacology, 2017




	Nicotine inhaler (pharmacologic)	E-Cigarettes	Tobacco heating systems (tobacco toasting systems)	Conventional cigarettes
Composition - Nicotine	+	+	+	+
- Tobacco leaves	-	-	+	+
- Propylene glycol (PG), glycerol	-	+	+	?
- Aromas	-	+	+	+
- Other additives	-	-[1]	+	+
Temperature	18-25°C	100-240°C	~330°C	640-780°C
Composition aerosol - Nicotine	+	+ to +++	+++	+++
- Carbon dioxyde (CO2)	-	-	+	++
- Carbon monoxyde (CO)	+	+	+	+
- Nitrogen monoxyde (NO)	-	-	+	+++
- Water (H20)	-	-	+	+++
- Polycyclic aromatic hydrocarbons (PAHs)	-	-	+	+++
- Organic volatile compounds (OVCs)	+	+ to +++	++	+++

Risks for somatic health and for developing addictive behaviours

Adapted from Abrams, DB, et al. Annu Rev Pub Health, 2028. DOI: 10.1146/annurev-publhealth-040617-013849

Cochrane Database of Systematic Reviews | Review - Intervention

New search | Conclusions changed

Electronic cigarettes for smoking cessation

Nicola Lindson, Ailsa R Butler, Hayden McRobbie, Chris Bullen, Peter Hajek, Rachna Begh, Annika Theodoulou, Caitlin Notley, Nancy A Rigotti, Tari Turner, Jonathan Livingstone-Banks, Tom Morris, Jamie Hartmann-Boyce

Authors' declarations of interest

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- There is high certainty that nicotine EC increases quit rates compared to nicotine replacement therapy (NRT) (RR 1.59, 95% CI 1.29 to 1.93; I^2 = 0%; 7 studies, 2544 participants).

- There is moderate-certainty evidence, limited by imprecision, that nicotine EC increases quit rates compared to non-nicotine EC (RR 1.46, 95% CI 1.09 to 1.96; I^2 = 4%; 6 studies, 1613 participants)

- Due to issues with risk of bias, there is low-certainty evidence that, compared to behavioural support only/no support, quit rates may be higher for participants randomized to nicotine EC (RR 1.88, 95% CI 1.56 to 2.25; I^2 = 0%; 9 studies, 5024 participants).

Background

- Efficacy:
  - Intervention in most randomized controlled trials (RCT) limited to one flavour/nicotine concentration in ENDS provided in intervention group

➔ Smokers who switch to ENDS after smoking cessation tend to use them over prolonged time. Long-term safety of ENDS use after smoking cessation essential.

- Safety:
  - Data on severe adverse events (SAE) and adverse events (AE) from RCT limited. Few RCT collected data on a priori defined safety outcomes and validated outcomes through medical chart review.
  - Tracking antibiotics use another way to estimate safety
- Further outcomes:
  - Respiratory symptoms key patient-reported outcomes related to tobacco smoking. Cough and phlegm expected to come from inhaled toxins through tobacco cigarettes smoke. Reduction of cough and phlegm would be a sign of improved lung health outcomes.

Aims

Primary aims:

- To assess the efficacy and safety of free ENDS in addition to standard care as compared with standard care alone with respect to abstinence from tobacco smoking at 6 months.

Secondary aims (pre-defined, not included in the statistical analysis plan (SAP)):

- To assess the effect of the intervention on respiratory symptoms

Methods: preparatory work

Phase 1

Select device model and e-liquid brand and flavors

Device selection

- Certifications
- Popularity
- Ease of use
- Autonomy
- Reservoir capacity
- Suitability for the target population

E-liquid selection

- Certifications
- Flavor popularity
- Composition (PG/VG ratio)
- Nicotine concentration
- Information on formulation

Phase 2

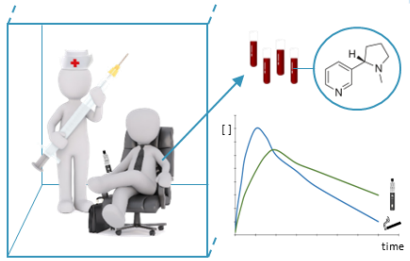
Toxicant concentrations under laboratory conditions

List of potential toxicants:

- Aldehydes
- Metals
- Polycyclic aromatic hydrocarbons (PAHs)
- Tobacco-specific nitrosamines (TSNAs)
- Volatile organic compounds (VOCs)

Phase 3

PBPK study on volunteers in an exposure chamber

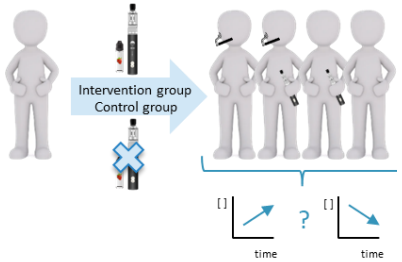


ENDS vs cigarette

- Compare the rate and degree of nicotine delivery in blood
- Determine pharmacokinetic parameters
- Evaluate user degree of craving and satisfaction

Phase 4

Randomized controlled trial on smoking cessation

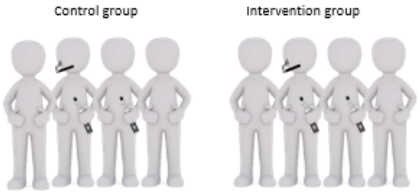


Efficacy, safety and toxicology of ENDS

- Continuous smoking abstinence (with biochemical verification)
- Adverse events and serious adverse events
- Health-related outcomes
- Analysis of urinary exposure biomarkers

Phase 4

Follow-up surveillance cohort



Survey and in-person visits

- Efficacy: Track use over time
  - Tobacco cigarettes
  - ENDS
  - Further nicotine delivery products
- Serious adverse events (SAE) and adverse events

Methods: design. selection of participants

- RCT: 1246 participants randomized at a 1:1 ratio; 5 study sites in Switzerland; follow-up at 6-months (later extended to 12-, 24- and 60 months).
- Inclusion criteria: >18, smoking 5 cig/day, willing to quit smoking
- Exclusion criteria: pregnant or planning pregnancy, regular use of ENDS or another smoking cessation drug in the last 3 months, unable to understand study processes. *No exclusion for somatic or mental health conditions*

Methods: intervention and control

- Control group: Standards-of-care smoking cessation counselling (SOC)
  - 30 minutes of counseling at baseline visit, then 2 months of phone counseling
  - NRT and other smoking cessation drug therapy allowed (they needed to purchase these themselves). Control group received a CHF 50 voucher they could use of any purpose, including for the purchase of NRT.
- Intervention group: SOC + free ENDS and choice of e-liquids for 6 months *ad libitum*, advice on use of products, no specific advice on e-liquid use or duration
  - 6 aromas (2 tobacco, 3 fruity, 1 menthol)
  - 4 nicotine concentrations (0, 6, 12, 19.6 mg/ml)

Methods: outcomes

Efficacy:

- Primary outcome:
  - 6-month continuous abstinence (self-reported no cigarette smoking from target quit date, biochemically validated by urinary levels of anabasine of less than 3 ng/ml). If anabasine data unavailable, validated by exhaled carbon monoxide (CO) of ≤9 ppm.
- Secondary outcomes:
  - 6-month sustained abstinence (allowing up to 5 cigarettes or a “grace period” of 2 weeks after target quit date)
  - 7-day point prevalence abstinence at 6-months, with and without validation

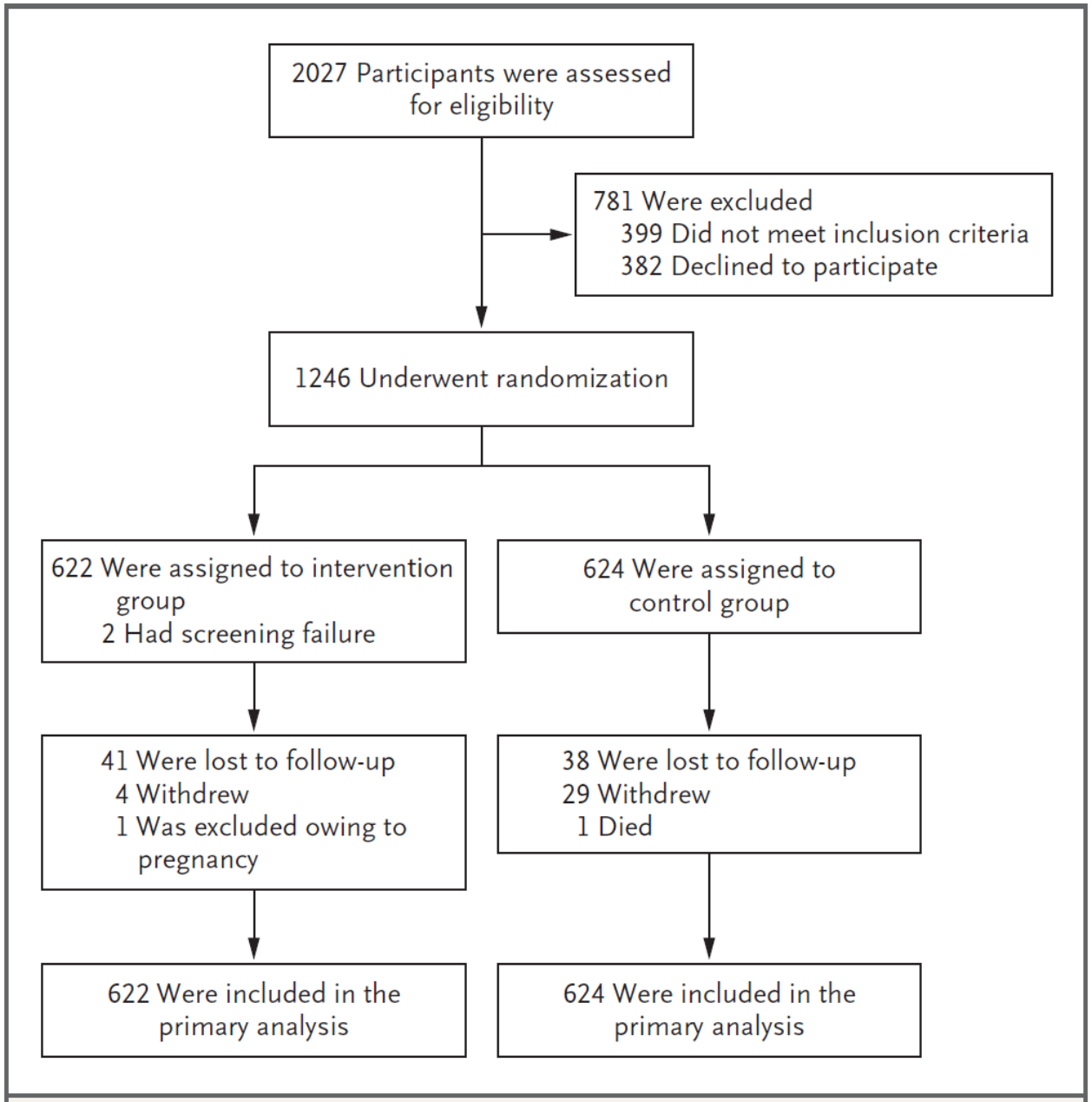
Safety:

- Serious adverse events (SAE) (validated by charts review)
- Adverse events (AE) (validated by charts review if consultation with physician)
- Antibiotics prescribed (self-report, validated by charts review)

Additional outcomes:

- Respiratory symptoms assessed with the chronic obstructive pulmonory disease (COPD) assessment test (CAT)

Results: flowchart



Results: participant characteristics

	Control group	Intervention group
	N=624	N=622
Age yr - median (IQR)	39 (30 - 52)	37 (28 - 51)
Women gender - no. (%)	295 (47.3)	290 (46.6)
Employed - no. (%)	465 (74.5)	438 (70.4)
Highest educational qualification - no. (%)		
Obligatory school; other; none	45 (7.2)	50 (8.0)
Secondary education	277 (44.4)	291 (46.8)
Tertiary education	302 (48.4)	281 (45.2)
Age started smoking yr - median (IQR)	16 (15 - 19)	16 (15 - 18)
Number of cigarettes per day - median (IQR)	15 (10 - 20)	15 (10 - 20)
Previous quit attempts (at least one) - no. (%)	530 (84.9)	531 (85.4)
Fagerström Test for Tobacco Dependence - mean (SD)	4.4 ± 2.3	4.3 ± 2.3
Expired CO level § - median (IQR) – p.p.m.	20 (12 - 29)	20 (13 - 29)

Results: efficacy

Outcome – no (%)	Control group, N=624	Intervention group, N=622	Crude relative Risk (95% CI)	Sensitivity analysis, Adjusted relative risk (95% CI)[1]	Absolute risk reduction (95%CI)
Primary outcome:					
Continuous abstinence, validated by anabasine and by CO if anabasine missing	102 (16.4)	180 (29.0)	1.77 (1.43 - 2.20)	1.71 (1.39 - 2.11)	12.7 (8.1 - 17.3)
Secondary outcomes:					
Continuous abstinence allowing a 2-week grace period, validated by anabasine and by CO if anabasine unavailable	110 (17.7)	191 (30.8)	1.74 (1.42 - 2.15)	1.70 (1.39 - 2.07)	13.1 (8.4 - 17.9)
Continuous abstinence, without biochemical validation	146 (23.4)	237 (38.2)	1.63 (1.37 - 1.94)	1.57 (1.33 - 1.86)	14.8 (9.7 - 19.9)
7 days point prevalence abstinence, without biochemical validation	200 (32.1)	332 (53.5)	1.67 (1.46 - 1.91)	1.56 (1.37 - 1.78)	21.4 (16.1 - 26.8)

[1] Multivariable adjusted model, adjusted for study site, age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström score with stabilized inverse probability of censoring weights (IPCW)

Table 3. Participant-Reported Use of Tobacco Cigarettes, E-cigarettes, and Nicotine-Replacement Therapy at 6 Months.*

Participant-Reported Use	Control Group N=504	Intervention Group N=552	Difference, Intervention vs. Control
	number (percent)		*percentage points*
No tobacco cigarettes: "tobacco abstainers"	194 (38.5)	329 (59.6)	21.1
No tobacco cigarettes, no e-cigarettes: "tobacco and e-cigarette abstainers"	179 (35.5)	62 (11.2)	–24.3
With nicotine-replacement therapy	14 (2.8)	1 (0.2)	–2.6
With smoking-cessation medication	1 (0.2)	0	–0.2
E-cigarettes and no tobacco cigarettes: "exclusive e-cigarette users"	15 (3.0)	267 (48.4)	45.5
E-cigarettes without nicotine	5 (1.0)	50 (9.1)	8.1
E-cigarettes with nicotine	10 (2.0)	217 (39.3)	37.3
E-cigarettes and nicotine-replacement therapy	0	1 (0.2)	0.2
E-cigarettes and smoking-cessation medication	0	0	0
No nicotine: "nicotine abstainers"†	170 (33.7)	111 (20.1)	–13.6
Tobacco cigarettes	310 (61.5)	223 (40.4)	–21.1
Tobacco cigarettes and no e-cigarettes: "exclusive smokers"	294 (58.3)	122 (22.1)	–36.2
Tobacco cigarettes and nicotine-replacement therapy	18 (3.6)	4 (0.7)	–2.9
Tobacco cigarettes and smoking-cessation medication	2 (0.4)	0	–0.4
E-cigarettes and tobacco cigarettes: "dual users"	16 (3.2)	101 (18.3)	15.1
Without nicotine in e-cigarettes	5 (1.0)	10 (1.8)	0.8
With nicotine in e-cigarettes	11 (2.2)	91 (16.5)	14.3
With nicotine-replacement therapy	1 (0.2)	4 (0.7)	0.5
With smoking-cessation medication	0	0	0

Results: safety

- **Serious adverse events (SAE)**
  - 26 SAE in 25 (4.0 %) participants in the intervention group
  - 34 SAE in 31 (5.0%) participants in the control group

    → RR 0.81; 95%CI: 0.48 to 1.35
- **Adverse events (AE)**
  - 272 (43.9%) participants reported 425 AE in the intervention group
  - 229 (36.7%) participants reported 366 AE in the control group

    → RR: 1.19; 95%CI: 1.04 to 1.37
- **Antibiotics prescription**
  - 54 (8.7%) participants in the intervention group reported 61 episodes of antibiotic use
  - 43 (6.9%) of those in the control group reported 56 episodes of antibiotic use

    → RR: 1.26; 95%CI: 0.86 to 1.85

Respiratory symptoms

- Difference in overall COPD assessment test score
  - **CAT total score control:** 5.7 (SD 4.5) and in intervention group 4.8 (SD 3.9)

	Difference in mean CAT-score (95%CI)	Adjusted difference in mean CAT-score (95%CI)*
Intervention vs control	-0.96 (-1.52 to -0.41)	-0.66 (-1.13 to -0.18)

* Multivariable adjusted linear regression with robust standard errors. Model adjusted for baseline covariates (age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström test score, study site and baseline CAT-score). We used stabilized inverse probability censoring weights to account for potential selective attrition. Confidence interval widths for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing.

… mostly through differences in cough and plegm

Limitations

- **Group allocation unblinded.**
  - Control group received a voucher at baseline.
  - Sensitivity analysis testing effect of preferred group allocation at baseline did not alter results.
- **Contrast of free ENDS added to SOC vs SOC alone.**
  - Not a contrast between ENDS and NRT

Conclusion

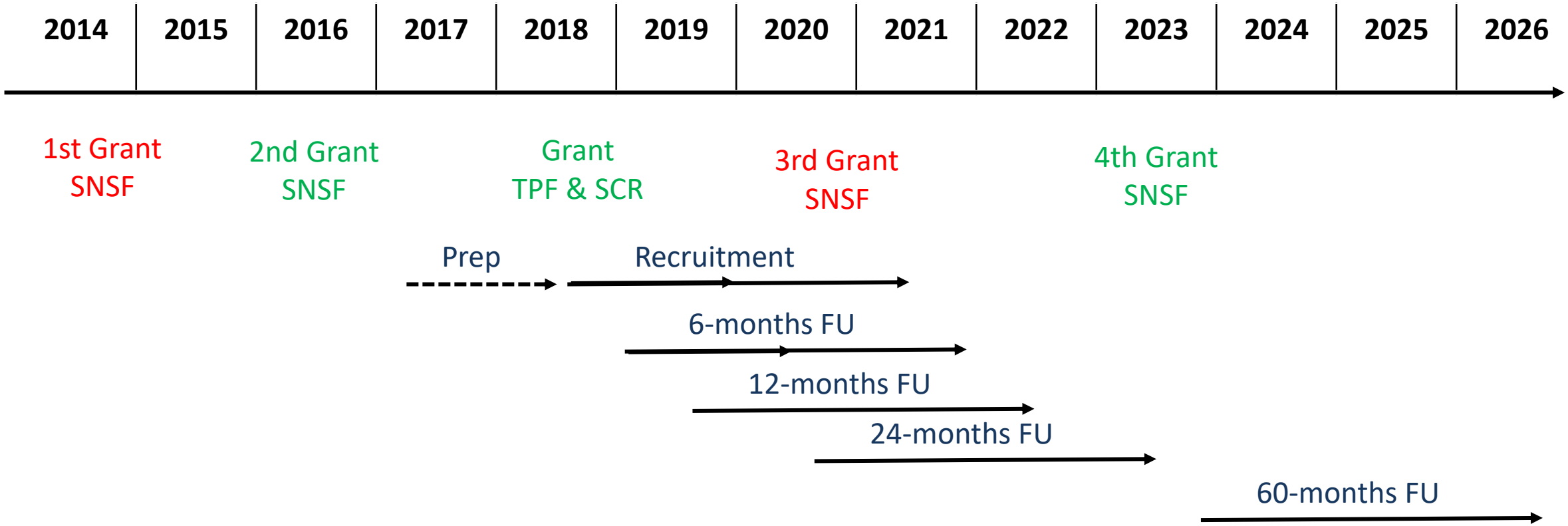
The addition of free ENDS to standard counselling resulted in greater abstinence from tobacco among smokers than standard counselling, but many of those who abstained from smoking tobacco continued using ENDS.

The intervention resulted in more adverse events but not more serious adverse events.

Significance

ENDS plus standard counseling may be a viable option for tobacco smokers who want to abstain from smoking without necessarily abstaining from nicotine but may be less appropriate for those who want to abstain from both tobacco and nicotine.

Timeline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2016
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2020
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2022
2023
2024
2025
2026
1st Grant SNSF
2nd Grant SNSF
Grant TPF & SCR
3rd Grant SNSF
4th Grant SNSF
Prep
Recruitment
6-months FU
12-months FU
24-months FU
60-months FU
Change Sample size
Law change E-liquids
EVALI
COVID-19
KEK-Decision design

What saved us

- Embrace change and challenges
- Focus on:
  - Recruitment
    - Increased advertisement budget from 12k to 120k over time
    - Monthly calls with study sites
    - Track response to advertisements to allocate funds effectively
  - Follow-up rates
    - Ask participants additional contact persons and GP
    - Rigorously track follow-up rates and discuss methods to optimize follow-up
  - Budget
    - Allocate funds to each study sites based on recruitment
    - Cross-fund study nurses with further grants
    - Embrace further collaborations and support further grant writing from others

What we did wrong

- Multiple entries on Clinicaltrials.gov -> misunderstood advice
- Not enough thoughts given to the Statistical Analytical Plan (SAP)
- Underestimated costs and challenges with laboratory samples
- Underestimated complexity of AE assessments in addition to SAE
  - Tobacco cigarettes impact ALL organs. All SAE and AE are of interest.
- Assumed intepretation of RCT and causal inference shared by PI involved in secondary outcomes
- For the 12- and 24- months follow-up. Lower follow-up rates.
- Limited international collaboration with key experts

Ethical considerations

- If health care professionals officially state that E-cigarettes are less harmful than tobacco cigarettes and that they help smokers quit:
  - Some **adult smokers** will quit smoking cigarette thanks to E-cigarettes
  - Some **adult non-smokers** will start using E-cigarettes
  - Some **adolescent smokers** will pick up E-cigarettes instead of smoking cigarettes
  - Some **adolescent non-smokers** will:
    - use E-cigarettes and become addicted to nicotine instead to cigarettes
    - use E-cigarettes and become addicted to nicotine because of e-cigarettes
    - use E-cigarettes and then start smoking cigarettes

Mitigating polarization (community engagement)

- In the development phase of the protocol
  - Work with association of persons vaping independent from the industry
  - Exchange intensively with expert detractors and proponents of e-cigarettes for smoking cessation
- Include collaborators with different opinions in the writing group
- Stakeholder involvement
  - Inform and exchange regularly about early results, involve stakeholders in the process of writing the media communication documents
- Coordinate message among study collaborators
- Multiple PI intervening in press to de-personalize debate

What we will keep on doing for the next RCTs

- Embrace empathic, collaborative, transparent leadership
- Collect multiple outcomes and encourage sub-studies to allow profiling/promoting students and junior faculty
- Advocate for implementation and dissemination sciences (IDS):
  - Interdisciplinary collaborations
  - Engage with stakeholders interested in the results from the start and intensively afterwards