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Effectiveness of Combining Feedback about Lung Age or Exhaled Carbon Monoxide Levels with Very Brief Advice (VBA) and Support for Smoking Cessation in Primary Care Compared to Giving VBA and Support Alone – Protocol for a Randomized Controlled Trial within the Breathe Well Research Program

Dragan Gjorgjievski[1]*, Radmila Ristovska[1], Katarina Stavrikj[1], Amanda Farley[3], Peymane Adab[2], Rachel Adams[2], Andy Dickens[2], Alexandra Enocson[2], Gjorgji Stanoevski[1], Nicola Gale[3], Sue Jowett[2], Kiran Rai[2], Alice Sitch[2], Aleksandra Stamenova[3], Emilija Krstevska[1], Rachel Jordan[2]

[1]Centre for Family Medicine, Faculty of Medicine, Ss Cyril and Methodius University of Skopje, Skopje, Republic of Macedonia; [2]Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom; [3]Faculty of Medicine, Institute of Social Medicine, Ss Cyril and Methodius University of Skopje, Skopje, Republic of Macedonia

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***Correspondence:** Dragan Gjorgjievski, Centre for Family Medicine, Faculty of Medicine, Ss Cyril and Methodius University in Skopje, Skopje, Republic of Macedonia. E-mail: dragan_gjorgjievski@yahoo.com
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Abstract

INTRODUCTION: In 2015, smoking prevalence in Republic of Macedonia was 36% in men and 21% in women We aim to assess the effectiveness and cost-effectiveness of two methods of motivating smokers to quit smoking compared with very brief advice (VBA) alone. To date, there are no studies investigating smoking cessation treatment in Republic of Macedonia.

METHODS/DESIGN: RCT with process evaluation and cost-effectiveness analysis within 31 general practices in Republic of Macedonia recruiting smokers currently smoking >10 cigarettes per day, aged >35 years, attending primary care practices for any reason, regardless of motivation to quit smoking. Respondents will be randomized into one of three groups: (1) VBA and assessment and communication of lung age; (2) VBA and additional assessment and communication of exhaled carbon monoxide (CO) levels; or (3) control group – VBA. All participants who attempt to quit smoking will be offered behavioral support based on the UK standard program for smoking cessation. Primary outcome: Proportion of smokers who are quit at 4 weeks (7-day point prevalence, confirmed by salivary cotinine level). Secondary outcomes: Proportion who have attempted to quit smoking or have quit smoking, a proportion that has reduced the number of cigarettes and motivation to quit smoking; cost-effectiveness analysis calculating cost per quality-adjusted life year. We will evaluate the fidelity to the intervention and will explore patients' and GPs' experience and the acceptability of the study intervention by interview.

DISCUSSION: The study will evaluate the effectiveness of combining feedback about lung age or exhaled CO levels with VBA and support for smoking cessation in primary care compared to giving VBA and support alone. It will explore how willing primary care physicians are to perform such interventions and the acceptability and effectiveness of such interventions to patients in Republic of Macedonia.

TRIAL REGISTRATION: The study is registered on the ISRCTN registry (ISRCTN54228638).

Introduction

Smoking is the leading cause of chronic disease and is the primary cause of mortality and morbidity in industrialized countries [1], [2]. Cigarette smoke affects not only smokers but also non-smokers; passive smoking can cause respiratory conditions, cancer, and heart disease [1].

The health benefits of quitting are well established. With few exceptions, the future risk is reduced when smokers stop smoking and continues to decrease while smoking-abstinence is maintained [3], [4], [5]. Progression of smoking-related illnesses is also slowed and life expectancy improves by an average of 10 years if people quit before the age of 40 [6]. For these reasons, smoking cessation interventions are central to many disease prevention strategies.

Republic of Macedonia has a long tradition of consuming tobacco. In 2015, smoking prevalence in Republic of Macedonia was 36% in men and 21%

in women. Tobacco control legislation in Republic of Macedonia includes the introduction of plain packaging, bans on advertising and a ban on smoking in public places, but no smoking cessation programs are offered, and pharmacotherapy is limited in availability due to high costs [7]. However, from 2017, two international projects were rolled out in Republic of Macedonia to support smoking cessation. Both were funded from the Global Bridges project and involved training small groups of physicians to train other physicians to offer very brief advice (VBA) to tobacco dependent patients. The first involved secondary and tertiary care doctors [8] and the second primary care physicians [9], this latter project was led by the Centre for Family Medicine at Saints Cyril and Methodius University of Skopje, Republic of Macedonia (CFM). The GPs in this latter project recognized the lack of cessation support available for smokers, so undertook training in behavioral support from the UK National Centre for smoking cessation training [10]. This behavioral support is provided by the GPs themselves and consists of five consultations over 8–12 weeks. The GP practices participating in this trial will begin offering VBA with behavioral support for those who wish to quit smoking as standard care when the trial commences.

Much research has investigated the effectiveness of various smoking cessation aids, particularly in high-income countries [11]. Brief advice from doctors and other health professionals has been shown to promote smoking cessation compared to no intervention (pooled estimated odd ratio 1.66; 95% confidence interval [CI] 1.42–1.94), with quit rates around 4% in patients unselected by motivation to quit smoking [12]. Quit rates are higher with more intensive behavioral interventions and/or with pharmacotherapy support [11]. Nicotine replacement therapy (NRT) is not cheap in Republic of Macedonia and alternative methods to promote smoking cessation need to be tested. Health reasons and the development of a chronic disease is a common motivator for patients to consider quitting [13]. Thus, presenting smokers with personalized evidence of the harmful effects of smoking might encourage them to quit [14].

A Cochrane systematic review found insufficient evidence of the effectiveness of several prompts (spirometry, partner support, and lung function feedback) in boosting quit rates [15]. However, two potential types of biomedical risk information that may promote quitting are lung age (LA) and exhaled carbon monoxide (CO). LA [16] is a biomarker which is easily understood and demonstrates to patients the premature lung damage suffered as a consequence of smoking. Although feedback of LA is recommended by some guidelines (e.g., Lung Foundation Australia) [17] for motivating smokers to quit, existing published trials are heterogeneous in design and results are inconsistent [18]. CO is a toxic gas inhaled by smokers that bind with greater affinity than oxygen to hemoglobin in the blood, compromising the transport of oxygen around the body and increasing the cardiovascular risk [19]. Measuring the level of CO in exhaled breath is quick, relatively inexpensive, and non-invasive. Similar to LA, a number of studies have tested the effectiveness of giving feedback on CO as a motivator for smoking cessation [20], [21], [22], [23], but the results are equivocal [15]. Previous trials of both the effectiveness of providing LA or exhaled CO have also rarely been conducted in low resource settings where there is limited established support such as in Republic of Macedonia.

Through links with the International Primary Care Respiratory Group (IPCRG), the CFM has joined with the University of Birmingham (UoB) National Institute for Health Research Global Health Research Group on Global chronic obstructive pulmonary disease (COPD) in primary care, breathe well. Given the introduction of training to GPs to offer VBA for smoking cessation in Republic of Macedonia, we propose testing the effectiveness and cost-effectiveness of adding feedback on LA or exhaled CO to VBA in comparison with VBA alone in unselected smokers in primary care (i.e., smokers will be included in the study regardless of their motivation to quit smoking). Drawing on the Medical Research Council (MRC) guidance [24] for process evaluation in randomized controlled trials of complex interventions, a process analysis will also be conducted to inform interpretation of the trial results, and to understand context specific issues around acceptability of delivering the interventions.

Methods

Aims and objectives

Study aims

1. Assess the effectiveness of combining feedback about LA or exhaled CO levels with VBA and support for smoking cessation compared to giving VBA and support alone
2. Conduct a process evaluation informed by MRC process evaluation guidance to understand: (a) Fidelity by GPs in delivery of the intervention, (b) acceptability to GPs of delivering the intervention, (c) participant understanding, acceptability, and responses to the intervention
3. Estimate the cost-effectiveness of both interventions compared with VBA and support alone.

Design

A randomized controlled trial of three alternative methods of motivating smokers to quit smoking conducted within GP practices in Republic of Macedonia (Figure 1).

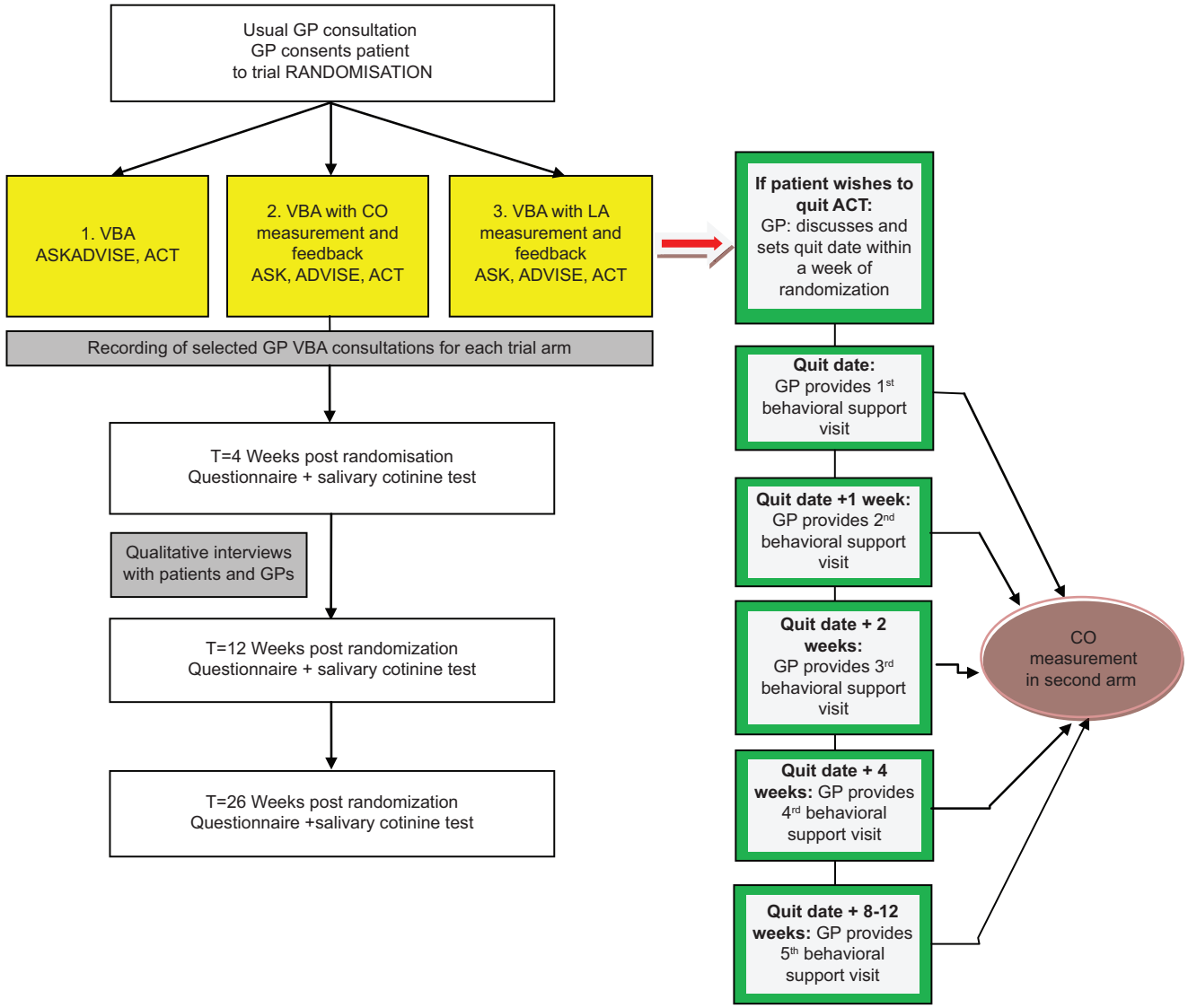

Figure 1: Flow chart of the study

Participants

Eligible participants will be recruited from approximately 31 primary care practices in Skopje and surrounding areas of Republic of Macedonia. GP practices will commence recruitment in four phases allowing adjustment of processes if necessary. Smokers consulting their GP for any reason and who fit the eligibility criteria, regardless of motivation to quit smoking, will be invited to take part, given a patient information leaflet, and asked to sign written consent. Anonymized data will also be collected from each GP practice on key characteristics of eligible patients who choose not to participate: Age, sex, and number of cigarettes smoked per day.

Eligibility criteria

Inclusion criteria

The following criteria were included in the study.

- Smoking >10 cigarettes (manufactured or roll up) per day
- Age >35 years.

Exclusion criteria

The following criteria were excluded from the study.

- Deemed unsuitable to participate in the trial by GP, for example, cognitive impairment, recent bereavement, and terminal illness
- Standard contraindications for spirometry [25]
- Previously received VBA to quit smoking
- Currently using e-cigarettes or NRT.

Randomization and allocation to trial arm

Allocation to the trial arm will occur when consented patients are registered on the database and the “randomize” option selected. A simple

randomization sequence will be computer generated by a statistician, stratified by GP practice, and will allocate participants in a ratio of 1:1:1. Allocation will be revealed to the GP and patient after completion of the baseline questionnaire.

Interventions

LA with VBA and support to quit smoking (VBA + LA)

In the LA intervention arm (VBA + LA), GPs will explain to patients that smoking can cause accelerated lung function decline and that this can be understood in terms of "lung age." GPs will also explain that smoking cessation slows down the rate of lung function decline, although it cannot repair the damage that is already done. GPs will assess LA using a hand held spirometer (Vitalograph COPD-6). This is a simple device which needs little training to administer and provides a measure of forced expiratory volume (FEV)1 and FEV6 as a proxy for forced vital capacity [20]. Three blows will be undertaken without the use of bronchodilators and the lowest LA, as displayed by the Vitalograph COPD-6 machine, will be fed back to the patient by the GP with explanation. If LA is equal to or less than the individual's chronological age, they will be informed that the test result is normal but they will be advised that it is still important to stop smoking before the damage is done. If LA is greater than chronological age, they will be given the "lung age" in years and be advised that although they cannot reverse the damage quitting smoking will prevent further damage. This will be combined with VBA for smoking cessation to all, with support to quit smoking for those who choose to attempt quitting (as described in the control arm).

Exhaled CO with VBA and support to quit smoking (VBA + CO)

In the exhaled CO intervention arm (VBA + CO), GPs will explain to patients that cigarette smoke contains CO and at high concentrations is toxic, displacing oxygen in the blood, compromising oxygen transportation, and increasing cardiovascular risk. GPs will assess exhaled CO using a Bedfont piCO Smokerlyzer, a simple device needing little training to administer and giving parts per million (ppm) of CO in exhaled breath. Participants hold their breath for 15 s and blow into the device which provides a reading. The GP will report the CO level, explaining the implications. This will be combined with VBA for smoking cessation, with support to quit smoking for those choosing to attempt quitting (as described in the control arm). Participants wishing to quit in this arm will have their exhaled CO repeated and fed-back at each support session.

VBA alone and support to quit smoking (VBA only)

GPs will deliver VBA. This includes "Asking" a patient's smoking status, "Advising" current smokers to quit smoking, and "Acting" to set up appropriate support to quit for patients wanting to make a quit attempt (Box).

GPs will:

- Ask: Confirm smoking status
- Advise
  - About the harms of smoking
  - Benefits of quitting
  - To stop smoking and the best way to stop
- Act
  - For participants not wanting to quit smoking, GPs will advise that the offer of support remains open should they want to take it up another time
  - For participants wanting to quit smoking, the GP will assist the patient with a quit plan including: Quit date, advice on how to deal with cravings/ withdrawal and a plan for support (pharmacological and behavioral)
  - All participants (regardless of quit intention) will receive a smoking information leaflet.

For participants who want to quit smoking, GPs will offer behavioral support adapted from the UK standard treatment program for smoking cessation published by the National Centre for Smoking Cessation Training [10], with sessions at quit date, then 1, 2, 4, and 8-12 weeks post-quit date. During these visits, patients will receive advice about medication, how to deal with cravings and withdrawal symptoms, and behavioral support. Citizen (Tabex) medication is available in Republic of Macedonia, but is expensive and patients have to pay for it themselves. Another NRT is only available if purchased online or in neighboring countries.

Outcomes

The primary outcome of the study will be:

1. Proportion of smokers who are quit at 4 weeks (7-day point prevalence confirmed salivary cotinine level of: (1) <10 ng/ml, or (2) <100 ng/ml for those who report exposure to second hand cigarette smoke in the home on a daily basis, or (3) ≥10 ng/ml in those who

report using NRT/e-cigarettes at any time point during the study, irrespective of exposure to second hand cigarette smoke)

The secondary outcomes of the study will be:

2. Proportion who have attempted to quit smoking measured at 4, 12, and 26 weeks
3. Proportion who have quit smoking at 4, 12, and 26 weeks (7-day point prevalence, self-report only)
4. Proportion who have quit smoking at 12 and 26 weeks (7-day point prevalence self-reported abstinence, confirmed as primary outcome)
5. Proportion who have reduced the number of cigarettes, they smoke per day at 4, 12, and 26 weeks
6. Motivation to quit at 4, 12, and 26 weeks
7. Cost per additional quitter at 4 weeks
8. Cost per quality-adjusted life year (QALY) gained at 26 weeks

Process outcomes:

9. Acceptability to the GPs of delivering the intervention
10. Acceptability, understanding, and response to the intervention of participants
11. Fidelity to the delivery of the intervention.

Acknowledging that the validity of smoking abstinence confirmation using cotinine testing may be limited when patients are using nicotine replacement products or are exposed to secondhand smoke; in a sub-sample, we will compare abstinence as defined in the primary and secondary outcomes with the following additional definitions:

1. Proportion who have quit smoking at 4, 12, and 26 weeks confirmed with CO monitor tests (7-day point prevalence self-reported abstinence with an exhaled CO reading of >10 ppm). To avoid influencing quit rates, the results will be concealed from participants unless a reading has already been taken earlier that day
2. Proportion who are quit at 4, 12, and 26 weeks (7-day point prevalence self-reported abstinence) with a narrower time window (past 4 days) for reported exposure confirmed with salivary cotinine level of:
   a. <10 ng/ml, or
   b. <100 ng/ml for those who report exposure to second hand cigarette smoke indoors in the past 4 days, or
   c. ≥10 ng/ml in those who report using NRT/e-cigarettes in the past 4 days, irrespective of exposure to second hand cigarette smoke.

Sample size

Few published studies report the effectiveness of LA or exhaled CO in combination with VBA to quit smoking, and none of these studies have been conducted in Republic of Macedonia. Only one study testing, the effectiveness of LA in combination with VBA is available that reports quit rates at 1 month (which is the primary outcome of our study), and this was conducted in Ireland [18]. Based on this study, we originally powered our study to detect a difference of 10% in the primary outcome between the control and each intervention arm at 4 weeks (12% VBA vs. 22% VBA + LA vs. 22% VBA + CO). At 90% power and a significance level of 5%, this required a sample size of 885 participants in total (295 participants per arm). However, after consideration by the trial steering committee (TSC), the sample size calculation was revised based on a lower proportion of quits in each arm and a 5% difference between arms, as the number of participants attempting to quit was much lower than anticipated and it became apparent that the Irish study findings may not be generalizable to the Macedonian population. To detect a difference of 5% in the primary outcome between the control and each intervention arm at 4 weeks (3% VBA vs. 8% VBA + LA vs. 8% VBA + CO) with 90% power and a significance level of 2.5%, we will recruit 1182 participants in total (394 participants per arm).

Data collection

The following data will be collected:

Study assessment visit 1 (Baseline)

Participants will complete a baseline questionnaire including sociodemographic information (gender, age, ethnicity, education, employment status and income level, residence [rural/urban], and marital status) and smoking related information (average cigarettes per day, smoking history, Fagerstrom test for nicotine dependence [26], motivation to quit smoking, previous attempts to quit smoking, and second-hand smoke exposure).

GPs will complete the further information on the duration of assessment visit, delivery of VBA components, CO reading/LA reading (depending on trial arm), quit intention following intervention and quit date if relevant, and motivation to quit using motivation to stop smoking scale immediately post VBA [27].

Study assessment visit 2-4 (4, 12, and 26 weeks follow-up)

Participants will attend follow-up visits to collect outcome data. If unable to attend, data will be collected over the telephone. Participants will self-report current smoking status and length of time since last cigarette smoked, number of quit attempts, number of cigarettes or other tobacco products used over the past week (per day or per week), motivation to quit

smoking (self-reported questionnaire) [27], use of any smoking cessation aids, cost of any smoking cessation aids used, and exposure to second-hand smoke (living or working with smoker(s)).

Abstinence from those reporting having quit smoking will be confirmed by measuring salivary cotinine using NicAlert test strips in the GP practice.

Process evaluation

Recording of consultations

To assess the fidelity of the intervention delivery, participants' consultations will be audio-recorded for 2–3 weeks while both recruitment and behavioral support visits are occurring. Two baseline and behavioral support visits from each arm per GP will be assessed for time required for, and GP fidelity to deliver VBA or support, and additional CO or LA components.

Qualitative interviews

A purposive sample of patients and GPs will be invited to participate in one-to-one interviews exploring their views on the trial and barriers and enablers to smoking cessation advice and support in general. Patients who have consented to participate will be interviewed after their 4-week follow-up appointment. GPs will be interviewed once they have completed recruitment. Interviews will be semi-structured, lasting 30–60 min, either face-to-face or over the phone, recorded, and transcribed. Participants will be sampled to represent a range of characteristics (GPs: Practice location, number of participants recruited, and age. Patients: Gender, age, and quit status at 4 weeks). Data will be collected until saturation has been reached (around 10–15 GPs and 10–15 patients from each intervention arm) [28]. Transcripts will be anonymized and all identifiable information removed.

Data analysis

Effectiveness analysis

Baseline characteristics will be reported as simple descriptive statistics. For the primary and secondary outcomes that are proportions, we will calculate RR (95% CI) using a Poisson model with robust standard errors adjusting for the stratification variables of the center with a random effect. In accordance with the Russell Standard [29], we will conduct an intention to treat analysis and assume those lost to follow-up are smokers.

Cost-effectiveness analysis

An incremental cost-effectiveness analysis will be undertaken to calculate the cost per additional quitter at 4 weeks for both interventions, with a cost-utility analysis also undertaken to calculate cost per QALY gained over 6 months, using data from the EQ-5D-5L questionnaire [30]. Data on all health-care resources required to deliver the intervention will be collected during the trial and any additional costs incurred either by the health services or the patient to assist with quitting smoking (e.g., additional prescriptions). The Macedonian version of the EQ-5D-5L will also be given to patients to complete at baseline, 4, 12, and 26 weeks. Sensitivity analysis will be performed on key assumptions made.

Qualitative analyses

Interview data will be analyzed using the framework approach [28]. Data coding will consist of a hybrid deductive-inductive approach and analyst triangulation carried out on 10% of interviews while developing the thematic framework.

Data management

Data will be collected on case report forms and participant questionnaires which will be kept in a locked cabinet in a secure location at the GP practice for 5 years. A copy will also be transferred and held at the Centre for Family Medicine, where it will be kept in a locked filing cabinet.

Case report forms and questionnaire data will be entered electronically onto a bespoke REDCap online database either by the GP or by the research team. The database will be accessed remotely by GPs or the research team and will be held on UoB computer servers.

Audio data from GP consultations and patient or GP interviews will be recorded on a Dictaphone and transferred onto a secure local computer server at the CFM as soon as possible. Anonymized transcripts may be transferred to the UoB for analytic triangulation.

Trial oversight

The study will be overseen by a TSC, consisting of one representative from each of the following stakeholder groups: Patient, clinician/policy maker, International Scientific Advisory Committee (ISAC), research team, and the Breathe Well executive committee. An additional representative from the ISAC will chair. Meetings will take place every 6–12 months as required. As this is a low risk trial, a separate Data Monitoring Committee will not be convened; rather the functions of this committee will be carried out by the TSC.

Regulatory issues

Ethics approval

Ethical permission to conduct the study has been granted by the ethics committees at Saints

Cyril and Methodius University, Skopje, Republic of Macedonia (UKUM034/95) and UoB (ERN_18-12408).

Consent

If the patient chooses to take part in the research study, the GP will set aside time, after the patient's appointment, to discuss the study with the patient, and any questions or concerns about the information sheet, study, or participation. No financial remuneration was offered for participation.

If the patient is happy to proceed, the GP will go through the consent process and complete the consent form in conjunction with the patient and collect the questionnaire. The questionnaire will not be collected in patients who decline to take part in the research study. Patients can withdraw participation in the study at any time without giving any reasons and without their medical rights being affected.

Participants will be given the option to be contacted in the future regarding other related studies or studies in the Breathe Well program. Information about this will also be clearly stated within the participant information sheet, which will explain that in particular some participants may be contacted to participate in a one-to-one interview to discuss their experiences and acceptability of the intervention. Participants will be advised that there is no obligation for them to provide permission for this section of the consent form.

Sponsorship and Indemnity

Sponsorship and indemnity will be provided by Dr. Labachevski Nikola MD, Ph.D., who is the director of the Institute of Preclinical and Clinical Pharmacology with Toxicology, Medical Faculty, Saints Cyril and Methodius University of Skopje. All research sites will have a risk assessment and monitoring plan as guided by the risk assessment.

Confidentiality

All members of the research team have completed Good Clinical Practice training. No personal information will be passed on to any third parties. All study participants will be assigned a study ID number. No identifiable data will be used on any research documents. Study data will be stored on a REDCap database, hosted on a UoB encrypted server which follows the General Data Protection Regulation.

Paper-based data will be stored in locked filing cabinets at the GP sites, with copies in locked filing cabinets at the CFM. Electronic data from the process evaluation and fidelity monitoring will be held securely on encrypted laptops and an encrypted server at the CFM. Data at the CFM will be stored in line with UoB policy for a minimum of 10 years after study completion. GP practice sites will hold the research data for a minimum of 5 years.

Discussion

This research is the first of its kind to be conducted in the Republic of Macedonia. It will explore the effectiveness and cost-effectiveness of combining feedback about LA or exhaled CO levels with VBA and support for smoking cessation in primary care compared to giving VBA and support alone. It will explore how willing primary care physicians are to perform such interventions and the acceptability and effectiveness of such interventions to patients in Republic of Macedonia.

Dissemination Policy

Results of the study will be disseminated through academic peer-reviewed publications and at relevant national/international academic conferences.

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