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Effectiveness of intensive smoking reduction counselling plus combination nicotine replacement therapy in promoting long-term abstinence in patients with chronic obstructive pulmonary disease not ready to quit smoking: Protocol of the REDUQ trial

Petra Hagens[a,*], Marcel Pieterse[a], Paul van der Valk[b], Job van der Palen[c,d]

[a] Department of Psychology, Health and Technology, Centre for eHealth and Wellbeing Research, University of Twente, Enschede, The Netherlands
[b] Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, The Netherlands
[c] Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands
[d] Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, The Netherlands

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ABSTRACT

Introduction: Limited tobacco dependence treatment resources exist for smoking COPD patients not ready to quit. Smoking reduction may be a viable treatment approach if it prompts quit attempts and subsequent abstinence. This article describes the protocol of the REDUQ (REDUce and Quit) study, which examines whether smoking reduction counselling plus combination nicotine replacement therapy (NRT) is (cost-)effective in achieving long-term abstinence in smoking COPD patients not ready to quit.

Methods/Design: We conducted a two-centre, parallel-group, randomised controlled trial with 18 months follow-up in smoking outpatients with COPD. Patients not ready to quit within the next month but willing to reduce their smoking, were randomised to receive either intensive smoking reduction counselling plus combination NRT or a single information meeting plus self-help manual. Outcomes were assessed at baseline, 6, 12 and 18 months. The primary outcome is ≥ 1-year prolonged abstinence. Secondary outcomes are point prevalence abstinence, successful (i.e. ≥ 50%) smoking reduction, and incidence of quit attempts reported at follow-up assessments. Smoking status is biochemically verified by salivary cotinine and expired CO. Other variables include smoking-related cognitions, intention and motivation to reduce and quit smoking, withdrawal symptoms, health-related quality of life, symptoms of anxiety and depression, state of mindfulness, lung function, use of health care resources, and costs.

Discussion: The outcomes of the REDUQ trial will advance knowledge on treatment of smoking COPD patients not ready to quit. If (cost-)effective, the smoking reduction intervention can be offered to this difficult-to-treat target group as a valuable adjunct to smoking cessation treatment.

1. Introduction

1.1. Background and rationale

Smoking cessation is the single most effective and cost-effective way to reduce the risk of developing chronic obstructive pulmonary disease (COPD) and slow or stop its progression [1,2]. It has been shown that smoking cessation reduces the accelerated decline in lung function caused by continued smoking [2–5], and decreases the risk of exacerbations [6] and mortality [7] in patients with COPD. Nonetheless, a large proportion (up to 77%) of COPD patients continue to smoke [8–12].

Attempts to quit smoking and cessation success have been linked to a person's readiness to quit as defined by the Transtheoretical (Stages of Change) Model (TTM) [13–16]. However, only 22.5% of Dutch smoking COPD patients are ready to quit smoking (i.e. intending to quit within one month) [17]. Current treatments of tobacco dependence, almost exclusively aiming at (abrupt) cessation, are thus not appealing to many, or even most, smoking COPD patients and unlikely to motivate them to enrol. Approaches that could coax these reluctant patients into smoking cessation treatment are therefore urgently needed.

Smoking reduction could be such an approach; a systematic review of smoking reduction trials showed that nicotine replacement therapy (NRT) as well as combined pharmacological and behavioural smoking

* Corresponding author. University of Twente, Department of Psychology, Health and Technology, P.O. Box 217, 7500 AE, Enschede, The Netherlands.
E-mail address: p.hagens@utwente.nl (P. Hagens).

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reduction interventions increase long-term cessation among otherwise healthy smokers who are initially not ready to quit [18].

Offering assistance to reduce smoking may also persuade reluctant COPD patients to engage in tobacco dependence treatment and successful smoking reduction may facilitate complete cessation in this specific patient group [19]. However, as far as we are aware, no smoking reduction interventions specifically targeting COPD patients not ready to quit smoking have yet been developed or tested. This constituted the rationale for the REDUQ (REDUce and Quit) trial.

1.2. Objectives and hypotheses

The primary objective of the REDUQ trial is to determine whether intensive smoking reduction counselling plus combination NRT is effective in promoting long-term abstinence in COPD patients not ready to quit, compared to a single information meeting plus a self-help manual as a control condition. Other objectives are to: (1) assess the effects of the intervention on point prevalence abstinence rates, reduction rates, number of quit attempts, intention and motivation to quit, attitude, social influence and self-efficacy; (2) investigate whether successful reduction (≥50% compared to baseline) and cessation influence health-related outcomes such as lung function and quality of life; (3) identify factors that moderate the effects of the intervention, as well as mechanisms through which intervention effects occur; and (4) estimate the cost-effectiveness of the intervention.

A priori, we hypothesised that the intensive NRT-aided smoking reduction intervention will result in higher reduction and (prolonged) abstinence rates compared to a self-help intervention and that the higher abstinence rate will primarily be the result of an increased number of patients who – after successful smoking reduction – decide to participate in a subsequent cessation programme.

The aim of this paper is to describe the design, methodology, and analysis plan of the REDUQ trial.

2. Methods/design

2.1. Study design and ethics

We conducted a two-site, parallel group, randomised controlled trial (RCT) with 18 months follow-up. Smoking COPD outpatients not ready to quit smoking were randomised in a 1:1 ratio to an intervention group (intensive group smoking reduction counselling plus free combination NRT) or control group (single information meeting plus self-help manual on smoking reduction). For participants in either group it was optional to participate in a concurrent smoking cessation programme as soon as they were ready to quit. Fig. 1 shows a flowchart of the study design.

The primary outcome is biochemically validated prolonged abstinence of at least one year at the final follow-up. The study was performed at the outpatient pulmonary clinics of Medisch Spectrum Twente (MST) Enschede and University Medical Centre (UMC) Groningen in the Netherlands.

The study protocol was approved by the accredited Medical Research Ethics Committee (MREC) Twente (P09-22/NL30620044) and subsequently by the Board of Directors of both centres. Written informed consent was obtained from all participants prior to enrolment and data collection. Participants did not receive any incentives or forms of payment to participate, yet they were reimbursed for parking fees. The study is registered at www.trialregister.nl (NTR2777).

2.2. Eligibility criteria

Patients were eligible for participation if they had a clinical diagnosis of COPD, were aged 40–80 years, smoked ≥10 cigarettes per day, had no intention to quit within the next month (i.e. not ready to quit) but were interested in reducing their smoking, and had made two or more failed lifetime quit attempts. Patients not meeting these criteria, and those who were pregnant or intended to become pregnant within the next 18 months, had a serious psychological condition, were contraindicated for all types of NRT, or had insufficient comprehension of the Dutch language, were excluded.

2.3. Recruitment and screening

Patients were recruited from medical records, by their chest physician during outpatient visits, through leaflets and posters in waiting rooms, and through advertisements in local newspapers. Potential participants were screened via telephone to determine interest in participation and initial eligibility. As we aimed to recruit patients not (yet) ready to quit smoking, we felt that it might be counterproductive to set abstinence as the primary treatment goal. Therefore, we communicated to potential participants that smoking cessation was highly recommended but not mandatory for participation and that the treatment programme would focus on smoking reduction, allowing patients to gradually take control of their smoking. We emphasised, however, that smoking cessation is the best way to change the course of the disease and that it was possible to engage in smoking cessation treatment during the entire study period as soon as a participant expressed readiness to quit.

2.4. Information and consent

Patients who were eligible following the initial screening were sent a study information letter and an informed consent form. In addition, they were invited to attend an orientation meeting to more fully explain the study and review the consent form. After written informed consent was obtained, patients were scheduled for a visit with a chest physician to assess final eligibility (i.e. verifying COPD GOLD stage and ruling out serious psychiatric morbidity) and, if found eligible, to undergo baseline assessments. Patients were informed that they could withdraw from the study at any time, without any consequences for their subsequent treatment.

2.5. Randomisation and blinding

After completing baseline assessments, the patients were assigned in a 1:1 ratio to either one of the study groups, using a computer-generated randomisation list prepared by a staff member with no involvement in the trial. Randomisation was stratified according to centre and nicotine dependence (Fagerström Test for Nicotine Dependence (FTND) [20] score ≤ 6 versus > 6) with variable block sizes of two and four. The allocation sequence was concealed until the interventions were assigned. Each patient was aware of the content of the intervention to which he or she was allocated, but unaware of whether it was the experimental or control condition. Research staff involved in follow-up remained blind to treatment allocation as much as possible and staff carrying out the primary outcome assessments (i.e. biochemical validation of smoking status) remained blind to study group assignment.

2.6. Interventions

2.6.1. Intensive smoking reduction intervention

2.6.1.1. Theoretical foundation. The theoretical foundation of the smoking reduction intervention is primarily formed by two models to explain and change health behaviours: the TTM [15] and the Attitude–Social influence–self-Efficacy (ASE) model [21,22]. The TTM recognizes behaviour change as a process that unfolds over time, involving progress through five stages [15,16], each representing a different temporal and motivational aspect of behavioural change [13]. The first three stages describe individuals' readiness to quit smoking. These stages include: (a) pre-contemplation, when smokers have no intention to quit; (b) contemplation, when smokers express an intention

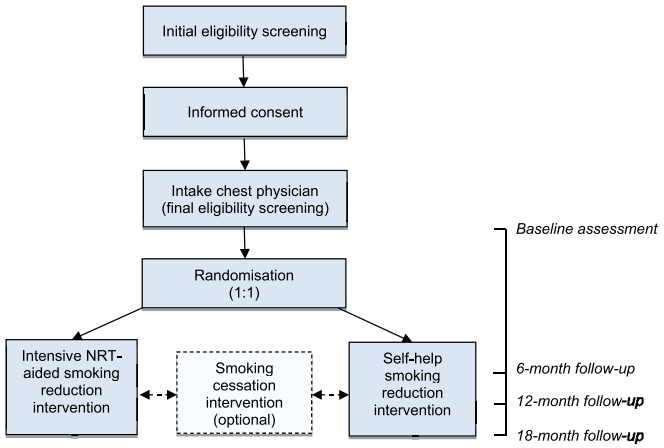

Fig. 1. Flowchart of study design.

to quit smoking within six months, but not within the next month; and (c) preparation, when smokers plan to quit smoking within the next month. When individuals have quit smoking and been abstinent up to six months, they are in the action stage. They are considered to be in the maintenance stage if they have been abstinent for more than six months after initial quitting. The REDUQ intervention is stage-based in the sense that it is designed to match smoking COPD patients in the pre-contemplation or contemplation stage of smoking cessation and help them progress from these stages to action and maintenance.

The ASE model, which is the core of the Integrated Change (I-Change) model [23], served as the theoretical framework for the analysis of the determinants of motivational and behavioural change, and for intervention development. According to the ASE model, the most proximal determinant of behaviour is the intention to perform this behaviour. Intention, in turn, is determined by three motivational constructs: attitude, consisting of the perceived advantages and disadvantages of the behaviour (change); social influence, including perceived social norms, social modelling and social support/pressure; and self-efficacy, or a person's level of confidence to perform the behaviour. These cognitive constructs are influenced by various distal factors such as predisposing factors (i.e. behavioural, psychological, biological, social and cultural factors), awareness factors (i.e. knowledge, cues to action, risk perception) and information factors (i.e. message, channel, source). Finally, a person's abilities (e.g. being able to create and execute action plans, actual behavioural skills) and perceived barriers can increase or decrease the likelihood that intentions will be transferred into actions [23,24].

2.6.1.2. Intervention delivery. The intervention was delivered by experienced counsellors of the hospitals' in-house smoking cessation services and consisted of eight small-group sessions and four telephone counselling sessions in between group meetings, and provision of free combination NRT. The group sessions were sequenced and gradually faded over time. Each group session lasted 90 minutes, except for the first session (120 minutes), and comprised of education, group discussion, sharing of experiences, and strategies to improve participants' self-efficacy to achieve and sustain reduced smoking levels. Patients received a comprehensive workbook, containing written information on all aspects of the intervention and homework assignments to be carried out prior to each session. The telephone sessions (10 minutes each) were tailored to the individuals' needs and progress towards the reduction objective and addressed, for example, current smoking status and experiences with smoking reduction and NRT. Appendix A provides a session-by-session outline of the intervention components.

2.6.1.3. Methods and techniques. Elements from cognitive behavioural therapy (CBT) [25], relapse prevention (RP) [26] and mindfulness-based relapse prevention (MBRP) [27] were used such as self-monitoring, goal setting, changing unhelpful thoughts/attitudes, teaching problem-solving strategies, exercises to cope with craving symptoms and negative affect, and preventing and learning from relapses.

Motivational interviewing (MI), a client-centred counselling method, was used to facilitate the participants' internal motivation to reduce and/or quit smoking by identifying dissonance between behaviours and values and resolving ambivalence [28]. Specific motivational techniques included, for example, scaling in the form of importance and confidence rulers, decisional balancing, reflective listening and evoking change talk.

To reduce smoking, we used 'scheduled reduced smoking', a procedure where smokers are instructed to smoke only at pre-specified times of the day and the interval between cigarettes is progressively increased [29,30]. By controlling the timing of smoking, associations between cues (e.g. presence of others smoking) and smoking behaviour are attenuated and smokers are forced to use coping strategies to overcome urges to smoke, yielding increased self-efficacy to quit [31]. For each participant, individualised smoking reduction schedules were constructed according to his or her baseline smoking rate, daily wakening cycle and success at meeting intermediate reduction goals. The first treatment week, participants were expected to follow a schedule with set smoking times without reducing daily cigarette consumption. Participants were subsequently instructed to reduce their smoking by 25% compared to baseline from week 2 to week 4 and by 50% in the subsequent four weeks (week 4–week 8). At each meeting, patients who were unsuccessful in meeting their (intermediate) reduction goal were motivated to reach this goal by the next meeting. From week 8 to week 13, those successful in achieving a 50% or greater reduction were highly encouraged to consider cessation and enter smoking cessation treatment. If they were not ready to quit smoking completely they were given the options to reduce further (e.g. 75% reduction compared to baseline) or maintain their current level of reduced smoking. Those who did not reach a reduction of at least 50% were encouraged to continue working on the 50% reduction goal. From three months onwards, all participants were encouraged to consider cessation, regardless of the reduction achieved at that point. Participants persistently unmotivated to quit were invited to contact the research team throughout the remainder of the study if they changed their mind.

To aid smoking reduction, from week 2 through week 13, participants were provided with combination NRT, consisting of a long-acting patch (Nicotinell® TTS 30/20/10) to provide a constant concentration of nicotine to relieve cravings and tobacco withdrawal symptoms plus a short-acting oral product of their choice (Nicotinell® 2 mg gum, lozenge or sublingual tablet) to be administered ad lib for immediate relief of breakthrough cravings and withdrawal symptoms. In accordance with the smoking schedule, participants were instructed to replace a cigarette missed with a type of acute NRT and encouraged to use this sufficiently to avoid smoking more than quota. Dosing of the patch was based on the number of cigarettes smoked per day at baseline and the (intermediate) reduction goal. For detailed information on NRT dosage see Fig. 2 and Appendix B.

2.6.2. Self-help intervention

The self-help intervention consisted of one 60 minute information meeting, addressing themes like smoking in relation to COPD, self-monitoring, high risk situations, ways to reduce the number of cigarettes smoked, and the use of NRT to aid smoking reduction. In addition, a non-tailored self-help manual was provided, describing the scheduled reduced smoking procedure and other ways to reduce smoking. The manual also contained tips on how to cope with urges to smoke and stress, and how to prevent relapse. Participants received no formal

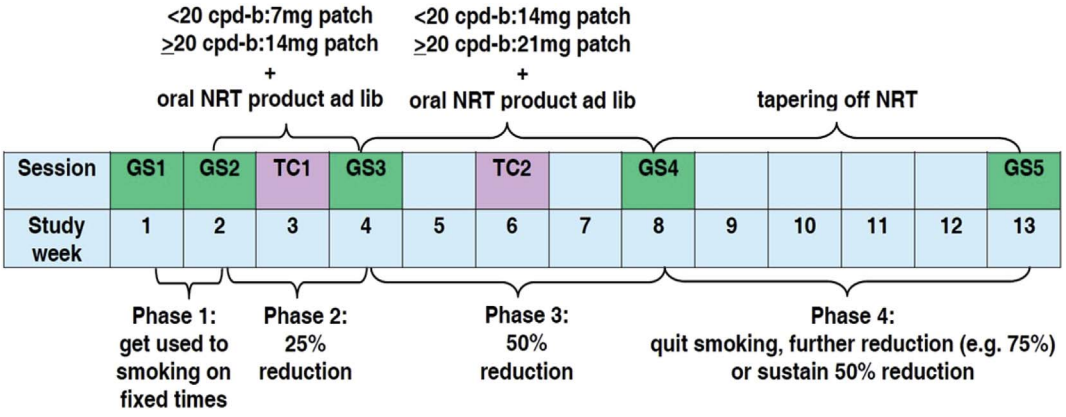

Fig. 2. Schematic overview of the first 13 weeks of treatment. cpd-b = cigarettes per day at baseline; GS = group session; TC = telephone call.

behavioural counselling for smoking reduction and there was no face-to-face contact except for the measurements at baseline, 6, 12 and 18 months. NRT was recommended but at the patients' own expense.

2.6.3. Smoking cessation intervention

An integral part of this study was that as soon as a participant of either group expressed readiness to quit, he was encouraged to enter the SmokeStopTherapy (SST) [32], a proven effective, high-intensity group smoking cessation programme for COPD patients delivered within the same outpatient clinic. To enable participants to enter this cessation treatment without delay due to group formation intervals, an individual counselling version of the SST was also offered. This individual smoking cessation treatment was generally similar to the original group-based intervention with regard to the topics and intensity. SST in both intervention components and overall intensity. It consisted of five to eight individual sessions of 20 minutes each, depending on the needs and wishes of the participant, and two to three telephone contacts of 10 minutes each.

To aid smoking cessation, participants were provided with free NRT, bupropion (Zyban®) or varenicline (Champix®/Chantix®). Smoking cessation treatment was offered alongside the patients' continued participation in their assigned reduction intervention, which enabled them to act as role models to other reduction group members. In addition, if participants moved to cessation and the quit attempt failed, they could resume the reduction programme and continue to control their smoking until they were ready to stop again.

2.6.4. Counsellor training

Five experienced smoking cessation counsellors of the in-house smoking cessation services were trained in two half-day training sessions. In the first session the principles of the smoking reduction intervention and practicalities of running the trial were discussed. The training also included readings on smoking reduction and cessation, motivational interviewing, CBT, and mindfulness. The second session was on-site and discussed in detail the counselling manual, the patients' workbook and audio-visual materials to support the group sessions. During the entire study, the counsellors used the manual and audio-visual materials, which enabled them to provide standardized counselling during each session. 'Hands-on' supervision was available for the first two to three group meetings. The research team contacted the counsellors before and after a treatment session, for case-sharing and evaluation. Although the counsellors received informal feedback, no formal measures of adherence to the protocol were collected.

2.7. Data collection and biochemical measurements

Study data, consisting of self-report questionnaire items, biochemical assessments and physical measures, were collected at the outpatient clinics at baseline and 6, 12 and 18 months after treatment initiation (see Table 1) by trained study staff. One to two weeks before each assessment, participants were sent an invitation and a paper-and-pencil questionnaire, which they were asked to complete and bring to their appointment. To minimise the burden for participants, assessment visits were scheduled before or after a group counselling session where possible. At each assessment visit, questionnaires were collected and checked for completeness. Lung function was assessed by post-bronchodilator spirometry at baseline and final follow-up. Weight measurements were obtained at each assessment visit using a calibrated medical scale. To verify self-reported smoking status, all participants, not only those who reported being abstinent, were asked to provide a saliva sample for cotinine assessment as well as a carbon monoxide (CO) sample at each visit. Saliva was collected in a plastic vial containing a sterile dental cotton roll (Salivette®; Sarstedt, Nümbrecht, Germany). Participants were asked to chew the cotton roll for one minutes and to replace it in the tube without touching it. The saliva samples were labelled, centrifuged and frozen at −20 °C until assayed by means of a gas chromatography–mass spectrometry (GC-MS) technique [33]. The accuracy and precision of the method and instrumentation were checked by means of reference samples. The CO concentration in expired air was obtained using a handheld Micro III Smokerlyzer (Bedfont Scientific, Maidstone, Kent, England). Patients were requested to inhale and hold their breath for 15 seconds before exhaling into the analyser. If a participant was unable to attend a follow-up visit, every attempt was made to reschedule the appointment or to collect a saliva and/or CO sample by mailed saliva kit or home visit.

The primary validation measure is cotinine, with 96–97% sensitivity and 99–100% specificity [34]. This major proximate metabolite of nicotine has an in vivo half-life of approximately 20 hours, and is typically detectable for several days (up to one week) after the use of tobacco [35]. Expired CO levels will be used to validate smoking status when cotinine levels are considered invalid, for example during nicotine replacement therapy, or when cotinine measures are missing. CO has a short half-life of four to five hours with both sensitivity and specificity around 90% [36]. A cotinine value of 15 ng/mL will be used as the cut-point to distinguish smokers from non-smokers [36], whereas a factory-prescribed cut-off point of 10 parts per million (ppm) will be used for CO verification of non-smoking status.

2.8. Measures

2.8.1. Primary outcome: prolonged abstinence

The primary outcome of this study is *prolonged abstinence* (PA) of at least one year, defined as biochemically verified self-reported abstinence from smoking from month 6 (first follow-up) or earlier through month 18 (final follow-up). A participant is considered to be prolonged

Table 1
Measures and measurement points.

Measure	Baseline	Month 6	Month 12	Month 18
Smoking outcomes				
Self-reported smoking status	×	×	×	×
Expired CO	×	×	×	×
Salivary cotinine	×	×	×	×
Quit attempts	×	×	×	×
Smoking covariates				
Smoking history	×			
Nicotine dependence (FTND)[20]	×			
Goal setting	×			
Withdrawal symptoms (WSWS) [37]	×[a]	×	×	×
Readiness to quit ('stage-of-change')	×	×	×	×
Attitudes towards smoking cessation	×	×	×	×
Social influence	×	×	×	×
Self-efficacy	×	×	×	×
Smoking reduction/cessation medication use	×	×	×	×
Use of other tobacco dependence treatments	×	×	×	×
Other (co)variates				
Socio-demographics	×			
Weight	×	×	×	×
Anxiety and depression (HADS) [38]	×	×	×	×
Mindfulness (MAAS)[39]	×	×	×	×
Health outcomes				
Lung function	×			×
Disease specific quality of life (CCQ)[40]	×	×	×	×
Generic health status (EQ-5D) [41,42]	×	×	×	×
Costs and resource use				
Health-care use	×	×	×	×
Costs of intervention delivery	×[b]	×[c]	×[c]	×[c]
Attendance, patient satisfaction and adherence				×

Note.
[a] Measured one month after treatment start;
[b] In the previous year;
[c] In the previous six months.

abstinent if (a) biochemically verified repeated seven-day point prevalence abstinence (PPA) at 6-, 12-, and 18-month follow-up is established; (b) the reported quit date was on or before the date of the six-month follow-up assessment and (c) the participant has reported to have been abstinent from smoking (not a single puff) since the reported quit date. Patients who lack both CO and cotinine readings at 12 months will be considered prolonged abstinent if they have reported to be abstinent for at least the preceding seven days at the 12-month assessment and biochemical data at both 6 and 18 months confirm self-reported seven-day abstinence. If data of both biomarkers are missing at 6 or 18 months, patients are considered treatment failures and therefore not prolonged abstinent. To enable comparison of outcomes with other studies employing varying follow-ups, we will also calculate PA of at least six months for 6–12 months and 12–18 months separately.

2.8.2. Secondary smoking outcomes

Secondary cessation outcomes were collected at all follow-up points and included: (a) a composite self-report measure of *cigarettes* per *day*, calculated based upon a weighted average: ((5 × weekday rate) + (2 × weekend rate))/7; (b) *point prevalence abstinence* (PPA), defined as biochemically validated abstinence from smoking (not a single puff) for at least the preceding seven days and (c) *the number of any self-reported quit attempts* and *quit attempts lasting at least 24 h* over the 18-month study period.

Our major measures of smoking reduction are (a) *percentage reduction in cigarettes per day* from baseline smoking, assessed at 6, 12 and 18 months; (b) *reduction of 50% or more* (i.e. successful smoking reduction) at 6, 12 and 18 months and (c) *sustained ≥ 50% smoking reduction* from months 6 to 12, 12 to 18 and 6 to 18. Self-report and biochemical reduction outcomes will be reported separately to provide insight in the utility of biochemical verification of smoking reduction in this patient population. Compensatory smoking (i.e. more intensive inhaling to compensate for reduced nicotine yield) [43] and/or errors in self-reported smoking status will be examined by estimating the ratio of cotinine and CO levels to self-reported cigarettes per day.

2.8.3. Other secondary outcomes

Health-related quality of life (HRQoL) was assessed at all assessment points with two instruments: the Clinical COPD Questionnaire (CCQ), which is a self-administered instrument that measures clinical control in patients with COPD life [40] and the EuroQol five dimensions questionnaire (EQ-5D) [41,42], a standardized instrument for measuring generic health status that is widely used for calculating quality-adjusted life years (QALYs) for assessing cost-effectiveness in healthcare.

To measure *intention to quit smoking* and the smoking-related cognitions of the ASE model: *attitude, social influence,* and *self-efficacy,* we used items from a questionnaire developed by Mudde et al. [45].

To test the influence of smoking reduction and cessation on *lung function* in terms of forced expiratory volume in one s (FEV_1), post-bronchodilator spirometry, 15 minutes after administration of 400 μg salbutamol, was performed at baseline and final follow-up.

2.8.4. Demographic and moderator variables

Background and potential moderator variables that were measured at baseline included *socio-demographics* (e.g. age, gender, educational level), *smoking history*, *nicotine dependence* (FTND) [20], *comorbidity*, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) *stage of COPD* [46]. We also measured *goal setting and action planning* by asking participants to rate on a five-point scale ranging from 'definitely not' to 'definitely yes' if they planned to carry out each of eight different preparatory plans (e.g. formulating reduction goals, making a relapse prevention plan).

Other potentially moderating variables that were measured at all measurement points included *body weight, withdrawal symptoms* (Wisconsin Scale for Withdrawal Symptoms; WSWS) [37]; symptoms of *anxiety* and *depression* (Hospital Anxiety and Depression Scale; HADS) [47]; and *state of mindfulness* (Mindfulness Attention Awareness Scale; MAAS) [39].

2.8.5. Cost and resource use data

To enable an economic evaluation, intervention costs will be calculated, taking into account staff time involved in being trained and delivering interventions, overhead costs and sessions provided. Health care resource use will be collected retrospectively for each participant (e.g. use of medication related to an exacerbation, hospital admission(s) for respiratory problems). All time related variables (e.g. staff time, training time, et cetera) will be converted to monetary units, based on available tables for the Netherlands [55].

2.8.6. Attendance, patient satisfaction and adherence

Programme attendance was recorded for each group session. At the final follow-up visit, patients of the intervention group were asked to rate overall appreciation of the intervention and the use and appreciation of four aspects of the intervention (i.e. telephone contacts, groups sessions, counsellor, workbook) on a 10-point scale. Control group patients were asked to complete a similar questionnaire, focussing on the information meeting and the self-help smoking reduction manual.

2.9. Statistical issues

2.9.1. Sample size and power

The sample size was based on the expected contrast between the intensive smoking reduction intervention and the self-help control group in their rates of ≥12 months biochemically validated prolonged abstinence. We expected 75% of the intervention group to do a serious cessation attempt of whom 80% would do so with the SST. Given a 19% SST success rate (12-month sustained abstinence) [48] and assuming a 6% prolonged abstinence rate among quitters without the SST, 12.3% in the intervention group should reach ≥ 12 months prolonged abstinence ((0.75 × 0.8 × 0.19) +(0.75 × 0.2 × 0.06) = 12.3%). We expected 25% of patients in the control group to do a quit attempt, of which 50% within the SST, leading to a 3.1% ≥ 12 months prolonged abstinence rate in this group ((0.25 × 0.5 × 0.19) + (0.25 × 0.5 × 0.06) = 3.1%). With an alpha of 0.05 (two-sided) and a power of 0.80, a minimum of 262 participants (131 per condition) needed to be recruited to demonstrate a treatment effect. No adjustment for possible drop-out was made, since drop-outs are considered to be still smoking.

2.9.2. Analysis plan

Baseline characteristics will be summarised using numbers with corresponding percentages, means and standard deviations, or medians and interquartile ranges, as appropriate. Group differences at baseline will be tested by Chi-square or Fisher exact tests for categorical variables, independent *t*-tests for normally distributed continuous variables and Mann-Whitney *U*-tests for non-normal continuous variables.

Differences between groups at follow-up on the dichotomous outcome measures (PA, 7-day PPA and ≥50% smoking reduction) will be analysed by logistic regression and results presented as odds ratios (OR) with 95% confidence intervals (CI), while continuous outcomes of smoking status (e.g. number of cigarettes smoked per day, number of quit attempts) and health outcomes will be analysed by multiple linear regression or ANCOVA. All regression analyses will be performed with and without covariates.

The change from baseline in number of cigarettes smoked per day, withdrawal symptoms, attitudes, social influence, self-efficacy and intention to quit smoking, will be analysed using a mixed model repeated measures analysis with baseline values as covariates.

The primary analyses will be performed using the intention-to-treat (ITT) dataset, including all those randomised. We will assume that missing and/or non-validated smoking data indicates that, since the previous assessment, neither abstinence, a quit attempt, nor reduction has occurred. However, we will test whether there are differences in compliance and dropout rate between both study groups and, if this is the case, we will use methods of multiple imputation as suggested by Hedeker et al. [49] and Blankers et al. [50] to explore the effect of assuming alternative associations between the missing data and smoking status. In case of missing data on continuous outcomes (e.g. number of cigarettes smoked per day), we will use the Last Observation Carried Forward (LOCF) as well as a Baseline Observation Carried Forward (BOCF) approach as a sensitivity analysis.

If the NRT-aided smoking reduction intervention is more effective in achieving the primary outcome compared to the control condition, then cost analyses will be undertaken to examine the cost-effectiveness of the intervention from a health-care perspective. The costs will be expressed in Euros and health benefits in units of health, such as exacerbations prevented, hospital days prevented and quality-adjusted life years (QALYs) gained. Cost-effectiveness ratios will be calculated by dividing the difference between the costs of the two interventions by the difference in health benefits obtained.

All statistical tests will be interpreted with a significance level of 5% (two-tailed). Analyses will be conducted using the Statistical Package for the Social Sciences version 23 (SPSS, Chicago, Ill., USA).

3. Discussion

In this paper, we presented the protocol of the REDUQ study. To the best of our knowledge, this study is the first RCT to assess whether an NRT-aided smoking reduction intervention is (cost-)effective in achieving prolonged abstinence in smoking COPD patients not ready to quit.

3.1. Limitations

This study has a number of limitations. An important consideration is that the intervention group actually received three interventions: scheduled reduced smoking, behavioural counselling, and combination NRT. Moreover, the behavioural intervention comprised many components (e.g. motivational interviewing, skills training, relapse prevention). This makes it difficult to identify the relative importance of each component. However, as the primary goal of the REDUQ study is to assess the overall effectiveness of a multicomponent reduction approach, the current design is adequate for this purpose. If the REDUQ intervention appears to be effective, future studies may be useful to identify which particular components are most important in achieving sustained reduction and cessation.

It should also be noted that in this study, participants in the intervention group were provided free of charge with combination NRT, whereas participants in the control group were only encouraged to use NRT at their own expense. Consequently, some control participants may have used NRT, while others have not. Prohibiting the use of NRT in the control group would have reduced the within-group variability to some extent. However, it would have increased the between-group variability and reduced the ecological validity of the study, because in the Netherlands over-the-counter NRT is readily available and can be used by smokers in the population to which we wish to generalise. We therefore will attempt to conduct additional analyses to examine the effect of NRT use between and within groups. However, as we have noted above, the goal of the current study is primarily to demonstrate increased efficacy of the complete intervention over a brief self-help intervention.

The self-help control treatment is not a true 'placebo' intervention, as it contains potentially effective elements. This may conceal the full effectiveness of the REDUQ intervention when compared to no intervention. However, available evidence from smoking cessation research suggests only a small effect is to be expected from the use of standard self-help materials on quit rates compared with no intervention [51,52]. In addition, no-treatment controls might be more likely to seek help elsewhere during the study due to disappointment about their allocation, leading to a greater potential for contamination by external interventions and/or differential dropout between groups.

3.2. Strengths of the study

This study also has a number of strengths. First, the study is innovative as it addresses three important issues in one design:

1. It may engage reluctant (i.e. not ready to quit) smoking COPD patients into tobacco dependence treatment, who would have otherwise refrained from seeking help and remained smoking as usual.
2. It has been shown that smoking cessation, even intermittent cessation, reduces the accelerated decline in lung function due to tobacco smoke [5]. Reduced smoking may serve as a strategy to shorten the intervals between quit attempts and provide an intermediate step towards complete cessation, while minimising health damage.
3. The REDUQ programme offers a continuum of treatment for a chronic dependency, integrating smoking reduction treatment and smoking cessation treatment into a more comprehensive tobacco control approach. Hereby, it accommodates shifts through episodes of smoking reduction and abstinence, whereby lapses and relapses

are not regarded as treatment failures but part of the behaviour change process.

Second, the trial was set up to explore whether smoking reduction facilitates smoking abstinence in COPD patients who are currently not ready to quit smoking rather than evaluating this method as a way to quit. By targeting reluctant patients instead of patients highly motivated to quit, we expect our trial to reflect this population more truly, and as such to approach everyday clinical COPD care.

Third, the length of follow-up (i.e. 18 months) is also a major strength of this study. Since the primary goal of our trial was cessation induction among patients not ready to quit, it is unlikely that they would begin a cessation attempt early in the study. On the contrary, quit attempts may only occur well after the smoking reduction phase of 12 weeks and a considerable follow-up period is needed to capture such delayed treatment effects. Also, a relatively long follow-up may approach lifelong tobacco abstinence more closely and be more appropriate to detect changes in health outcomes.

A fourth strength is the biochemical verification of smoking status, which has been recommended by the Subcommittee on Biochemical Verification of the Society for Research on Nicotine and Tobacco (SRNT) to be used in harm reduction studies and in patients with smoking related diseases [36]. Self-reporting of cessation by COPD patients is not always trustworthy and misreporting rates up to 52% have been found [53], thus overestimating treatment effectiveness systematically if not corrected for. The dual use of exhaled CO and salivary cotinine for the assessment of smoking status at all measurement points allows for the validation of smoking status, regardless of continued NRT use. More importantly, this study will contribute to the limited knowledge on biochemical validation of smoking reduction. This may be an even more critical issue than in cessation trials because of compensatory smoking behaviour [54] and recall error.

3.3. Conclusions and implications

Despite the urgent need for quitting, prevalence of smoking is high in COPD patients. The outcomes of the REDUQ trial will advance knowledge and treatment of smoking COPD patients not (yet) ready to quit. Specifically, if found to be (cost-)effective, the smoking reduction intervention can be an important treatment modality for this difficult-to-treat target group.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MP, JvdP and PvdV conceived the original idea for this trial and obtained funding. PH was responsible for the conduct of the REDUQ trial and drafted the initial manuscript. MP and JvdP were supervisors and PvdV served as advisor during the execution and day-to-day management of the trial. All authors contributed to and approved the final manuscript.

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Appendix A

Session-by-session outline of the intervention components

Week	Session	Content
1	Group session 1	Orientation and introductions Provide information on link between COPD and smoking (cessation) Provide information on tobacco dependence Discuss current and past smoking behaviour and quit attempts Identify smoking patterns and triggers (by means of completed self-monitoring forms) Discuss motivation to reduce smoking and reasons to participate Provide information on smoking reduction Identify pros and cons of smoking and smoking reduction (i.e., decisional balance) Run through homework assignments for the next group session
2	Group session 2	Share experiences since group last group session Discuss homework assignments: - Scaling questions (importance, confidence and readiness to change rulers) - Decisional balance - Identify barriers to smoking reduction Identify high-risk situations/triggers for craving Provide information and advice on withdrawal symptoms Provide information and advice on NRT Run through homework assignments for the next group session
3	Telephone session 1	Review smoking status Discuss experiences with smoking reduction Discuss experiences with NRT (e.g. usage, side-effects, benefits)

4	Group session 3	Share experiences Discuss homework assignments: - Scaling questions - Identify and overcome barriers to smoking reduction - Identify and cope with high-risk situations/triggers for craving Discuss methods of self-control (e.g. avoiding high-risk situations, seeking support) Discuss strategies to cope with urges and craving Run through homework assignments for the next group session
6	Telephone session 2	Review smoking status Discuss experiences with smoking reduction Discuss experiences with NRT
8	Group session 4	Share experiences Discuss homework assignments: - Scaling questions - Self-control techniques - Cope with urges and craving (e.g. mindfulness exercises 'urge surfing' and 'SOBER') Discuss goal setting, goal pursuit and goal adjustment Identify and cope with social (peer) pressure Run through homework assignments for the next group session
13	Group session 5	Share experiences Discuss homework assignments: - Scaling questions - Set/adjust goals - Cope with peer pressure Provide information on lapses (temporarily smoking more than planned), relapses (return to baseline smoking level) and emergency plan Discuss irrational/unhelpful thoughts Run through homework assignments for the next group session
26	Group session 6	Share experiences Discuss homework assignments: - Scaling questions - Prepare emergency plan - Change negative/unhelpful thoughts Discuss ways to stay motivated (e.g. rewards) Discuss relationship between wishes, plans and (interim)goals Run through homework assignments for the next group session
40	Telephone session 3	Review smoking status Discuss experiences with smoking reduction/cessation
52	Group session 7	Share experiences since last group session Discuss homework assignments: - Scaling questions - Change negative/irrational thoughts - Develop motivational plan Run through homework assignments for the next group session
65	Telephone session 4	Review smoking status Discuss experiences with smoking reduction/cessation
78	Group session 8	Share experiences since last group session Discuss homework assignment: - Scaling questions - Evaluate programme Discuss future plans regarding smoking behaviour and options for smoking cessation support

Appendix B

Combination nicotine replacement therapy

To aid smoking reduction, from week 2 through week 13 combination patch plus short-acting NRT was administered. Owing to possible contra-indications, cardiologists had to approve the delivery of NRT for patients with cardiac comorbidities. Nicotine patches were administered for 24 hours/day. Dosing of the patch was as follows. Participants who smoked less than 20 cigarettes per day at baseline were instructed to use a daily 7 mg patch for two weeks (weeks 2–4: 25% reduction phase), followed by a 14 mg patch for the next four weeks (weeks 4–8: 50% reduction phase). Participants who smoked 20 cigarettes per day or more at baseline were instructed to begin with a 14 mg patch for two weeks (25% reduction phase), followed by a 21 mg patch for the next four weeks (50% reduction phase). In addition to patch, participants had free choice of 2 mg gum, 2 mg sublingual tablets or 2 mg lozenges. They were instructed to use their preferred oral product when smoking reduction was difficult because they felt irritable, edgy, and experienced urges to smoke when smoking was 'not allowed' according to their smoking schedule and to use NRT sufficiently to

avoid smoking more than quota. From week 8–13, all participants were asked to taper off the dose. As off week 13, NRT was no longer provided free of charge, but patients were allowed to continue NRT up to the six-month assessment at their own expense.

At each session while using the patch, participants were asked about side effects they might be experiencing. Participants who experienced problems with insomnia or difficulties with vivid dreams were instructed to use the patch for 16 hours daily, instead of 24 hours. Participants who had skin reactions to the patch that were not controlled by using other locations, switched to short-acting NRT only. Participants who showed symptoms of overdose had the dose reduced. Although participants were strongly encouraged to use both a patch and a short-acting form of NRT concurrently, they were allowed to use only one form of NRT to satisfy their wishes and to avoid non-compliance. Also, they were allowed to change their NRT at any time during the trial.

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