TOB-STOP-COP: TOBacco STOP in COPd-Trial – Study Protocol

A randomised open-label, superiority, multicentre, two-arm intervention study of the effect of "high-intensity" vs. 'low-intensity' smoking cessation intervention in active smokers with chronic obstructive pulmonary disease.

Participants

Mohamad Isam Saeed[1], Pradeesh Sivapalan[1,12], Josefin Eklöf[1], Charlotte Suppli Ulrik[2], Charlotta Pisinger[6], Therese Lapperre[3], Philip Tønnesen[4], Nils Hoyer[1], Julie Janner[2], Marie Lavesen Karlsson[5], Charlotte Sandau Bech[2], Kristoffer Marså[7], Nina Godtfredsen[2], Eva Brøndum[2], Birgit Munk[8], Merete Raaschou[10], Andrea Browatzski[5], Pernille Lütken[9], Jens-Ulrik Stæhr Jensen[1,11]

[1]Department of Internal Medicine C, Section of Respiratory Medicine, Herlev and Gentofte University Hospital
[2]Department of Respiratory Medicine, Hvidovre University Hospital, Hvidovre
[3]Department of Respiratory Medicine, Bispebjerg and Frederiksberg Hospital
[4]Department of Respiratory Medicine, Rigshospitalet
[5]Department of Respiratory and Infectious Medicine, Nordsjællands Hospital
[6]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital
[7]Palliation Unit, Herlev and Gentofte University Hospital
[8]Rygestopcaféen, Hvidovre University Hospital
[9]Rygestopkonsulenterne ApS
[10]Patient representative
[11]PERSIMUNE & CHIP, Department of Infectious Medicine, Rigshospitalet, Copenhagen Ø
[12]Department of Internal Medicine, Zealand University Hospital, Roskilde

Principal investigator:
Jens-Ulrik Stæhr Jensen, MD PhD.
Specialist senior consultant & Research associate professor at University of Copenhagen
Department of Internal Medicine C, Respiratory Medicine Section
Herlev-Gentofte Hospital

Primary Committee

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Scientific Project sponsor

Chronic Obstructive Pulmonary Disease Trial Network: COP: TRIN - a network of independent COPD researchers in Denmark: www.coptrin.dk. Contact person: Specialist senior consultant, Research associate professor, Jens-Ulrik Stæhr Jensen, PhD.

Steering Committee:

1. Department of Internal Medicine, Respiratory Medicine Section, Gentofte Hospital: Specialist senior consultant Jens-Ulrik Jensen, PhD; Senior consultant Jon Torgny Wilcke, PhD, associate professor.
2. Department of Internal Medicine, Respiratory Medicine Section, Hvidovre Hospital: Chief physician in charge Pia Thaning; Chief Medical Officer Mia Moberg PhD, Post Doc; Professor, Chief Medical Officer Charlotte Suppli Ulrik, Dr. Med .; MD Julie Janner, PhD, Post Doc.
3. Department of Respiratory Medicine, Bispebjerg Hospital: Senior Consultant, Helle Frost Andreassen, PhD; Chief Physician, Thérèse Lappere, PhD;
4. Department of Respiratory Medicine, Odense University Hospital: Chief Physician, Ingrid Titlestad, PhD
5. Department of Respiratory Medicine, Aalborg University Hospital: Chief Medical Officer Ulla M. Weinreich, PhD
6. Department of Respiratory Medicine, Næstved Hospital: Chief physician Uffe Bødtger, PhD
7. Department of Respiratory and Infectious Medicine, Nordsjælland Hospital, Hillerød: Senior Consultant, Thyge Lynghøj Nielsen, PhD; consultant Andrea Browatski.
8. Department of Internal Medicine, Vejle Hospital: Professor, Chief Physician Ole Hilberg, MD.
9. Palliation Unit, Herlev Hospital: Chief physician Kristoffer Marså
10. The University of Manchester: Professor, Senior Consultant Jørgen Vestbo, MD, DMSc.
11. Patient representative, Merete Raaschou, cand.psych.

SPIRIT checklist is filled in “Additional file 1”.

Abstract

Background: Cigarette smoking is the leading cause of chronic obstructive pulmonary disease (COPD) and it contributes to the development of many other serious diseases. Smoking cessation in COPD patients is known to improve survival and reduce the number of hospitalization-requiring acute exacerbations of COPD. However, smoking cessation interventions in these patients have only been successful for approximately 15-20% for consistent smoking abstinence in 12 months. Thus, more effective interventions are needed for this patient group. The aim of this study is to determine whether a high-intensity intervention compared to a low-intensity intervention can increase the proportion of persistent (>12 months) anamnestic and biochemical smoking cessation in active smokers with COPD.

Methods: This study is a randomized controlled trial. A total of 600 active smokers with COPD will be randomly assigned 1:1 to either a standard treatment (guideline-based municipal smoking cessation programme, "low intensity" group), or an intervention group ("high-intensity" group), which consists of group sessions, telephone consultations, behaviour design, hotline, “buddy-matching” (smoker matched with COPD patient who has ceased smoking). Both groups will receive pharmacological smoking cessation. The primary endpoint is anamnestic and biochemical (cotinine analysis in urine) validated smoking cessation after 12 months.

Discussion: The potential benefit of this project is to prevent smoking-related exacerbations of COPD and thereby reduce logistics and costs of hospitalization and treatment of COPD. In addition, the project can potentially benefit from increasing the quality of life and longevity of COPD patients and reducing the risk of other smoking-related diseases.

Trial Registration: ClinicalTrials.gov: NCT04088942, registered 13th September 2019, (https://clinicaltrials.gov/ct2/show/NCT04088942)

Key Words: COPD, Randomized Controlled Trial, Smoking Cessation, exacerbations, varenicline.

Background

COPD is a life-threatening and incurable lung disease characterized by persistent breathing problems and poor airflow in the lungs that usually worsens over time. Globally, it is estimated that approx. 250 million people have COPD and that approx. three million deaths annually, corresponding to 5% of all deaths, are caused by COPD [4]. In Denmark, it has been estimated that approximately 320000 people suffer from COPD, leading to around 5500 deaths due to COPD each year, making the disease the third most frequent cause of death in Denmark [5]. Worldwide, cigarette smoking is by far the most important cause of COPD by causing persistent lung inflammation. Cigarette smokers have a higher incidence of respiratory symptoms and abnormal lung functions, a greater annual decline in FEV_1 (forced expiratory volume in 1.second) and a greater mortality rate than non-smokers [6]. Other types of tobacco e.g. pipes, cigar, hookahs are also risk factors for the development of COPD [6, 7]. Passive exposure to cigarette smoke (passive smoking) can also contribute to respiratory symptoms and COPD by increasing the overall burden on the lungs of inhaled particles and gases [6].

In addition, active cigarette smoking and smoking of other tobacco products is the main reason for the development of lung cancer, both with regard to individual and population risk [8]. Individual risk increases with greater number of cigarettes smoked per day and several years of smoking, and population risk increases with the incidence of current smokers [8]. Acute exacerbation of COPD is a worsening of the patient's respiratory symptoms, such as shortness of breath, cough, etc. that lasts for several days and requires medical treatment beyond the patient's usual medicine. Exacerbations of COPD are associated with increased risk of mortality due to decreasing lung function and activity level and often lead to hospitalization [9, 10]. This is one of the biggest costs

for the healthcare system for treatment of COPD [11]. In addition, there is evidence that exacerbations of COPD increase the risk of myocardial infarction [12] and strokes [13].

In this way, smoking cessation will be the most effective intervention to stop the development of COPD, as well as increase survival and reduce morbidity [14]. Overall, tobacco smoking thus increases mortality and serious morbidity as well as symptoms in COPD patients, and smoking cessation should be the top priority in treating COPD.

Current evidence of smoking cessation:

Smoking cessation is only successful in a proportion of patients with COPD. In an intervention study from 2011 (N = 499), the 12 months of results showed that 18.6% of COPD patients treated with varenicline had stopped smoking, while only 5.6% of COPD patients in the placebo group continued to have had quit smoking after 12 months (carbon monoxide-confirmed continuous abstinence rate, CAR) [15]. Despite a significant difference in absolute risk of 13% between the varenicline and placebo group, it is still >80% of COPD patients in the varenicline group who continued to smoke after 12 months, which is not satisfactory. Offers of varenicline is the standard municipal smoking cessation intervention and thus our choice of comparator.

Another intervention study from 2006 (N = 370) showed that 17% of COPD patients treated with sublingual nicotine tablets (Nicotine Replacement Therapy, NRT) had discontinued smoking after 12 months, whereas 10% of COPD patients in the placebo group discontinued in the same time period [16]. Both groups also received behavioural support from a nurse, some received "low support", i.e. four visits and six phone calls from the nurse, while those assigned "high-support" got seven visits and four phone calls [16]. There was no difference in the results between "high-support" and "low-support" [16]. However, behavioural support has had an impact on getting

more people to stop smoking, which also shows that 10% from the placebo group stopped smoking after 12 months. Behavioural support personal or by telephone to people using pharmacotherapy to stop smoking has a small but important effect [17], however, this study does not take into account differences in smokers with COPD and without COPD. Smoking cessation advice turns out to be most effective combined with NRT treatment in COPD patients [18], but the studies so far have not used varenicline.

A Cochrane review from 2016 (16 studies, involving 13,123 participants) shows among other things: from two studies, sublingual nicotine tablets and varenicline increased smoking cessation rates compared to placebo over twice as much, respectively. RR 2.60 (95% CI 1.29-5.24) and RR 3.34 (95% CI 1.88-5.92) [19]. Pooled results from two other studies also showed a positive effect of bupropion compared to placebo (RR 2.03 (95% CI 1.26-3.28)) [19]. By combining these four studies there was high quality evidence for the effect of pharmacotherapy plus high-intensity behavioural therapy compared to placebo plus high-intensity behaviour therapy (RR 2.53 (95% CI 1.83-3.50)) [19].

A meta-analysis from 2018 (comprising 61 RCTs) showed that during the 12-month attempt at smoking cessation, it was approx. 20% of participants in drug studies (varenicline, NRT or bupropion) who stopped smoking [20]. In comparison, 12% of the participants in the placebo groups abstained from smoking for 12 months [20]. This makes the net benefit of drug treatment 8% after the first 12 months. Within one year, the benefits of using the mentioned drugs (varenicline, NRT or bupropion) fall from 17% after three months to 12% after six months to 8% after 12 months [20], so more and more people re-started smoking after some time despite having received smoking cessation drugs.

In a study from 2008, smoking cessation rates was examined in a group of patients with COPD who participated in a one year smoking cessation program (N = 247) and were compared with a group of COPD patients who received normal care (N = 231) with follow-up one year and three years after starting the program [21]. The smoking cessation program included a two-week period of admission to hospitals, group sessions where NRT and exercise were recommended/advised in, and in addition telephone calls with specially trained staff who gave feedback and support for smoking cessation throughout the year [21]. In the smoking cessation program, 52% of patients ceased smoking after one year and 38% after three years, correspondingly in the normal care group 7% after one year and 10% after three years [21]. However, the study is not in a controlled design, still the results are inspiring.

Rationale for the study - scientific perspective:

Although many different methods of smoking cessation and several years of preventive action have been tried, they have all had very little effect. And this despite the many known harmful effects of continued smoking. Thus, more effective interventions are needed for this patient group.

The hypothesis in the study described here is that a person-adapted, multi-component, intensive smoking cessation intervention, results in a higher incidence of anamnestic and biochemical smoking cessation after 12 months in people diagnosed with COPD and as the last 8 weeks before inclusion in the study, are current daily smokers than a standard smoking cessation intervention with municipal smoking cessation offers and offers of varenicline.

A few sub-hypotheses will also be examined:

1) Discontinuation of tobacco smoking leads to fewer depressive symptoms and anxiety symptoms, as well as lower consumption of antidepressant drugs.

Rationale for this hypothesis:

Anxiety and depression are common co-morbidities in COPD and have substantial effects on patients, their families, the community and the disease course [22]. The incidence of depression, in a longitudinal study (N = 71444) with a follow-up of 10 years, was 16.2 cases per 1000 person-years in the COPD group compared with 9.4 cases per 1000 person-years in the control group without COPD [23]. The same study also showed that patients with severe COPD were most at risk of depression (OR 2.01 (95% CI, 1.45-2.78)) [23]. Furthermore, COPD is associated with a higher risk of developing anxiety [24]. In a review, 20 quantitative studies showed that anxiety and depression led to a marked increase in the probability that COPD patients were admitted to the hospital [25]. These co-morbidities also led to an increased hospitalization time and a greater risk of mortality after discharge [25]. In addition, depression and anxiety symptoms have detrimental effects on physical function and social interaction in COPD patients. [26]. In a meta-analysis from 2014, 26 studies taken together showed that smoking cessation led to: reduced stress, depression, anxiety, improved mood and quality of life [27]. There was as much effect as with medical antidepressant treatment and just as good effect in people with known mental illness [27]. By reducing depression and anxiety symptoms in COPD patients, the hospitalization time and number of hospitalizations may be reduced and possibly increase the quality of life of COPD patients. In addition, the consumption of antidepressant drugs can be reduced.

2) Significant changes in the respiratory microbiome in COPD patients will appear when they cease smoking, defined as at least one of the three most common microorganisms found in the respiratory tract of active smokers with COPD (after smoking cessation for a minimum of 6 months) no longer is among the three most common microorganisms in the respiratory tract.

Rationale for this hypothesis:

The lower respiratory tract microbiome environment was previously thought to be sterile unless pathogens invaded the area. However, next-generation sequencing (NGS) and culture techniques in studies in COPD patients showed that the microbial composition fluctuates with the severity of COPD, exacerbations of COPD, smoking, antibiotic consumption etc. [28, 29], however, there are limited data on the microbiome in the respiratory tract, especially for COPD. Although the social structure of the microbiome does not change with exacerbations of COPD, there are remarkable changes in its composition [29]. In addition, it has been observed that increasing the severity of COPD is associated with a reduction in microbial diversity [29, 30]. This pattern of reduced microbial diversity has also been observed in cystic fibrosis [30]. Understanding the effect of lung microbiome on COPD progression and the risk of exacerbation by cigarette smoke will lead to new and improved treatment and prevention of COPD progression and aggravation.

Hypothesis

A "high-intensity" smoking cessation intervention increases the likelihood that active smokers with COPD choose to stop smoking compared to a conventional "low-intensity" smoking cessation intervention.

Smoking cessation will reduce disease progression in COPD, and by that lead to a reduction in excess lung function decline and number of exacerbations together with an improvement in mental health/well-being/quality of life.

Aims

Smoking cessation in COPD patients improves survival [1] and reduces the number of exacerbations [2]. Unfortunately, relatively few people stop smoking even with pharmacological support [3].

Primary aim: to determine if a high-intensity intervention compared to a low-intensity intervention can increase the proportion of persistent (>12 months) anamnestic and biochemical smoking cessation in active smokers with COPD.

Secondary aim 1: In addition, to investigate, within the randomized study design, long-term follow-up over two years and five years, whether the occurrence of depressive symptoms and anxiety symptoms is different in the "high-intensity" and "low-intensity" groups. This is assessed by a. Depression questionnaires and b. Filling prescriptions of pharmaceuticals that is primarily prescribed for these conditions.

Secondary aim 2: to characterize changes in the respiratory microbiome between active smokers with COPD and COPD patients who have stopped smoking and see if the airway microbiome adapts/changes after smoking cessation.

Methods

Design

Study A) A randomized open-label, superiority, multicentre, 2-arm intervention study, in which it is examined if a "high-intensity" intervention causes fewer people (diagnosed with COPD) to smoke after 12 months than in a "low-intensity" intervention in people diagnosed with COPD. The effect on survival for 12, 24 and 48 months, incidence of COPD exacerbations, number of admissions for all causes and cardiovascular admissions will also be analysed at the same times.

Study B) Depression/anxiety within the framework of the randomized study ("high-intensity" vs. "low-intensity" group). Measured by means of questionnaires and by recording the prescription of drugs for depression and anxiety.

Study C) A microbiological study within the framework of the randomized study, which aims to investigate the respiratory microbiome and possibly changes in participants in the two randomized groups. Subgroup analyses for participants who actively smoke vs. has ceased and exploratory analyses to determine if the microbiome changes within 6 months after smoking cessation.

Recruitment and inclusion

Participants for the trial will be recruited from persons who have 1) COPD, 2) have not been admitted with COPD exacerbation in the last 24 months, and 3) are not managed at a respiratory outpatient clinic because of COPD disease. Recruitment takes place through advertisements and announcements in local newspapers, daily newspapers, via the Danish Lung Association and its member magazine, where the participants then per mail or telephone can contact trial staff (see under Data collection) and then receive the written participant information per mail or other ways

if the participant wants this. Later, an information meeting with trial staff can be agreed on one of the participating departments' cadastre, in a booked room that is approved for patient examination. The participant will be informed of the right to an assessor in the first contact, and the right will also be clarified in the written participant information. For the meeting, oral participant information will be provided by trial staff, and the aim is to ensure that trial staff do not have work during recruitment and if they have, the work telephone is handed over to other staff during the meeting. After the meeting, a 24-hour reflection period will be given, and informed consent will be obtained upon the signed consent declaration, provided that the participant will participate in the project.

Inclusion criteria:

- Age ≥ 50 years
- Competent and capable
- Have diagnosed COPD *[spirometry verified and evaluated by pulmonary specialist]*
- Current daily smoker *[Minimum 1 cigarette daily]*
- Have smoked minimum 20 pack years (1 pack year = 20 cigarettes daily in 1 year)
- Want to or try to stop smoking
- Do not mind taking varenicline or NRT during the trial
- Are willing to give blood and urine samples according to the protocol

Exclusion criteria:

- Previously included in the trial
- Hospitalized with COPD-exacerbation within the last 24 months
- Are associated with hospital outpatient clinic for COPD disease treatment
- Have FEV_1<50%.

- Pregnancy/breastfeeding
- Life expectancy less than 1 year
- Severe linguistic problems or inability to give informed consent
- Severe mental illness that is not controlled with medication
- Active alcohol or substance abuse
- Active cancer disease*

*The person can participate if he or she has had a cancer disease that is now referred to as curative/radically treated. Basal cell carcinoma of the skin does not count as an exclusion criterion.

Assessments

The following assessments will be carried out during the project, cf. Figure 1. Details of the low- and high-intensity interventions are described in the section “Interventions”.

Figure 1 (SPIRIT Figure): Overview of assessments that each participant will undergo and the time schedule for the project.

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation/Follow-up (months)					
Timepoint	-24 hours	0	1	3	6	12	24	36
ENROLMENT:								
Informed consent	X							
Eligibility screening	X							
Allocation		X						
INTERVENTION:								
Low-intensity		←	—	→				
High-intensity		←	—	—	→			
ASSESSMENTS:								
*Pregnancy test (urine-hCG)		X						
Smoking history		X						
Urine sample (urine-cotinine)		X	X	X	X	X	X	X
Blood sample		X	X	X	X	X	X	X
COPD Assessment Test (CAT)		X	X	X	X	X	X	X
MRC-dyspnoea scale		X	X	X	X	X	X	X
Hospital Anxiety and Depression Scale (HADS)		X	X	X	X	X	X	X
Induced-sputum sample		X				X		
Weight measurement		X			X	X	X	X
Height measurement		X						
Lung function measurement (spirometry)		X		X	X	X	X	X
Hamilton Depression scale (HAM-D)		X				X	X	X

*All women of fertile age

Smoking history: The age of smoking debut is obtained, the number of years smoked, the number of cigarettes/cigars/cheroots/grams of tobacco smoked, the number of smoking cessation attempts in total, if they have tried to stop smoking within the last year and motivation for smoking cessation.

Blood tests: Standard blood samples: electrolyte parameters (sodium, potassium), kidney parameters (creatinine, carbamide), liver parameters (albumin, bilirubin, ALAT, alkalic phosphatase, INR), CRP, glucose, HbA1c, hematologic differential blood cell count, haemoglobin and iron content.

Questionnaires: Standardized questionnaires are used. CAT and MRC dyspnoea scale are short and simple tests that provide an understanding of the severity and impact of COPD on the participant's daily life. HADS is used to screen for anxiety and depression, and HAM-D is used to suggest a risk of developing depression.

Data collection

The primary daily project management is handled by the project manager. In addition, a project group (investigators), consisting of health professionals from the departments involved, is trained to assist the project manager with recruitment, sampling and follow-up of participants. Recruitment in general practice is done by the project-trained nurse.

Upon entering the program and all visits in the future (after 1, 3, 6, 12, 24 and 36 months), the participant is summoned to a conversation with staff, asking if the participant smokes (yes vs. no), and if yes, how much. In addition, a urine sample is taken. cotinine analysis for biochemical verification of smoking status and standard blood samples to examine health status at these visits

(analysed on Department of Clinical Biochemistry, KBA). In addition, questionnaires (CAT, MRC and HADS) are completed with the participant.

In the case of inclusion and follow-up visits after 3, 6, 12, 24 and 36 months, lung function measurement is also carried out at regular intervals by spirometry. Smoking anamnesis and height measurement are done by inclusion in the study along with weight measurement, which is the only further measured after 6, 12, 24 and 36 months to monitor BMI.

The HAM-D score is measured at inclusion, and again after 12, 24 and 36 months and if the score becomes high (≥25), i.e. that there is a high risk of developing depression, the participant will be advised to see their GP for further evaluation.

In addition, sputum samples are induced for microbiome analysis the time of inclusion into the study, and again after 12 months in the first 50 participants in the "high-intensity" group who quit smoking, and in the first 50 participants in the "low-intensity" group, who do not quit smoking.

Survival and death (including the cause of death) are obtained from the Cause of Death Register (DAR). Admissions, hospitalization and the participant's diagnoses are retrieved from their records. Comorbidities and prescribed therapy and filled prescriptions are recorded and by inclusion and on an ongoing basis during study visits. During the trial, the following are also recorded: side effects and analyses from the paraclinical tests. At the same time, it is also stated that varenicline does not cause critical interactions with other drugs (see www.interaktionsdatabasen.dk and product summary).

Collected data will be treated confidentially by the staff associated with the project. Data will be reported in Electronic Case Report Forms (eCRF) specific to each participant, which are encrypted

and stored in servers protected by Danish data security authorities with double login to REDCap etc. In addition to the above information, the following data are recorded by inclusion: demographic data, health status, current and previous drug consumption, current and past diseases. Physical copies of CRF are kept in locked archives for the departments involved for 15 years.

Interventions

A total of 600 participants will be included with start-up 1st January 2020 and is expected to be completed 3 years later, January 2023. Participants are randomized (random allocation) 1:1 to a "low-intensity group" and a "high-intensity group". Stratified for age (>65 years vs. ≤65 years) and number of daily cigarettes (>10/day vs. ≤10/day). Blocked randomization through REDCap with blocks of varying sizes (4-8), which will not be disclosed. Participants, their data and laboratory specimens etc. will be assigned a coded identification number, ID, to maintain participant confidentiality.

Participants will be randomized to one of the following two treatment groups:

a) "Low-intensity group": encouraged to quit smoking via own GP and varenicline is prescribed for 12 weeks.
b) "High-intensity group":
    a. Varenicline for 12 weeks
    b. Group-sessions – in all 30 sessions divided into 6 months
        i. Preparation phase*: 5 sessions
        ii. Day 1-14: 5 sessions
        iii. Day 15-30: 5 sessions
        iv. Day 31-60: 5 sessions
        v. Day 61-90: 5 sessions

vi. Day 90-180: 5 sessions

*During the preparation phase, participants are allowed to smoke, smoking cessation starts at Day 1.

Group sessions are controlled by:

I. Respiratory nurse [Mapping of different smoking patterns and different reasons for smoking. When is smoking the greatest? When in the process, smoking starts to fall. Dangerous situations regarding smoking relapses. Working closely with psychologist - see below. Initial focus on nicotine-craving and coping methods]

II. Respiratory physician [Lung function, Lung age, Anatomy, Physiology, Pathophysiology of lung cancer and COPD]. Focus on why smoking cessation is good. Is there anything you want to experience in your life that smoking can prevent? Either by death or because illness would prevent it?

III. Psychologist [In close cooperation with nurse. Focus on behaviour before smoking and how this behaviour is slowed down at an early stage. Coping by smoking. Cognitive smoking cessation strategies. Handle digito-oral habit].

IV. Physiotherapist [Training on how to improve general physical performance status based on individual training programs].

V. Dietician (focus on keeping weight (both ways), nutrition). Suggestions for what to eat at episodes of smoking craving.

c. Relationships and retention via these:

i. Hotline and scheduled phone consultations:

1. A hotline is established which the "high-intensity group" can call.

2. Weekly calls to all participants in the project for 26 weeks. Call for 5-10 min. If the participant has not had relapse, there will be called week 34 and week 42. If the participant has had relapse, calls continue until relapse-free for 10 weeks, then week 34 and week 42.

d. ”Buddy-arrangement”:

i. Participants who have completed the program and have become smoke-free, are matched with new ones in the program. A meeting frequency of approx. every 7-14 days. The first participants are matched with patients from respiratory medical outpatient clinic (COPD clinic) who have ceased smoking.

Extraction of biological material

Blood samples are taken by venepuncture, and throughout the study period of up to 36 months, the blood withdrawn will be up to 120 ml of blood (a maximum of 18 ml per visit).

Collection of induced sputum will be done by mask inhalation with hypertonic saline solution[31]. Participants are thoroughly instructed by a respiratory nurse to expectorate into a container. Samples are frozen in -80°C freezer within 24 hours.

Research biobank

A research biobank is created for storing blood samples, urine samples and sputum samples. In total, up to 120 mL of blood will be taken from each participant from inclusion to 36 months of follow-up. All samples are stored in a freezer in a locked room for analysis before the project ends. Microbiome analyses are performed on the sputum samples at Statens Serum Institut or other laboratory that has recognized expertise in microbiome analysis. All samples are kept in

pseudoanonymised form for 15 years, where they are analysed and will be done in the years after recruitment is completed. This research biobank will be used to answer the hypotheses described in this protocol, including sub-studies. The research biobank ends at the end of the recruitment process, and all surplus material is transferred to a biobank for future research (see below). The analyses consist of standard blood sample analyses to check health status: electrolyte parameters (sodium, potassium), kidney parameters (creatinine, carbamide), liver parameters (albumin, bilirubin, ALAT, alkalic phosphatase, INR), CRP, glucose, HbA1c, hematologic differential blood cell count, haemoglobin and iron content. Additionally, at inclusion, cotinine is analysed in the blood for immediate analysis, and all excess material is transferred to the research biobank. The urine sample is analysed for cotinine content for biochemical smoking status, and the sputum samples are examined for the microorganism composition (microbiome analysis).

Biobank for future research

Permission to create a new biobank for future research with the excess material will be sought from The Danish Data Protection Agency. Following the end of the project and the research biobank, the excess material will be transferred to this new biobank for future research within the COPD disease. The samples (the excess material from the research biobank) will be locked away and stored pseudonymized for 15 years in accordance with current legislation incl. data protection laws. Informed consent to participation in the project permits biological material to be stored in the research biobank and the excess material in the biobank for future research.

Risks, adverse effects and events

When taking blood samples, transient discoloration of the puncture site is observed frequently (in 5-15%) due to a minor blood accumulation under the skin (bruising). In addition, there is a risk of slight pain during insertion of needle and minimal risk of infection.

There are no known risks and side effects associated with urine and sputum collection.

It is a general rule that all effective medications can also have side effects. For varenicline, mild nausea and vivid dreams are the most common side effects. According to pro.medicin.dk there are:

Very common (> 10%): Nausea, Nasopharyngitis, Abnormal dreams, Headache and Insomnia.

Common (1-10%): Decreased appetite, fatigue, weight gain, increased appetite, abdominal pain, diarrhoea, dyspepsia, flatulence, gastroesophageal reflux disease, Hepatic effects, Meteorism, dry mouth, constipation, vomiting, abnormal taste, tooth pain, dyspnoea, sinusitis, arthralgia, myalgia, back pain, somnolence, dizziness, Skin itching, skin rash and upper respiratory tract infection.

Uncommon (0,1-1%): Haematochezia, Stomatitis, Angina pectoris, Dysphonia, Hypertension, Airway Inflammation, Airway obstruction, myocardial infarction, Hyperglycaemia, Aggression, Anxiety, Depression, hallucinations, mood disturbances, Hypoesthesia, Convulsion, Lethargy, suicidal ideation, thought disorders, tremor, erythema, fungal infections, viral infections Conjunctivitis, Tinnitus and eye pain.

Rare (0,01-0,1%): Cysts, Hematemesis, Atrial fibrillation, Cerebrovascular events, ECG changes, Thrombocytopenia, Diabetes mellitus, Glucosuria, Hypocalcaemia, Costochondritis, Joint stiffness, Behavioural disturbance, Bradyphrenia, Coordination disorders, Psychosis, Speech Symptoms,

Increased Muscle Tone, Severe skin reactions (including erythema multiforme and Stevens-Johnson syndrome), Angioedema, Abnormal sperm test, Sexual disturbances, Myopia and visual disturbances.

It should be said that smoking cessation itself can give rise to several symptoms, and it may be difficult to distinguish between these symptoms and the side effects of the treatment. The Summary of Product Characteristics of varenicline is used as a reference document when assessing whether a serious adverse reaction (SAR) is expected/unexpected and thus may be a suspected unexpected serious adverse reaction (SUSAR).

Investigator must report all serious incidents / side effects (SAR) to the sponsor as soon as possible. Thus, the sponsor can immediately report on to the Danish Medicines Agency and the Danish Committee on Health Research Ethics if it is deemed to be a SUSAR. In case of fatal or life-threatening side effect, this must be recorded and reported to the National Board of Health within 7 days of the sponsor being aware of such a suspected adverse reaction. Within 8 days of the report, the sponsor must notify the National Board of Health of all relevant information about the sponsor's and investigator's follow-up to the report. All other SUSARs must be reported to the Danish Medicines Agency no later than 15 days after the sponsor has gained knowledge of these. At the same time, test managers are informed at the other centres.

An annual list of all SUSARs that have occurred during the trial period is prepared and a report on the safety of the participants is submitted to the National Board of Health. In addition, all adverse reactions and events are reported at the end of the trial in the final report to the National Board of Health.

Outcomes

Primary end-point:

- Anamnestic and biochemical* validated smoking cessation after 12 months

*Cotinine is analysed in a urine sample, as validated point-prevalence for the last 7 days

Secondary end-points:

- Number of admissions for exacerbations of COPD or death within 12 months
- Number of admissions for all causes or death within 12 months
- Number of cardiovascular events[1] within 12 months
- Changes in CAT-score over 12 months
- Changes in FEV_1 from baseline over 12 months
- Changes in BMI[2] over 12 months
- Clinically relevant changes in HADS-score over 12 months
- Occurrence of DNA from the following: M. catarrhalis, H. influenzae and P. aeruginosa over 12 months[3]
- Changes in the total lung microbiome over 12 months[3]
- Occurrence of smoking-related cancer[4] within 12 months
- Number of admissions requiring NIV treatment or admissions to intensive care or death within 12 months
- Changes in status from MRC-dyspnoea score from < 3 to 3 ≥, over 12 months

[1]Defined as cardiovascular death, acute myocardial infarction or unstable angina pectoris [32].

[2]BMI loss more than 1 unit.

[3]These end-points are only examined on the first 50 who stop smoking from the "high-intensity" group against the first 50 who do not stop smoking from the "low-intensity" group.

[4]Lung cancer, urothelial cancer, pancreatic cancer, oesophageal cancer, pharyngeal cancer, laryngeal cancer, tongue cancer, oral cancer, tonsil cancer.

Long-term (follow-up) end-points:

- Occurrence of depression within 36 months.
    1. Admission to psychiatry with depression as primary diagnosis
    2. New start of antidepressant treatment after baseline
    3. Clinically relevant changes in HADS score over 36 months
    4. Changes in status from HAM-D score from baseline over 36 months
- Number of days during antidepressant treatment over 36 months
- Changes in FEV_1 over 36 months

Sample-size (statistical power calculation)

Type 1 error limit (α) of 5%. Power (1-β) of 90%.

The maximum smoking cessation rate for the "low-intensity group" is expected to be 10% in 12 months.

With the above-described person-adapted, multi-component, intensive smoking cessation intervention in the "high-intensity group", ≥ 20% of participants are expected to cease tobacco smoking for at least 12 months.

Thus, a 10% absolute improvement in likelihood of smoking cessation is expected, in this case equivalent to the relative risk of smoking cessation on 2.0.

This gives a sample size of 532 (266 + 266) persons. To ensure greater impact and statistical security 600 participants will be recruited for the project by the likelihood of trial participants withdrawing from the project.

Analyses

We will use Fisher's exact test and chi-squared test for dichotomous outcomes and T-test for continuous outcomes. The timed dichotomous outcomes will be visualized through Kaplan-Meier plots. Furthermore, adjusted analyses will be performed with multivariable Cox proportional hazards model, adjusting for baseline variables and calculating hazard ratio.

Discussion

Scientific ethics statement

The study is performed according to the Helsinki Declaration and is carried out in accordance with the rules in the Personal Data Act and the Health Act. Approval will be sought from the Danish Data Protection Agency. Recruitment and inclusion will take place as previously described. Participation requires a signed informed consent statement. Participants can withdraw their consent at any time and withdraw from the research project without affecting their right to current or future treatment. Participants who do not wish to participate in the trial will be offered treatment according to current guidelines. The participant also has the right to bring an advisor to the information conversation and is entitled to a reflection period before any consent form is signed. If, during the experiment, significant information emerges about the individual's state of health, this will be disclosed both in writing and orally to the participant, unless he or she has refused to do so in advance in the signed consent statement.

Patients with COPD fear acute exacerbations as it increases dyspnoea, cough, sputum and is associated with significant morbidity and mortality. Smoking cessation is the best intervention for exacerbations and progression of COPD in active smokers with COPD. The potential benefit of this project is to prevent smoking-related exacerbations of COPD and thereby reduce logistics and costs of hospitalization and treatment of COPD. In addition, the project can potentially benefit from increasing the quality of life and longevity of COPD patients and reducing the risk of developing lung cancer and other smoking-related diseases. Possibly, the project may also cause "healthy" smokers to stop smoking. Based on this, we believe that the experiment is scientifically sound and that the trial participants will not be exposed to irresponsible risks.

Information from patient journals

Information from the trial participants' journals are obtained under the study to obtain study-relevant information (information to be used for the study-specific Case Report Form or corresponding to data to be obtained for subsequent approved additional protocols). If informed consent is obtained from the trial participants, it is permissible for the investigators to obtain this information from the patient record. Study-relevant information includes data on COPD severity, risk profile, disease development and relevant co-morbidity to answer the hypothesis described. If informed consent is obtained from the trial participants, it is permissible for the investigators to obtain this information from the patient record. The informed consent also gives investigators, COP:TRIN, their representatives and eventual monitoring authority direct access to obtain information in the participant's journal etc., including electronic journal, in order to see information about the participant's health conditions, which are necessary in order to complete the research project and in monitoring purposes, including self-monitoring, quality monitoring, as

these are required to be performed. No information from patient records is obtained until informed consent has been obtained from participants.

Economy

The initiative for the trial was taken by the steering committee of the COP: TRIN (Chronic Obstructive Pulmonary Disease: Trial Network) and Pulmonary Medicine Department, Gentofte Hospital, Herlev Hospital, Hvidovre Hospital, Bispebjerg Hospital, Nordsjælland Hospital and Aalborg Hospital. Funding has been sought from foundations (so far: TrygFonden, Lundbeck Foundation, Novo Nordisk Foundation and RegionH Research Fund) to the persons responsible for the project (researchers and supervisors), salary to auxiliary staff, payment of laboratory analyses, equipment, medications and potential hospitalizations. As funding is obtained, the Danish Committee on Health Research Ethics and the trial participants will be informed about who the donors are, how much an amount they each contribute with how the support forms part of the project, for example in the form of salary to personnel or analyses etc. In addition, it is also stated whether the support is paid directly to the investigators, their department/institute or other, and whether the investigators are financially connected to the donors.

The investigators are not financially linked to private companies, foundations etc. with interests in the research project in question.

Remuneration/Services

No remuneration is paid to the study participants.

Publication of results

The trial has been registered at ClinicalTrials.gov (NCT04088942). The results from the project will be published in a peer-reviewed journal regardless of whether they are positive, negative or

inconsistent with authorship according to the Vancouver recommendations. If publication in a scientific journal is not possible, the results of the trial will be published in report format, which will be made available via the Internet.

Exclusion from or interruption of trial

If the physician responsible for the study considers it necessary, the person may at any time terminate the study if there is a medical justification (e.g. development of allergy to medication), a safety risk, or other circumstances. However, this must be done in agreement with the coordinating investigator. The participant may at any time, as mentioned in the above paragraph, withdraw their informed consent and withdraw from the investigation. It will not have any consequences for the further treatment.

Information about compensation or reimbursement schemes

The trial is covered by the patient compensation scheme if, contrary to expectation, damages occur during the trial and by inclusion.

Trial status

This protocol is version 8 from 18th June 2019. Recruitment of participants is anticipated to begin 1st January 2020 and planned to end by 1st January 2023.

Declarations

Ethics approval and consent to participate

The study will be carried out to include the protection of human participants according to the Helsinki Declaration and in accordance with Good Clinical Practice Guidelines. Participants will be informed about the study on inclusion day and will be included if accepting to participate. A

603 completed patient informed consent form is required from all participants in the study and must
604 be signed by the participant and the informing personnel. The study has been approved by the
605 Danish Committee on Health Research Ethics (H-19013085).

606 Consent for publication:

607 Not applicable.

608 Availability of data and materials

609 Not applicable. The data from the TOB-STOP-COP study will be available once the study is
610 completed. Applications for data require a formal application and will be decided upon by the
611 board of the TOB-STOP-COP study group.

612 Competing interests

613 The authors declare that they have no competing interests.

614 Funding

615 Funding has been sought from TrygFonden, Lundbeck Foundation, Novo Nordisk Foundation and
616 RegionH Research Foundation.

617 Authors' contributions

618 JUJ conceived of the study. All authors and Jørgen Vestbo contributed to the study design,
619 intervention methods and statistical endpoints. MIS wrote the protocol and translated it to
620 English. MIS applied for approval at the Danish Committee on Health Research Ethics, and MIS and
621 JUJ applied for grants from TrygFonden, Lundbeck Foundation, Novo Nordisk Foundation and
622 RegionH Research Fund. All authors contributed to refinement of the final study protocol.

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Appendices:

1. Informed consent form:

Informed consent for participation in a health science research project.

Title of the research project: **TOB-STOP-COP: TOBacco STOP in COPd Trial**

"Clinical trial on the effect of a" high-intensity "smoking cessation intervention in active smokers with COPD rather than a" low-intensity "smoking cessation intervention".

Statement from the participant:

I have been given written and oral information and I know enough about purpose, method, benefits and disadvantages to say yes to attend.

I know that participating is voluntary and that I can always withdraw my consent without losing my current or future rights to treatment.

I agree to participate in the research project and to have my biological material extracted for the purpose of storage in a research biobank and the excess in a biobank for future research. I have received a copy of this consent sheet as well as a copy of the written information about the project for my own use.

Name of participant: _____

Date: _____ Signature: _____

If any new essential health information about you appears in the research project you will be informed. If you will **decline** information about new significant health information that will appear in the research project, please mark here: _____ (set x)

Do you want to be informed about the results of the research project and any eventual consequences for you?

Yes _____ (set x) No _____ (set x)

Declaration by the provider of information:

I declare that the participant has received oral and written information about the trial.
In my opinion, enough information has been provided to enable participation in the trial.

Name of the provider of information: _____

Date: _____ Signature: _____