Sources of bias in tobacco research trials and recommendations for reporting and mitigation

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Conflicts of interest

NO direct or indirect funding/payment from, or relationships with, the pharma, tobacco or e-cigarette industry or their lobby organisations.

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Aim for today

To discuss some important sources of **bias** in randomised controlled trials **(RCTs)**, commonly found in the field of tobacco research*, and proposals for their **reporting** and **mitigation**

*and all other fields, of course!

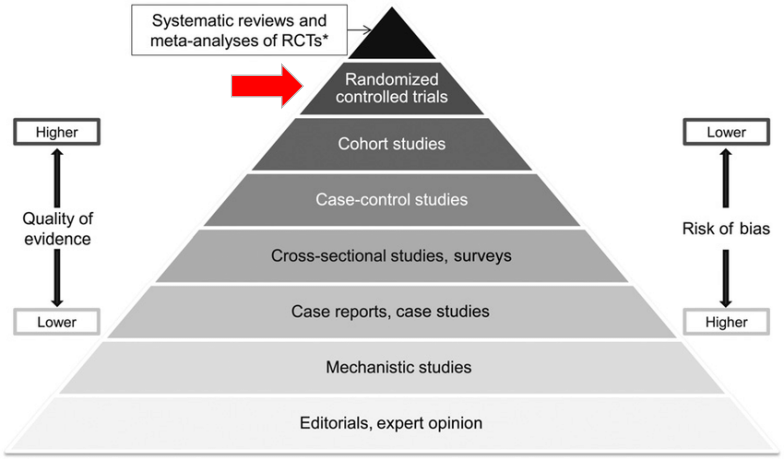
Background of today's work

Addiction journal

- Commissioned task (Methods & Techniques paper)
- Extensive review of the literature on bias in RCTs

The randomised controlled trial (RCT)

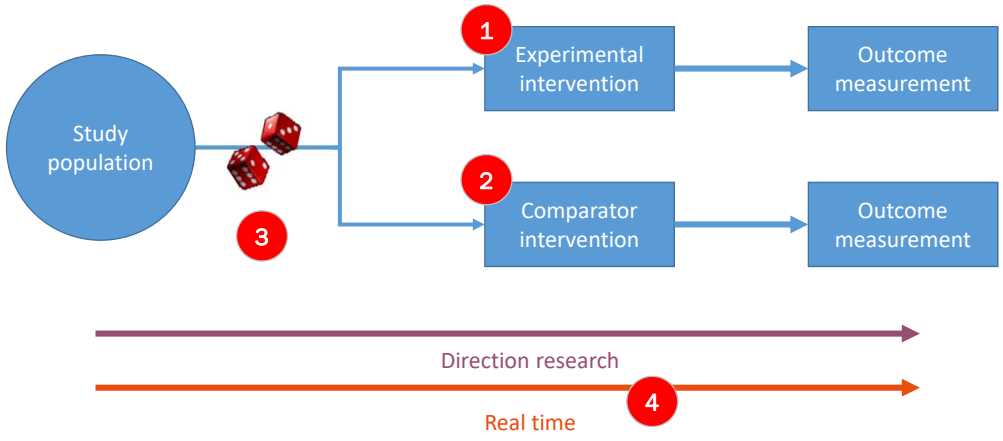
"Hierarchy of evidence"



[10]

Main design features RCT

(individually randomised parallel group trial)



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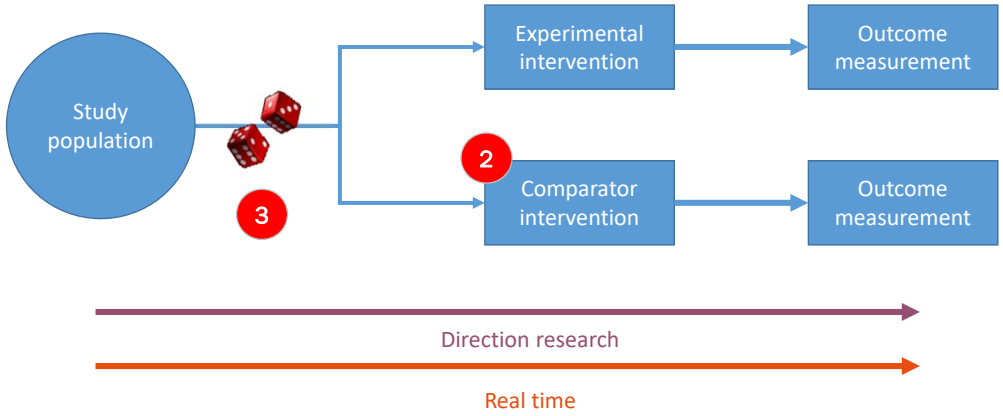

Why a control group?

- Observed effect (OE) ≠ specific effect (SE) of the intervention
- OE = SE + EV + NC + ME
  external variables (EV)
  natural course (NC)
  measurement error (ME)

[11]

Why a control group?

- Observed effect (OE) ≠ specific effect (SE) of the intervention
- OE = SE + EV + NC + ME
  external variables (EV)
  natural course (NC)
  measurement error (ME)

Example:

Abstinence from tobacco ≠
Smoking cessation treatment

Tobacco dependence
Spontaneous quitting
Self-report (no biochemical verification)

[11]

Why a control group?

- $OE_i = SE_i + EV_i + NC_i + ME_i$
- $OE_c = SE_c + EV_c + NC_c + ME_c$
- **$OE_i - OE_c = SE_i - SE_c$**

i = intervention
c = control

[11]

Why randomisation?

- $OE_i = SE_i + EV_i + NC_i + ME_i$
- $OE_c = SE_c + EV_c + NC_c + ME_c$
- **$OE_i - OE_c = SE_i - SE_c$**

only if:
$EV_i = EV_c$ (same non-specific effect)
$NC_i = NC_c$ (same prognosis)
$ME_i = ME_c$ (same measurement error)

i = intervention
c = control

Randomisation
can potentially eliminate bias resulting from differences in pre-existing characteristics of participants, prognostic factors in particular, in intervention and comparator conditions [1]

[11]

RCT: internal vs. external validity

- RCTs – if designed and conducted well – have high **internal validity** [2-4]
  = *inferences of causal relationships (i.e., that an intervention causes an outcome to change) are free of* ***systematic error (or bias****)*
- Internal validity **≠ precision** and **external validity** [3,5]
  = the extent to which study results are free from random error (precision)
  = generalisability or applicability of study results (external validity)
  - RCTs can suffer from problems of generalisability
  - Advantages of randomisation outweigh the limitations in generalizability

The "problem" with RCTs

- Practical issues with RCTs can compromise the integrity of design features and lead to bias
- Many sources of bias can occur during the whole process of research (during design, conduct, analysis, report) [6-8]
- Such bias can reduce the internal validity of an RCT, leading to a distortion of the true treatment effect [5,7]

The updated Cochrane tool for assessing Risk of Bias in randomised trials (RoB 2) [9]

5 Domains to assess the risk of bias
1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in the measurement of the outcome
5. Bias in selection of the reported results

See: www.riskofbias.info

A more fine-grained distinction of sources of bias in RCTs

Specific for RCTs	Non-specific	
1. Adherence bias	1. Allegiance bias	8. P-hacking
2. Lack of blinding	2. Attrition bias	9. Selection bias
3. Contamination	3. Dissemination bias	10. Selective reporting
4. Fidelity bias	4. Funding bias	11. Small study effects
5. Randomisation failure	5. Measurement bias	12. Subgroup analyses (incorrect/unclear)
	6. Missing data	13. Statistical adjustment (incorrect/unclear)
	7. Optimism bias	

When they occur vs. when they can be dealt with

- Biases can **occur** during any of the four main stages of an RCT
  I. Design
  II. Conduct
  III. Analysis
  IV. Report
- Biases can potentially be **mitigated** (by design and during conduct, analysis, report) at a **different stage** than they mostly occur

Adherence bias

Bias that arises when participants who are compliant with the treatment protocol differ from those who are non-compliant, and in ways that might affect the outcome being measured [12]

Adherence bias occurs during the **conduct** of an RCT.

Example: in trials using a "care as usual" control group, bias is introduced when participants in the control group also change their behaviour, e.g. use the smoking cessation treatment from the intervention group, due to study participation and the effect of measurements [13]

Adherence bias

Bias that arises when participants who are compliant with the treatment protocol differ from those who are non-compliant, and in ways that might affect the outcome being measured [12]

→ Inform participants well about trial protocol prior to randomisation → Offer an acceptable and relevant treatment (also in the control arm) → Limit burden of a treatment → Offer incentives for treatment continuation	**Design**

Adherence bias

Bias that arises when participants who are compliant with the treatment protocol differ from those who are non-compliant, and in ways that might affect the outcome being measured [12]	
→ Implement good communication with participants during the trial → Collect data on adherence (if possible: reasons for non-adherence)	**Conduct**

Adherence bias

Bias that arises when participants who are compliant with the treatment protocol differ from those who are non-compliant, and in ways that might affect the outcome being measured [12]	
→ Employ methods for dealing with missing data (e.g., sensitivity analyses, multiple imputation techniques) → Adhere with basic principle of analysing trial data according to the intention-to-treat (ITT) principle [7,15]	**Analysis**

Adherence bias

Bias that arises when participants who are compliant with the treatment protocol differ from those who are non-compliant, and in ways that might affect the outcome being measured [12]

→ Report which exact information was given to participants during the informed consent procedure and submit the participant information letter as supplementary material alongside the trial report [16] → Report data on adherence and results from methods dealing with it (if any) → Discuss if bias could have been introduced and how this affects the interpretation of the study findings*	**Report**

*standing item

Lack of blinding

Blinding (sometimes also called masking) refers to keeping individuals involved with a trial unaware of assignment of participants to the trial arms [23]

Example: in a pragmatic trial comparing two forms of behavioural support for smoking cessation in primary care complete blinding of all individuals was impossible [28]

Mitigation (analysis): the statistical analysis was planned a priori and the statistician analysing the trial data was blinded with regard to group allocation [28]

Lack of blinding

Blinding (sometimes also called masking) refers to keeping individuals involved with a trial unaware of assignment of participants to the trial arms [23]	
→ Try to blind as many categories of people involved with a trial: both providers and recipients of an intervention; researchers involved with the trial conduct; data analysists	**Design**
→ Clearly describe which categories of people had been blinded [23] → Discuss if bias could have been introduced and how this affects the interpretation of the study findings	**Report**

Contamination

Contamination occurs when participants in one trial condition seek out or are being exposed to elements of the trial's comparison condition or another experience that is similar, and can be a result of participants' treatment preferences

Example: in the landmark open label trial by Hajek et al. on e-cigarettes versus NRT for smoking cessation, expectation effects could have occurred due to strong product preferences participants have [29]

Mitigation (by design)**:** an attempt was made to reduce the risk of contamination by excluding smokers who had a strong preference to use or not to use NRT or e-cigarettes or who were currently using either type of product [29]

Contamination

Contamination occurs when participants in one trial condition seek out or are being exposed to elements of the trial's comparison condition or another experience that is similar, and can be a result of participants' treatment preferences	
→ When contamination is likely, use alternative design, e.g. a cluster RCT	**Design**
→ Measure the preferences of participants prior to randomisation	**Conduct**
→ Incorporate data on preferences in sensitivity analyses	**Analysis**
→ Report data on preferences and results from methods dealing with it → Discuss if bias could have been introduced and how this affects the interpretation of the study findings	**Report**

Fidelity bias

Fidelity bias (or performance bias) refers to systematic differences between trial arms in how interventions are delivered, or in exposure to factors other than the intervention of interest [21,53]

Example: in a smoking cessation trial where the intervention was implemented in routine TB (tuberculosis) care, fidelity to the intervention delivery as planned was found to be high for TB-related messages but less so for smoking cessation messages [55,56]

Mitigation (conduct, report): a fidelity index [58] was developed and audio-recordings of intervention sessions were coded for TB-related and cessation messages delivered [56]

Fidelity bias

Fidelity bias (or performance bias) refers to systematic differences between trial arms in how interventions are delivered, or in exposure to factors other than the intervention of interest [21,53]	
→ Develop an a priori list of potentially active ingredients of the intervention. If these include behavior change techniques (BCTs), base these on a common BCT taxonomy [59] → Develop protocols for the standardisation of the delivery of intervention components (including descriptions of BCTs) and implementation of trials procedures → Train all individuals involved with the trial on those protocols → Apply blinding of individuals delivering intervention components	**Design**

Fidelity bias

Fidelity bias (or performance bias) refers to systematic differences between trial arms in how interventions are delivered, or in exposure to factors other than the intervention of interest [21,53]	
→ Measure the fidelity of treatment components and any co-interventions during the trial (as part of a larger process evaluation)	**Conduct**
→ Incorporate data on fidelity in sensitivity analyses	**Analysis**
→ Report data on fidelity and results from methods dealing with it → Discuss if bias could have been introduced and how this affects the interpretation of the study findings	**Report**

Randomisation failure

The aim of randomisation is balancing measured and unmeasured confounders between trial arms at baseline, allowing an unbiased estimation of the intervention effect [80,81]

Example: procedures using an open random allocation schedule; assignment using envelopes without appropriate safeguards (e.g, unsealed, non-opaque, not sequentially numbered) [81]

Mitigation: impossible (~~randomised~~ controlled trial)

Randomisation failure

The aim of randomisation is balancing measured and unmeasured confounders between trial arms at baseline, allowing an unbiased estimation of the intervention effect [80,81]

→ Apply an appropriate method of randomisation → Develop an adequate allocation concealment mechanism and describe how the method was implemented [23,24,85,89] → Describe in the statistical analysis plan (which should be part of the study protocol) how you will deal with potential baseline imbalances during the analysis of trial data and pre-specify the covariates you will use for adjusted analyses, if any	**Design**

Randomisation failure

The aim of randomisation is balancing measured and unmeasured confounders between trial arms at baseline, allowing an unbiased estimation of the intervention effect [80,81]	
→ Assess baseline imbalances between trial arms in relevant potential confounders (in particular demographic characteristics and factors which are prognostically important) [83] → In case of random differences between trial arms at baseline consider adjusted analyses for the observed differences in covariates [80,82]	**Analysis**
→ Report baseline data and results from methods dealing with any differences → Discuss if bias could have been introduced and how this affects the interpretation of the study findings	**Report**

Responsibilities for dealing with biases

- **Researchers of the trial**

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Example for planning/transparent reporting

Cluster RCT on the effectiveness of training GPs to deliver brief stop-smoking advice (5As vs. ABC)

- Funding application, review ethics committee, pilot study
- Study protocol (incl. findings from pilot study): BMC Family Practice 2019;20:107
- Trial registration: German Clinical Trials Register DRKS00012786
- Elaborated statistical analysis plan with detail + stats software code
  - Test statistical software code on "blinded" data set
- Published **prior to data analysis** on OSF: https://osf.io/fj4m2/

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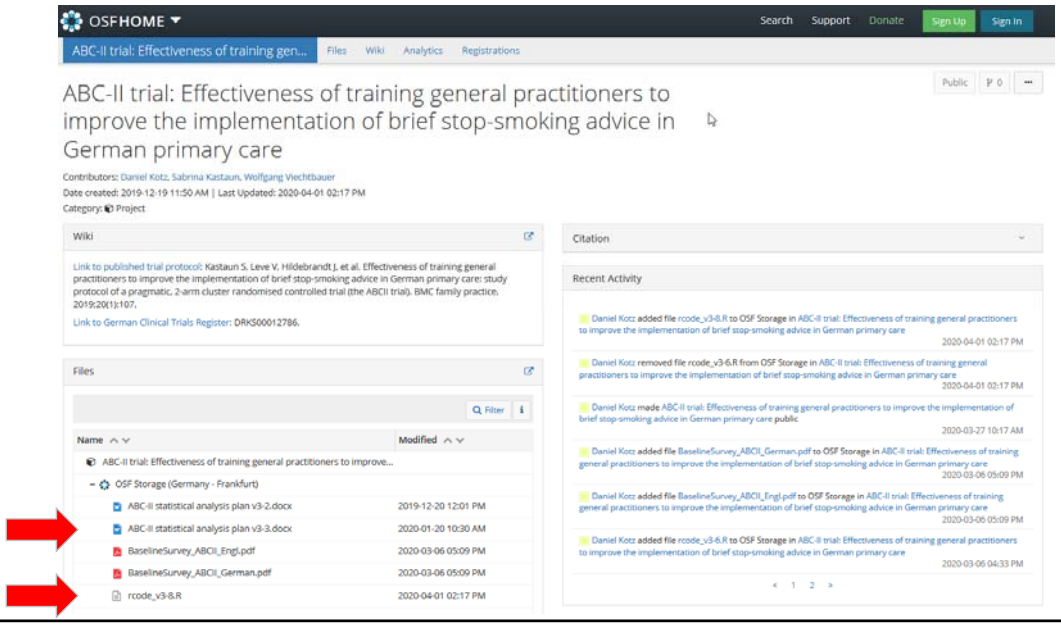

Statistical analysis plan of the ABC-II trial

Version 3.3 | 17 January 2020 | Published on OSF: https://osf.io/ffd4m2/

Version	Status/changes to previous version
3.3	Adaptation of statistical models for secondary outcomes (page 2, marked red)
3.2	First version uploaded on OSF, prior to data analysis

AUTHORS
Wolfgang Viechtbauer, Sabrina Kastaun, Daniel Kotz

BACKGROUND INFORMATION
Trial registration: German Clinical Trials Register (DRKS00012786); registered on 22nd August 2017 (prior to the first patient in).

A priori published trial protocol: Kastaun S, Leve V, Hildebrandt J, et al. Effectiveness of training general practitioners to improve the implementation of brief stop-smoking advice in German primary care: study protocol of a pragmatic, 2-arm cluster randomised controlled trial (the ABCII trial). BMC Family Practice. 2019;20(1):107.

We wrote the statistical analysis code based on a blinded dataset; i.e. with the values of the primary (pre vs. post training measurement) and secondary exposure variables (SA vs. ABC training method) shuffled randomly. The code and additional material can be found at: osf.io/ffd4m2/.

CHANGES TO THE PUBLISHED STUDY PROTOCOL

1. We will not adjust analyses for the variable motivation to stop smoking. Explanation: motivation to stop smoking is not a confounder but a variable in the causal pathway between exposure (GP's brief advice) and outcome (attempts to quit).
2. We will not perform a complete case analysis for the primary outcome (i.e., an analysis in which all cases with missing data on the primary outcome will be excluded from the analysis). Explanation: missing data on the primary outcome are very rare (only 4 cases).
3. For the adjusted analyses, we will impute missing data of the potential confounders (age, sex, level of education, time spent with urges to smoke, strength of urges to smoke) using multiple imputation (mice package in R). Explanation: less potential for bias compared to a complete case analysis.
4. We will assess two additional secondary outcomes (marked S_{+1} and S_{+2} in Table 1).
   a. S_{+1} = received recommendation/prescription from GP during previous consultation for NRT, varenicline or bupropion. Explanation: this outcome lumps all forms of pharmacotherapy together (combination of outcomes S_2 and S_3). This is likely to be necessary, as usage rates of pharmacotherapy for smoking cessation are very low in Germany [1]
   b. S_{+2} = received recommendation/prescription from GP during previous consultation for a combination therapy of NRT, varenicline or bupropion with individual or group behavioural counselling. Explanation: this is a relevant outcome as this is the most effective evidence-based method of quitting [2]
5. We will run the multilevel mixed-effects logistic regression models in R using the lme4 package. We will run sensitivity analyses using the GLMMadaptive and glmmTMB packages. Explanation:

running the model with different software packages increases confidence in the results. We had not described this level of detail in the study protocol.

6. We will run the following subgroup analyses for the primary outcome (P: pre vs. post training effect on brief advice to quit; see Table 2). Results by subgroup will only be reported in case the interaction effect between the subgroup variable and the exposure variable is statistically significant at p<0.05. Explanation: subgroup analyses are explorative but can yield useful information. We had not yet described subgroup analyses in the study protocol.
   a. Patient's sex: male vs. female
   b. Patient's age: below average age of the study population vs. above
   c. Patient's level of education: low vs. middle vs. high
   d. Patient's number of cigarettes smoked per day: <=10 vs. >10
   e. GP's sex: male vs. female
   f. GP's number of years in clinical practice: below median number of years vs. above
   g. GP's practice type: single practice vs. other type
   h. GP's smoking status: ever smoker (current or ex) vs. never
7. We will run less complex models (i.e., multilevel mixed-effects logistic regression models without a random effect for the time effect pre- versus post training) for the analysis of secondary outcomes $S_{+1}, S_{+2}, S_3, S_4, S_5, S_6, S_7, S_8, S_9$. Explanation: the outcomes appeared to be so rare upon data inspection (in particular smoking cessation medication is rarely prescribed by GPs in Germany) that the complex models (with a random effect for the time effect pre- versus post training) cannot be fitted.

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Table 1: Overview of pre-specified outcomes and analyses

Protocol identifier	R code identifier	Outcome definition (self-reported by patient)	Pre-specified analyses (with multilevel mixed-effects logistic regression models)
P (primary)	0	Received **advice to quit** from GP during previous consultation	1. Imputed data[a], adjusted for potential confounders[b] *(primary)* 2. Complete cases data, adjusted for potential confounders[b]
S_1	1	Received recommendation/prescription from GP during previous consultation for **individual or group behavioural counselling** in own practice or elsewhere	3. Imputed data[a], adjusted for potential confounders[c]
S_2	2	Received recommendation/prescription from GP during previous consultation for **NRT**	4. Imputed data[a], adjusted for potential confounders[d]
S_3	3	Received recommendation/prescription from GP during previous consultation for **varenicline or bupropion**	5. Imputed data[a], adjusted for potential confounders[e]
S_{+1}	4	Received recommendation/prescription from GP during previous consultation for **NRT, varenicline or bupropion** (= S_2 or S_3)	6. Imputed data[a], adjusted for potential confounders[f]
S_{+2}	5	Received recommendation/prescription from GP during previous consultation for a **combination therapy** of NRT, varenicline or bupropion with individual or group behavioural counselling	7. Imputed data[a], adjusted for potential confounders[g]
S_4	...	Made a **quit attempt** in the period between consultation with the GP and follow-up **week 4**	8. Imputed data[a], adjusted for potential confounders[c]
S_5	...	Made a **quit attempt** in the period between consultation with the GP and follow-up **week 12**	9. Imputed data[a], adjusted for potential confounders[d]
S_6	...	Made a **quit attempt** in the period between consultation with the GP and follow-up **week 26**	10. Imputed data[a], adjusted for potential confounders[e]
S_7	...	**Abstinent** from smoking at follow-up **week 4**	11. Imputed data[a], adjusted for potential confounders[f]
S_8	...	**Abstinent** from smoking at follow-up **week 12**	12. Imputed data[a], adjusted for potential confounders[g]
S_9	...	**Abstinent** from smoking at follow-up **week 26**	13. Imputed data[a], adjusted for potential confounders[c]
S_{SA_0}	0	= P, but for SA vs. ABC method (interaction with pre vs. post measurement)	14. Imputed data[a], adjusted for potential confounders[d] 15. Complete cases data, adjusted for potential confounders[d]
S_{SA_1}	1	= S_1, but for SA vs. ABC method (interaction with pre vs. post measurement)	16. Imputed data[a], adjusted for potential confounders[c]
S_{SA_2}	2	= S_2, but for SA vs. ABC method (interaction with pre vs. post measurement)	17. Imputed data[a], adjusted for potential confounders[c]
S_{SA_3}	3	= S_3, but for SA vs. ABC method (interaction with pre vs. post measurement)	18. Imputed data[a], adjusted for potential confounders[c]
S_{SA_+1}	4	= S_{+1}, but for SA vs. ABC method (interaction with pre vs. post measurement)	19. Imputed data[a], adjusted for potential confounders[c]

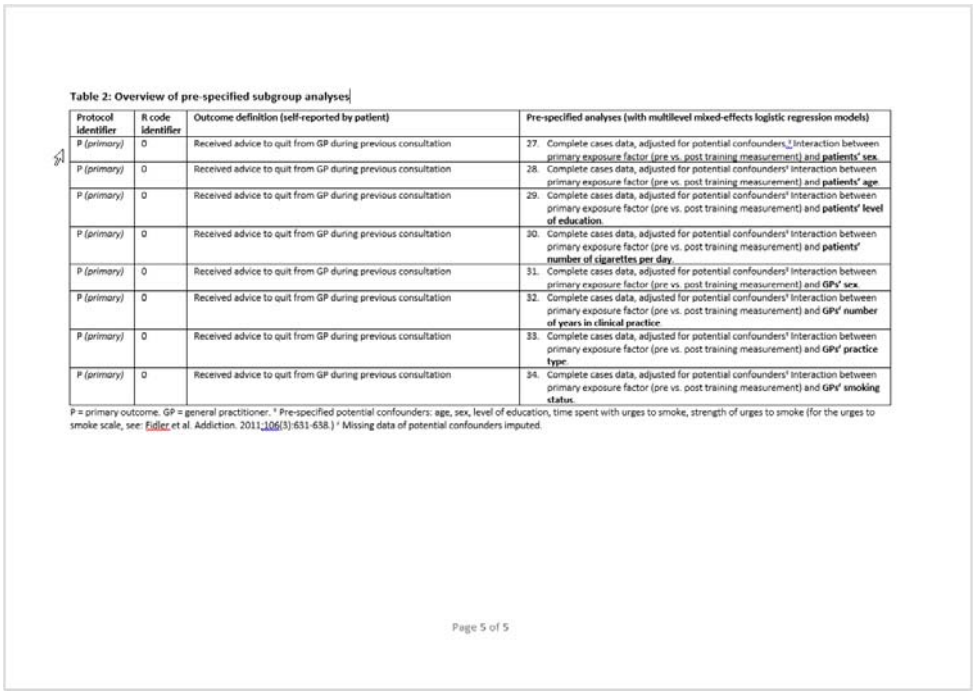

Table 2: Overview of pre-specified subgroup analyses

Protocol identifier	R code identifier	Outcome definition (self-reported by patient)	Pre-specified analyses (with multilevel mixed-effects logistic regression models)
P (primary)	0	Received advice to quit from GP during previous consultation	27. Complete cases data, adjusted for potential confounders,[2] Interaction between primary exposure factor (pre vs. post training measurement) and **patients' sex**.
P (primary)	0	Received advice to quit from GP during previous consultation	28. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **patients' age**.
P (primary)	0	Received advice to quit from GP during previous consultation	29. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **patients' level of education**.
P (primary)	0	Received advice to quit from GP during previous consultation	30. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **patients' number of cigarettes per day**.
P (primary)	0	Received advice to quit from GP during previous consultation	31. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **GPs' sex**.
P (primary)	0	Received advice to quit from GP during previous consultation	32. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **GPs' number of years in clinical practice**.
P (primary)	0	Received advice to quit from GP during previous consultation	33. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **GPs' practice type**.
P (primary)	0	Received advice to quit from GP during previous consultation	34. Complete cases data, adjusted for potential confounders[2] Interaction between primary exposure factor (pre vs. post training measurement) and **GPs' smoking status**.

P = primary outcome. GP = general practitioner. [2] Pre-specified potential confounders: age, sex, level of education, time spent with urges to smoke, strength of urges to smoke (for the urges to smoke scale, see: Fidler et al. Addiction. 2011;106(3):631-638.) [3] Missing data of potential confounders imputed.

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Example for transparent reporting

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  - Test statistical software code on "blinded" data set
- Published **prior to data analysis** on OSF: https://osf.io/fj4m2/
- Pre-print publication on medRxiv: https://doi.org/10.1101/2020.03.26.20041491

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5. Randomisation failure	5. Measurement bias	**12. Subgroup analyses (incorrect/unclear)**
	6. Missing data	**13. Statistical adjustment (incorrect/unclear)**
	7. Optimism bias	

Responsibilities for dealing with biases

- **Researchers of the trial**

- Reviewers of funding applications and trial reports
  - Be aware of potential biases when critically reviewing an application/manuscript
  - Take into account information from trial registration platform, published trial protocol, and supplementary material (compare reported analyses and outcomes with the originally planned analyses and outcomes!)
- Editors and publishers of journals
  - Make publication conditional on prospective registration of a trial
  - Promote publication of high-quality "negative" studies
  - Implement two-step review procedure blinded to study outcomes: (1) introduction and methods, (2) results and discussion
  - Adopt "registered reports" procedure (see, e.g.: https://cos.io/rr/)

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Key conclusions

- 5 specific and 13 non-specific sources of bias exist in RCTs (at least…)
- Biases can occur during all 4 stages: design, conduct, analysis, report
- Biases can be mitigated (though not always fully eliminated)
  - When designing the study, procedures, analyses → careful planning early on!
- Biases should be described and discussed during report
- Researchers, but also reviewers of trial reports and journal editors/publishers should be aware and take responsibility
  - Critical appraisal of every single research study remains important

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