BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022685
Article Type:	Protocol
Date Submitted by the Author:	01-Mar-2018
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Keywords:	Chronic Obstructive Pulmonary Disease, Asthma < THORACIC MEDICINE, Nebulizers and Vaporizers

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

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WORD COUNT

3186 words

REGISTRY

This RCT protocol is registered in clinicaltrials.gov, with the number NCT03449316.

PROTOCOL VERSION

This is the first version of this RCT protocol.

ABSTRACT

Introduction

COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis

A multicentre single-blinded RCT will be set, comparing a placebo-device training programme versus usual care, with a one-year follow-up, in elderly patients with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Discussion

This will be the first study to test if inhaler performance education significantly reduces exacerbation rate and improves clinical and functional control.

Ethics and dissemination:

Every participant will sign a consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor stop earlier criteria. Identity of all participants will be protected. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS

Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Elderly patients with COPD or Asthma use their inhaler incorrectly, thus being more susceptible to exacerbations.
- No previous study has addressed specific teaching methods in these patients.
- This is the first study to address, in an isolated manner, a specific placebo device education programme in this subgroup of elderly patients.
- We expect to confirm the hypothesis that the intervention group will have a significant reduction on exacerbation rate and an improvement in clinical and functional parameters during the follow-up.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have their symptoms uncontrolled [1]. In Asthma, particularly, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled [2 3], and the elderly population is particularly vulnerable to this condition [3]. In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring [4]. Hospitalization rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions achieving half of the cases [5-7].

Inhaler technique

Inhaled therapy is the most widely used way to treat this patients [8], but up to 90% of them do not use their inhalers correctly [9 10]. Several inhaler devices are available in the market and it seems that differences either in device type or in patient characteristics may significantly influence performance [11]. However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy [12], but it is well established that poor inhaler technique leads to poor clinical control [13 14] and also to an increased health costs [15].

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes [16]. Some studies show that teaching of inhaler technique may lower the risk of exacerbations and death [6 17 18]. However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied in patients [19 20]. Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients [21 22]. Furthermore, they also present lower adhesion rates [9] and are more resistant to correct performance [23 24]. However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials.

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact upon major outcomes [25]. Nevertheless, some studies suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person [26-28]. This study will focus upon elderly patients and aims at testing the effect of a structured and regular placebo device training approach upon exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

The research question of this work is whether an inhaler technique education programme in elderly patients with Asthma or COPD reduces the risk of disease exacerbations. The main hypothesis is that an established programme of regular education of inhaler technique using a placebo device-based training approach in elderly patients can reduce the exacerbation risk by 50%.

RESEARCH DESIGN AND METHODOLOGY

Study Design

Two arms single blinded randomised controlled trial with a 1 year follow up (fig.1). Participants will be allocated to each group on a random basis, which is defined by a computerized generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thus maintaining a minimization randomization process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the *Chi square independent group proportions* approach of *STATA Statistical Package*©, considering the event proportion in control group of 50% (0.5 annual rate) as reported in bibliographic findings [17 18 29] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. At last, the sample size was upward readjusted, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria

Patients with a diagnosis of COPD or Asthma, medicated with any kind of inhaler device (pressurized Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged ≥65 years and being a regular user of primary health care services (defined as having at least one consultation performed in the last two years with his/her own Family Doctor). In order to minimize diagnostic inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and according to GINA and GOLD strategies [30 31].

Exclusion Criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD class I), since these patients do not need to take inhaler medication on a daily basis, and tend to have a low frequency of disease exacerbations.

Predictors/Intervention

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. A teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly at each evaluation. There will be visits at baseline and after 3, 6 and 12 months to assess outcomes. In each visit, and prior to the main intervention with the primary investigator, assessment of

the inhaler technique and application of all questionnaires (clinical control, treatment adhesion and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary consultations according to his real life judgment. Besides this, this group will perform visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adhesion and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded.

If any adjustments are made in drug classes or device types in every participants, this information will be recorded.

Outcomes of interest

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalization or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms inducing the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalization or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.

All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Health Care facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and according to the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) [32] and Asthma Control Test (ACT) for Asthma [33].
- Quality of Life using St. George's Respiratory Questionnaire [34] and Clinical COPD Questionnaire (CCQ) [35] for COPD and Asthma Quality of Life Questionnaire (AQLQ) [36].
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.

- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) [37].
- Number of errors in inhaler technique (that will be standardized to a score up to 100% scale) [To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used [38], evaluating all the recommended steps for inhaler use on each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*®, Ellipta, Spiromax and Forspiro)].

All questionnaires will be used in validated Portuguese versions [32-37 39 40]. All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
    - Exacerbation history.
    - Years of diagnosis.
    - Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)[30]
    - COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)[31].
- Social class according to Graffar classification (Portuguese version)[41].
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese[42].
- Frailty state in elderly, using a self-reported instrument in Portuguese [43].
- Cognitive function using Montreal Cognitive Assessment (MOCA)in Portuguese [44]
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique with a placebo device approach.

The principal investigator will collect all baseline data prior to allocation and randomization, and this will be recorded in a proper form.

Statistical Analysis

The hypothesis testing approach will be the following:

H0: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD.

HA: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD.

Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Test statistic: Two-sample proportions Chi-square test
Data will be analysed using the *STATA Statistical Package*© software.
The primary outcome will be analysed using a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and comparing groups using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses. In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Secondary outcomes will be analysed using parametric tests, such as T test for comparison of mean values and Chi-square test for association of qualitative variables. A subgroup analysis will be performed according to secondary variables, such as age, sex, years of diagnosis, disease classification/stage, previous teaching of inhaler technique and device type. This will be performed using regression models to multivariate analyses.
Missing data will be treated as missing completely at random. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalized linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature [45].
An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 [46].

Study Setting
The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of Asthma and COPD of 8% among this population, there is a potential target population of almost 250 patients in each health care facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.
All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and the subsequent randomisation. Diagnosis will be confirmed according to state of art and the previously mentioned updated guidelines, and with an actual spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline
Study protocol final version: August 2017
Ethics consent and scientific academic authorization: December 2017
Clinical administrative authorizations: first semester of 2018
Multicentre team gathering: first semester of 2018
Beginning of recruitment: second semester of 2018
End of recruitment: second semester of 2019
Data analysis and dissemination: during 2020

DISCUSSION

This is the first study designed to test a specific intervention on inhaler education in elderly patients, and it was designed to detect a significant reduction on exacerbation rate. It is expected to observe approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in all clinical and functional parameters during the follow-up in the intervention group.

This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. the behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group will maintain their usual care in their own family doctors, who are completely free from any influence of the study design. For this reason, control group participants will not receive any intervention from the primary investigator, but only with the secondary one, who is completely blinded to randomization. With this approach, the Hawthorne effect will not contaminate the control group, and it will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will be blinded to the endpoints and outcomes (PROBE setting).

The standardization of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardization of all procedures of intervention and it will be provided ahead by the coordination team of the study.

ETHICS AND DISSEMINATION

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.

Every participant will sign a consent form (Appendix I). A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time achieved at that time. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.

Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They also will be invited to sign a proper informed consent that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each

participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Health Care Service Number (eg. *Name FirstSurname SecondSurname*, 123456789 -------> code "NF89").

The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.

The results obtained from this study will be presented to publish in peer-reviewed journals and presented in scientific meetings of primary health care and respiratory fields. All data recorded during the study will be stored for a period of 5 years, according to the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to the elaboration of this protocol in every stage of its design and writtng.

COMPETING INTERESTS STATEMENT

Dr. Correia-de-Sousa reports other from Harvard Medical School, during the conduct of the study. Also other from Boheringer Ingelheim, other from AstraZeneca, other from Boheringer Ingelheim, outside the submitted work; all these fees were received by a non-profit organisation to be used in CME and research. The remaining authors declare only from Harvard Medical School, during the conduct of the study.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
This work was developed without any funding support or financial source. The academic affiliation of this protocol is the Life and Health Sciences Research Institute (ICVS)/3B's at University of Minho and the Faculty of Health Sciences at the University of Beira Interior in Portugal.
This work was prepared with scientific support from Harvard Medical School, in accordance with the Portuguese Clinical Scholarship Research Training Program.

ACKNOWLEDGMENTS

The authors endorse acknowledgment to Prof. Jonh Groarke, from the Harvard Medical School, for his important scientific support and input in reviewing the final version of this manuscript.

DATA ACESS

All data from the trial will be kept in a safe place of the principal investigator`s institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

FIGURE LEGENDS

Figure 1 – Study design diagram.

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APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.
Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.
A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.
A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.
O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.
O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional]

Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante

Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente]

Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|
Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio na unidade de saúde.

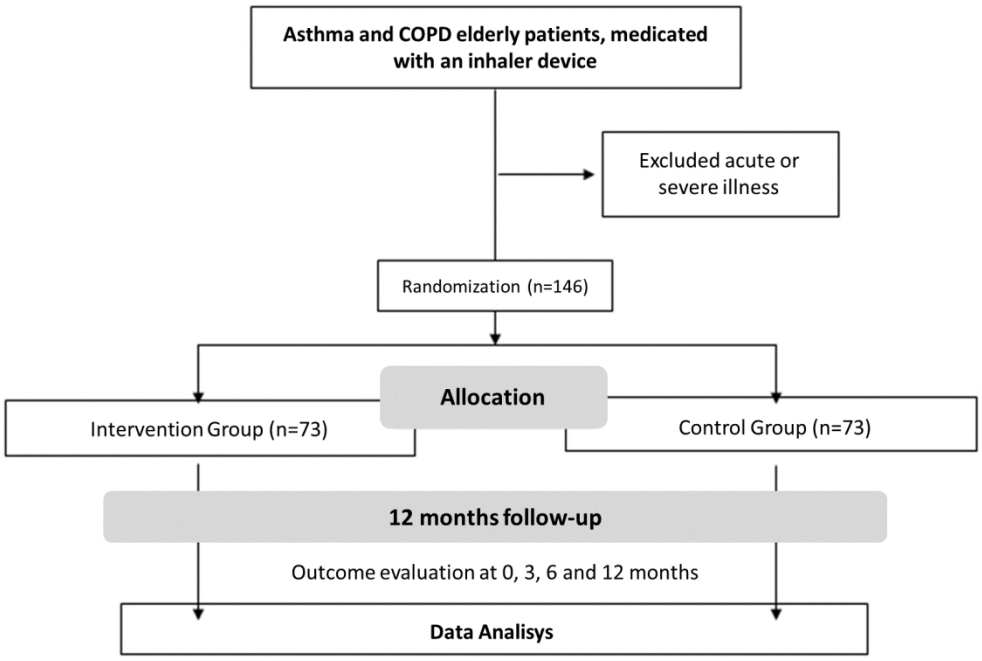

Figure 1 - Study Design Diagram

446x297mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial (SPIRIT).

Instructions to authors

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	NA

		ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug	4

		tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4-5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4-5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	7

		trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6-7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6-7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6-7
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7-8

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7-8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7-8
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022685.R1
Article Type:	Protocol
Date Submitted by the Author:	09-May-2018
Complete List of Authors:	Maricoto, Tiago; Aveiro-Aradas Family Health Unit, ACeS Baixo Vouga; Faculty of Health Sciences, University of Beira Interior Correia-de-Sousa, Jaime; Life and Health Sciences Research Institute (ICVS)/3B's — PT Government Associate Laboratory, University of Minho; Horizonte Family Health Unit, Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	Chronic Obstructive Pulmonary Disease, Asthma < THORACIC MEDICINE, Nebulizers and Vaporizers

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

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WORD COUNT

3186 words

PROTOCOL VERSION

This is the second version of this RCT protocol.

ABSTRACT

Introduction

COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis

A multicentre single-blinded RCT will be set up, comparing a placebo-device training programme with usual care, with a one-year follow-up, in elderly patients with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination:

Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on the 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS

Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

REGISTRY

This RCT protocol is registered in clinicaltrials.gov, with the number NCT03449316.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to address, in an isolated manner, a specific placebo device education programme in elderly patients with Asthma or COPD.
- No previous study has addressed this teaching method in these patients, as it seems to be the most efficient one.
- Our study has a randomised design, which has been a major limitation in previous studies.
- The one-year follow up period, with two interim evaluations, allow this study to comprehensively address the real impact of a regular education programme.
- The main limitation of this study is the single blinded design, due to the nature of intervention itself, which may introduce some performance bias.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms [1]. In Asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled [2 3], and the elderly population is particularly vulnerable to this condition [3]. In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring [4]. Hospitalisation rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases [5-7].

Inhaler technique

Inhaled therapy is the most widely used way to treat asthma and COPD patients [8], but up to 90% of them do not use their inhalers correctly [9 10]. Performance errors have been described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand on the specificities of different inhaler use as well as the impact of different inhaler teaching methods [11] Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance [12]. However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy [13 14], but it is well established that poor inhaler technique leads to poor clinical control [15 16] and also to an increased health costs [17]. In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical [18 19]

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes [20]. Some studies show that teaching inhaler technique may lower the risk of exacerbations and death [6 21 22]. However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients [23 24]. Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients [25 26].These patients also present lower adherence rates [9] and are more resistant to correct performance [27 28]. Furthermore, other major characteristics may influence inhaler use, such as educational level, previous teaching, or even age itself (i.e. age above 75 years) [29] However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but none has yet addressed inhaler review alone or in a regular education programme [21 30-33].

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact upon major outcomes [34 35]. Nevertheless, some studies suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person [36-38]. In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the

necessary steps of inhaler use [39]. This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.
This study will focus upon elderly patients and aims at testing the effect of a structured and regular placebo device training approach upon disease exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD..
The main hypothesis is that regular education of inhaler technique using a placebo device-based approach in elderly patients can reduce the exacerbation risk by 50%.

RESEARCH DESIGN AND METHODOLOGY

Study Design

Two arms single blinded randomised controlled trial with a 1 year follow up (fig.1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the *Chi square independent group proportions* approach of *STATA Statistical Package*©, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies [21 22 40] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria

Patients with a diagnosis of COPD or Asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged ≥65 years and being a regular user of primary health care services (defined as having had at least one appointment in the last two years with his/her own Family Doctor). In order to minimise diagnostic inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies [41 42].

Exclusion Criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. A teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly at each evaluation. There will be visits at baseline and after 3, 6 and 12 months to assess outcomes. In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according to his/her real life judgment. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.

All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Health Care facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) [43] and Asthma Control Test (ACT) for Asthma [44].
- Quality of Life using St. George's Respiratory Questionnaire [45] and Clinical COPD Questionnaire (CCQ) [46] for COPD and Asthma Quality of Life Questionnaire (AQLQ) [47].
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) [48].
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale) [To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used [49], evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*®, Ellipta, Spiromax and Forspiro)].

All questionnaires will be used in validated Portuguese versions [43-48 50 51]. All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
    - Exacerbation history.
    - Years of diagnosis.
    - Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)[41]
    - COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)[42].
- Social class according to Graffar classification (Portuguese version)[52].
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or

acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).

- Depression using Geriatric Depression Scale in Portuguese[53].
- Frailty state in elderly, using a self-reported instrument in Portuguese [54].
- Cognitive function using Montreal Cognitive Assessment (MOCA)in Portuguese [55]
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.)..
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical Analysis

The hypothesis testing approach will be the following:

H0: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD.

HA: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Test statistic: Two-sample proportions Chi-square test

Data will be analysed using the *STATA Statistical Package*© software.

The primary outcome will be analysed using a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and comparing groups using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses. In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Secondary outcomes will be analysed using parametric tests, such as T test for comparison of mean values and Chi-square test for association of qualitative variables. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device type, as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.

Missing data will be treated as missing completely at random. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature [56]. As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 [57].

Study Setting

The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate

prevalence of Asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each health care facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.
All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines, and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline
Study protocol final version: August 2017
Ethics consent and scientific academic authorisation: December 2017
Clinical administrative authorisations: first semester of 2018
Multicentre team gathering: first semester of 2018
Beginning of recruitment: second semester of 2018
End of recruitment: second semester of 2019
Data analysis and dissemination: during 2020

Patient and Public Involvement
No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

DISCUSSION

This is the first study designed to test this specific intervention in inhaler performance in elderly patients with a regular education programme, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.
This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.
Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group ("usual care") will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group ("usual care") participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting).

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available – INCA device[58]. Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide, and also in Portuguese [48]. Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of asthma and COPD patients. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardization of all procedures of intervention and it will be provided ahead by the coordination team of the study.

ETHICS AND DISSEMINATION

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.

Every participant will sign a written consent form (Appendix I). A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.

Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be

invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Health Care Service Number (eg. *Name FirstSurname SecondSurname*, 123456789 -------> code "NF89").

The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.

The results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary health care and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to the elaboration of this protocol in every stage of its design and writing. TM elaborated the first draft of the study, JCS and LTB gave inputs to all necessary design adjustments, and all authors have carried out final revisions of the manuscript.

COMPETING INTERESTS STATEMENT

Dr. Correia-de-Sousa reports competing interests from Harvard Medical School, during the conduct of the study, as scientific support. He also reports from Boheringer Ingelheim and from AstraZeneca outside the submitted work, and all these fees were received by a non-profit organisation to be used in CME and research.
The remaining authors declare only from Harvard Medical School, during the conduct of the study, as scientific support.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
This work was developed without any funding support or financial source. The academic affiliation of this protocol is the Life and Health Sciences Research Institute (ICVS)/3B's at University of Minho and the Faculty of Health Sciences at the University of Beira Interior in Portugal.
This work was prepared with scientific support from Harvard Medical School, in accordance with the Portuguese Clinical Scholarship Research Training Program.

ACKNOWLEDGMENTS

The authors endorse acknowledgment to Prof. Jonh Groarke, from the Harvard Medical School, for his important scientific support and input in reviewing the final version of this manuscript.

DATA ACESS

All data from the trial will be kept in a safe place of the principal investigator`s institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

FIGURE LEGENDS

Figure 1 – Study design diagram.

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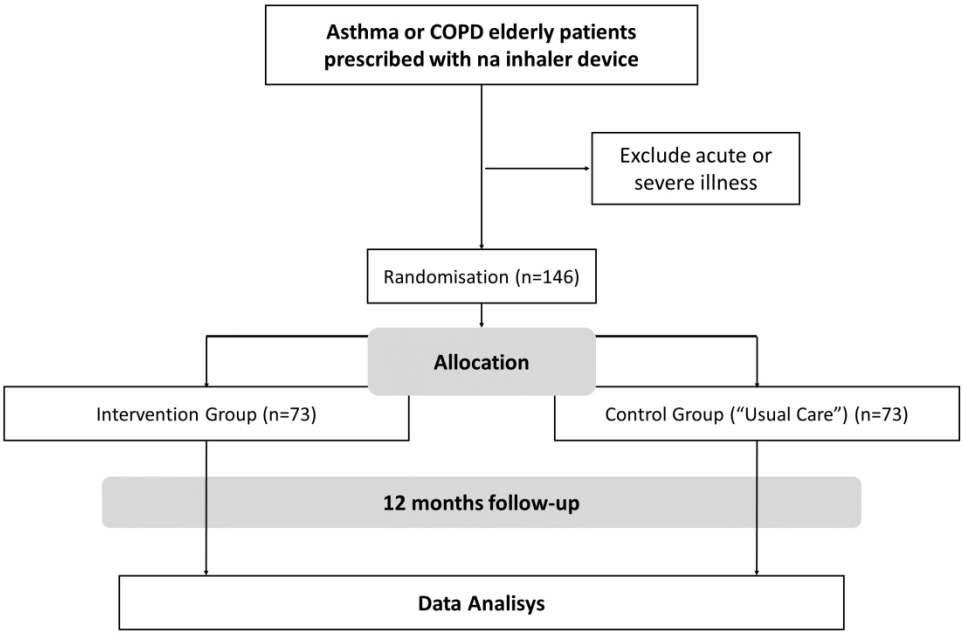

Figure 1 - Study Design Diagram

APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.

Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.

A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.

A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.

O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.

O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional**]**
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente**]**
Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio

Reporting checklist for protocol of a clinical trial (SPIRIT).

Instructions to authors

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	NA

		ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug	9

		tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5,8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5,8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6,9

		trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6,9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10,11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10,11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Apx.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022685.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2018
Complete List of Authors:	Maricoto, Tiago; Aveiro-Aradas Family Health Unit, ACeS Baixo Vouga; Faculty of Health Sciences, University of Beira Interior Correia-de-Sousa, Jaime; Life and Health Sciences Research Institute (ICVS)/3B's — PT Government Associate Laboratory, University of Minho; Horizonte Family Health Unit, Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	Chronic Obstructive Pulmonary Disease, Asthma < THORACIC MEDICINE, Nebulizers and Vaporizers

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

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WORD COUNT

3186 words

PROTOCOL VERSION

This is the second version of this RCT protocol.

ABSTRACT

Introduction

COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis

A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with placebo-device training versus usual care, with a one-year follow-up, in elderly patients with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination:

Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on the 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS

Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

REGISTRY

This RCT protocol is registered in clinicaltrials.gov, with the number NCT03449316.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to address a specific placebo device education programme alone, without any other aspects, in elderly patients with Asthma or COPD.
- No previous study has addressed this teaching method in these patients, as it seems to be the most efficient one.
- Our study has a randomised design, which has been a major limitation in previous studies.
- The one-year follow up period, with two interim evaluations, allow this study to comprehensively address the real impact of a regular education programme.
- The main limitation of this study is the single blinded design, due to the nature of intervention itself, which may introduce some performance bias.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms [1]. In Asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled [2 3], and the elderly population is particularly vulnerable to this condition [3]. In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring [4]. Hospitalisation rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases [5-7].

Inhaler technique

Inhaled therapy is the most widely used way to treat asthma and COPD patients [8], but up to 90% of them do not use their inhalers correctly [9 10]. Performance errors have been described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand on the specificities of different inhaler use as well as the impact of different inhaler teaching methods [11] Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance [12]. However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy [13 14], but it is well established that poor inhaler technique leads to poor clinical control [15 16] and also to an increased health costs [17]. In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical [18 19]

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes [20]. Some studies show that teaching inhaler technique may lower the risk of exacerbations and death [6 21 22]. However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients [23 24]. Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients [25 26].These patients also present lower adherence rates [9] and are more resistant to correct performance [27 28]. Furthermore, other major characteristics may influence inhaler use, such as educational level, previous teaching, or even age itself (i.e. age above 75 years) [29] However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. None has yet addressed inhaler review alone or in a regular education programme [21 30-33].

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact upon major outcomes [34-37]. Nevertheless, some studies including adult patients as well, suggest that the most efficient method seems to be using a teach-to-goal

approach with placebo device demonstration and training provided in person [38-42]. In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the necessary steps of inhaler use [43]. This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.
This study will focus upon elderly patients and aims at testing the effect of a structured and regular placebo device training approach upon disease exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD.
The main hypothesis is that regular education of inhaler technique using a placebo device-based approach in elderly patients can reduce the exacerbation risk by 50% after a one-year follow-up.

RESEARCH DESIGN AND METHODOLOGY

Study Design

Two arms single blinded randomised controlled trial with a 1 year follow up (fig.1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the *Chi square independent group proportions* approach of *STATA Statistical Package©*, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies [21 22 44] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria

Patients with a diagnosis of COPD or Asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged ≥65 years and being a regular user of primary health care services (defined as having had at least one appointment in the last two years with his/her own Family Doctor). In order to minimise diagnostic

inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies [45 46].

Exclusion Criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly. This will be performed at each follow-up evaluation. There will be visits at baseline and after 3, 6 and 12 months to assess outcomes, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions [21 30 32]. In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according to his/her real life judgment. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting β_2 agonists on a daily basis

- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.
All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Health Care facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) [47] and Asthma Control Test (ACT) for Asthma [48].
- Quality of Life using St. George's Respiratory Questionnaire [49] and Clinical COPD Questionnaire (CCQ) [50] for COPD and Asthma Quality of Life Questionnaire (AQLQ) [51].
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) [52].
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale) [To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used [53], evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*®, Ellipta, Spiromax and Forspiro)].

All questionnaires will be used in validated Portuguese versions [47-52 54 55]. All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
    - Exacerbation history.
    - Years of diagnosis.
    - Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)[45]

- COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)[46].
- Social class according to Graffar classification (Portuguese version)[56].
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese[57].
- Frailty state in elderly, using a self-reported instrument in Portuguese [58].
- Cognitive function using Montreal Cognitive Assessment (MOCA)in Portuguese [59]
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.)..
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical Analysis

The hypothesis testing approach will be the following:

Null hypothesis: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Alternative hypothesis: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Data will be analysed using the *STATA Statistical Package*© software.

Test statistic for primary outcome: Dichotomous data will be analysed with a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and both arms will be compared using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses.

Test statistic for secondary outcomes: Continuous data will be analysed using parametric tests, such as T test for comparison of mean values and dichotomous data will be analysed using Chi-square test. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature [60]. As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Missing data will be treated as missing completely at random. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device type, as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.

An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 [61].

Study Setting

The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of Asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each health care facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.

All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines, and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline

Study protocol final version: August 2017
Ethics consent and scientific academic authorisation: December 2017
Clinical administrative authorisations: first semester of 2018
Multicentre team gathering: first semester of 2018
Beginning of recruitment: second semester of 2018
End of recruitment: second semester of 2019
Data analysis and dissemination: during 2020

Patient and Public Involvement

No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

DISCUSSION

This is the first study designed to test this specific intervention in inhaler performance in elderly patients with a regular education programme, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.

This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group ("usual

care") will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group ("usual care") participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting).

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available – INCA device[62]. Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide, and also in Portuguese [52]. Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of asthma and COPD patients. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardization of all procedures of intervention and it will be provided ahead by the coordination team of the study.

ETHICS AND DISSEMINATION

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.

Every participant will sign a written consent form (Appendix I). We decided to use "usual care" as the main comparator instead of another intervention method, since all methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. Using other education methods would minimise the effect detection of our intervention. Moreover, all of the randomised studies performed in elderly patients also used "usual care", which will be important when comparing them with our results.

A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.

Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Health Care Service Number (eg. *Name FirstSurname SecondSurname*, 123456789 -------> code "NF89").

The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.

The results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary health care and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to the elaboration of this protocol in every stage of its design and writing. TM elaborated the first draft of the study, JCS and LTB gave inputs to all necessary design adjustments, and all authors have carried out final revisions of the manuscript.

COMPETING INTERESTS STATEMENT

Dr. Correia-de-Sousa reports competing interests from Harvard Medical School, during the conduct of the study, as scientific support. He also reports from Boheringer Ingelheim and from AstraZeneca outside the submitted work, and all these fees were received by a non-profit organisation to be used in CME and research.
The remaining authors declare only from Harvard Medical School, during the conduct of the study, as scientific support.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
This work was developed without any funding support or financial source. The academic affiliation of this protocol is the Life and Health Sciences Research Institute (ICVS)/3B's at University of Minho and the Faculty of Health Sciences at the University of Beira Interior in Portugal.
This work was prepared with scientific support from Harvard Medical School, in accordance with the Portuguese Clinical Scholarship Research Training Program.

ACKNOWLEDGMENTS

The authors endorse acknowledgment to Prof. Jonh Groarke, from the Harvard Medical School, for his important scientific support and input in reviewing the final version of this manuscript.

DATA ACESS

All data from the trial will be kept in a safe place of the principal investigator`s institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

FIGURE LEGENDS

Figure 1 – Study design diagram.

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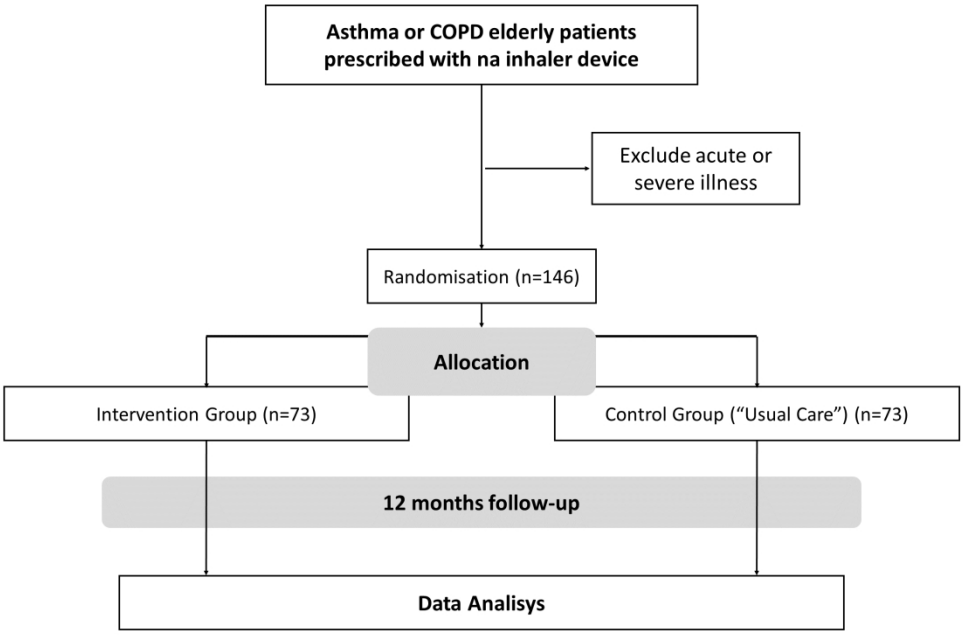

Figure 1 - Study Design Diagram

APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.

Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.

A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.

A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.

O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.

O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional**]**
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente**]**
Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio

Reporting checklist for protocol of a clinical trial (SPIRIT).

Instructions to authors

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	NA

		ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug	9

		tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5,8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5,8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6,9

		trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6,9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10,11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10,11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Apx.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022685.R3
Article Type:	Protocol
Date Submitted by the Author:	03-Sep-2018
Complete List of Authors:	Maricoto, Tiago; Aveiro-Aradas Family Health Unit, ACeS Baixo Vouga; Faculty of Health Sciences, University of Beira Interior Correia-de-Sousa, Jaime; Life and Health Sciences Research Institute (ICVS)/3B's — PT Government Associate Laboratory, University of Minho; Horizonte Family Health Unit, Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	Chronic Obstructive Pulmonary Disease, Asthma < THORACIC MEDICINE, Nebulizers and Vaporizers

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

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WORD COUNT

3186 words

PROTOCOL VERSION

This is the second version of this RCT protocol.

ABSTRACT

Introduction

COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis

A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care, with a one-year follow-up, in patients above 65 years of age with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination:

Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on the 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS

Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

REGISTRY

This RCT protocol is registered in clinicaltrials.gov, with the number NCT03449316.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to address a specific placebo device education programme alone, without any other aspects, in elderly patients with Asthma or COPD.
- No previous study has addressed this teaching method in these patients, as it seems to be the most efficient one.
- Our study has a randomised design, which has been a major limitation in previous studies.
- The one-year follow up period, with two interim evaluations, allow this study to comprehensively address the real impact of a regular education programme.
- The main limitation of this study is the single blinded design, due to the nature of intervention itself, which may introduce some performance bias.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms [1]. In Asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled [2 3], and the elderly population is particularly vulnerable to this condition [3]. In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring [4]. Hospitalisation rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases [5-7].

Inhaler technique

Inhaled therapy is the most widely used way to treat asthma and COPD patients [8], but up to 90% of them do not use their inhalers correctly [9 10]. Performance errors have been described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand on the specificities of different inhaler use as well as the impact of different inhaler teaching methods [11] Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance [12]. However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy [13 14], but it is well established that poor inhaler technique leads to poor clinical control [15 16] and also to an increased health costs [17]. In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical [18 19]

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes [20]. Some studies show that teaching inhaler technique may lower the risk of exacerbations and death [6 21 22]. However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients [23 24]. Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients [25 26].These patients also present lower adherence rates [9] and are more resistant to correct performance [27 28]. Furthermore, other major characteristics may influence inhaler use, such as educational level, previous teaching, or even age itself (i.e. age above 75 years) [29] However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. None has yet addressed inhaler review alone or in a regular education programme [21 30-33].

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact upon major outcomes [34-37]. Nevertheless, some studies including adult patients as well, suggest that the most efficient method seems to be using a teach-to-goal

approach with placebo device demonstration and training provided in person [38-42]. In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the necessary steps of inhaler use [43]. This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.
This study will focus upon elderly patients and aims at testing the effect of a structured and regular placebo device training approach upon disease exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD.
The main hypothesis is that, among elderly patients with Asthma or COPD, regular education of inhaler technique using a teach-to-goal placebo device-based approach, and delivered by family doctors at baseline, 3 and 6 months, can reduce the exacerbation risk by 50% after a one-year follow-up, when compared to usual care.

RESEARCH DESIGN AND METHODOLOGY

Study Design

Two arms single blinded randomised controlled trial with a 1 year follow up (fig.1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the *Chi square independent group proportions* approach of *STATA Statistical Package*©, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies [21 22 44] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria

Patients with a diagnosis of COPD or Asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged

≥65 years and being a regular user of primary health care services (defined as having had at least one appointment in the last two years with his/her own Family Doctor). In order to minimise diagnostic inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies [45 46].

Exclusion Criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used with correction of identified errors. Then we will ask patients to demonstrate the inhaler technique, and again, committed errors will be corrected by demonstration. We will repeat all correct steps as many times as needed in order for patients to perform them correctly. This intervention will be performed at baseline, 3 and 6 months. Outcomes will be assessed at baseline and after 3, 6 and 12 months, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions [21 30 32]. In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according to his/her real life judgment. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded, since it will be important to analyse and control for the true effect size of intervention.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics

- Hospitalisation or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.

All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Health Care facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) [47] and Asthma Control Test (ACT) for Asthma [48].
- Quality of Life using St. George's Respiratory Questionnaire [49] and Clinical COPD Questionnaire (CCQ) [50] for COPD and Asthma Quality of Life Questionnaire (AQLQ) [51].
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) [52].
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale)
  [To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used [53], evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*®, Ellipta, Spiromax and Forspiro)].

All questionnaires will be used in validated Portuguese versions [47-52 54 55]. All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
  - Exacerbation history.
  - Years of diagnosis.

- Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)[45]
- COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)[46].

- Social class according to Graffar classification (Portuguese version)[56].
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese[57].
- Frailty state in elderly, using a self-reported instrument in Portuguese [58].
- Cognitive function using Montreal Cognitive Assessment (MOCA)in Portuguese [59]
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.)..
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical Analysis

The hypothesis testing approach will be the following:

Null hypothesis: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Alternative hypothesis: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Data will be analysed using the *STATA Statistical Package*© software.

Test statistic for primary outcome: Dichotomous data will be analysed with a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and both arms will be compared using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses.

Test statistic for secondary outcomes: Continuous data will be analysed using parametric tests, such as T test for comparison of mean values and dichotomous data will be analysed using Chi-square test. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature [60]. As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Missing data will be treated as missing completely at random. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of

diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device type, as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.
An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 [61].

Study Setting
The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of Asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each health care facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.
All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines, and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline
Study protocol final version: August 2017
Ethics consent and scientific academic authorisation: December 2017
Clinical administrative authorisations: first semester of 2018
Multicentre team gathering: first semester of 2018
Beginning of recruitment: second semester of 2018
End of recruitment: second semester of 2019
Data analysis and dissemination: during 2020

Patient and Public Involvement
No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

DISCUSSION

This is the first study designed to test this specific intervention in inhaler performance in elderly patients with a regular education programme, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.
This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group ("usual care") will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group ("usual care") participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting). Using usual care as the comparator arm also brings some limitations to consider, because it is not a perfect comparator due to its nature. It is not sufficient for good patient outcomes and it is not standardized. This aspect is due, for instance, to the fact that patients on usual care can receive interventions on inhaler education and self-management tools from other uncontrolled sources. To overcome that we will retrospectively query patients in this arm and their own family doctor for any type of interventions that may have been delivered during the study period.

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available – INCA device[62]. Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide, and also in Portuguese [52]. Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of asthma and COPD patients. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardization of all procedures of intervention and it will be provided ahead by the coordination team of the study.

ETHICS AND DISSEMINATION

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.
Every participant will sign a written consent form (Appendix I). We decided to use "usual care" as the main comparator instead of another intervention method, since all interventional methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. We thus believe that comparing with other education methods would minimise the effect detection of our teach-to-goal placebo-device intervention. Moreover, all of the randomised studies that included mostly elderly patients also used "usual care" as a comparator, which will be important when comparing them with our results. However, we highlight the fact that those studies did not use the same age criteria as we are using, since they also included non-elderly adult patients in their samples. In addition, they did not just focus on inhaler teaching, since they provided additional sessions with other program elements, such as self-management care. There is, thus, insufficient evidence about the efficacy of inhaler education as an isolated intervention, and for that reason, our approach will be novel and will significantly contribute towards clarifying those issues.
A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.
Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Health Care Service Number (eg. *Name FirstSurname SecondSurname*, 123456789 -------> code "NF89").
The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.
The results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary health care and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to the elaboration of this protocol in every stage of its design and writing. TM elaborated the first draft of the study, JCS and LTB gave inputs to all necessary design adjustments, and all authors have carried out final revisions of the manuscript.

COMPETING INTERESTS STATEMENT

Dr. Correia-de-Sousa reports competing interests from Harvard Medical School, during the conduct of the study, as scientific support. He also reports from Boheringer Ingelheim and from AstraZeneca outside the submitted work, and all these fees were received by a non-profit organisation to be used in CME and research.
The remaining authors declare only from Harvard Medical School, during the conduct of the study, as scientific support.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
This work was developed without any funding support or financial source. The academic affiliation of this protocol is the Life and Health Sciences Research Institute (ICVS)/3B's at University of Minho and the Faculty of Health Sciences at the University of Beira Interior in Portugal.
This work was prepared with scientific support from Harvard Medical School, in accordance with the Portuguese Clinical Scholarship Research Training Program.

ACKNOWLEDGMENTS

The authors endorse acknowledgment to Prof. Jonh Groarke, from the Harvard Medical School, for his important scientific support and input in reviewing the final version of this manuscript.

DATA ACESS

All data from the trial will be kept in a safe place of the principal investigator`s institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

FIGURE LEGENDS

Figure 1 – Study design diagram.

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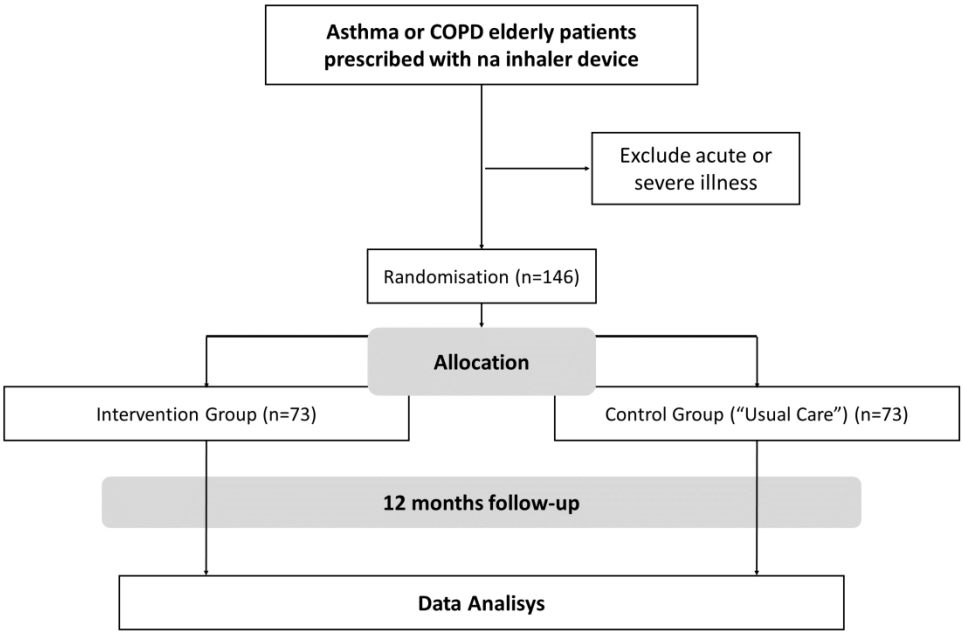

Figure 1 - Study Design Diagram

APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.

Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.

A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.

A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.

O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.

O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional**]**
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente**]**
Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio

Reporting checklist for protocol of a clinical trial (SPIRIT).

Instructions to authors

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	NA

		ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug	9

		tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5,8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5,8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6,9

		trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6,9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10,11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10,11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Apx.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022685.R4
Article Type:	Protocol
Date Submitted by the Author:	10-Nov-2018
Complete List of Authors:	Maricoto, Tiago; Aveiro-Aradas Family Health Unit, ACeS Baixo Vouga; Faculty of Health Sciences, University of Beira Interior Correia-de-Sousa, Jaime; Life and Health Sciences Research Institute (ICVS)/3B's — PT Government Associate Laboratory, University of Minho; Horizonte Family Health Unit, Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	Chronic Obstructive Pulmonary Disease, Asthma < THORACIC MEDICINE, Nebulizers and Vaporizers

Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

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WORD COUNT

3186 words

PROTOCOL VERSION

This is the second version of this RCT protocol.

ABSTRACT

Introduction

COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis

A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care, with a one-year follow-up, in patients above 65 years of age with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination:

Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on the 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS

Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

REGISTRY

This RCT protocol is registered in clinicaltrials.gov, with the number NCT03449316.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is innovative because it includes exclusively elderly patients with Asthma or COPD, addressing, in a one-year follow-up, a specific placebo device education programme, alone, without any other aspects.
- No previous study has addressed this teaching method in these patients, as it seems to be the most efficient one.
- Our study has a randomised design, which has been a major limitation in previous studies.
- The one-year follow up period, with two interim evaluations, allow this study to comprehensively address the real impact of a regular education programme.
- The main limitation of this study is the single blinded design, due to the nature of intervention itself, which may introduce some performance bias.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms [1]. In Asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled [2 3], and the elderly population is particularly vulnerable to this condition [3]. In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring [4]. Hospitalisation rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases [5-7].

Inhaler technique

Inhaled therapy is the most widely used way to treat asthma and COPD patients [8], but up to 90% of them do not use their inhalers correctly [9 10]. Performance errors have been described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand on the specificities of different inhaler use as well as the impact of different inhaler teaching methods [11] Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance [12]. However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy [13 14], but it is well established that poor inhaler technique leads to poor clinical control [15 16] and also to an increased health costs [17]. In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical [18 19]

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes [20]. Some studies show that teaching inhaler technique may lower the risk of exacerbations and death [6 21 22]. However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients [23 24]. Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients [25 26].These patients also present lower adherence rates [9] and are more resistant to correct performance [27 28]. Furthermore, other major characteristics may influence inhaler use, such as educational level, previous teaching, or even age itself (i.e. age above 75 years) [29] However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. None has yet addressed inhaler review alone or in a regular education programme [21 30-33].

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact upon major outcomes [34-37]. Nevertheless, some studies including adult patients as well, suggest that the most efficient method seems to be using a teach-to-goal approach with

placebo device demonstration and training provided in person [38-42]. In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the necessary steps of inhaler use [43]. This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.
This study will focus upon elderly patients and aims at testing the effect of a structured and regular placebo device training approach upon disease exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD.
The main hypothesis is that, among elderly patients with Asthma or COPD, regular education of inhaler technique using a teach-to-goal placebo device-based approach, and delivered by family doctors at baseline, 3 and 6 months, can reduce the exacerbation risk by 50% after a one-year follow-up, when compared to usual care.

RESEARCH DESIGN AND METHODOLOGY

Study Design

Two arms single blinded randomised controlled trial with a 1 year follow up (fig.1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the *Chi square independent group proportions* approach of *STATA Statistical Package*©, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies [21 22 44] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria

Patients with a diagnosis of COPD or Asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged ≥65 years and being a regular user of primary health care services (defined as having had at least one

appointment in the last two years with his/her own Family Doctor). In order to minimise diagnostic inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies [45 46].

Exclusion Criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used with correction of identified errors. Then we will ask patients to demonstrate the inhaler technique, and again, committed errors will be corrected by demonstration. We will repeat all correct steps as many times as needed in order for patients to perform them correctly. This intervention will be performed at baseline, 3 and 6 months. Outcomes will be assessed at baseline and after 3, 6 and 12 months, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions [21 30 32]. In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according to his/her real life judgment. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded, since it will be important to analyse and control for the true effect size of intervention.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics

- Hospitalisation or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting β_2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.
All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Health Care facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) [47] and Asthma Control Test (ACT) for Asthma [48].
- Quality of Life using St. George's Respiratory Questionnaire [49] and Clinical COPD Questionnaire (CCQ) [50] for COPD and Asthma Quality of Life Questionnaire (AQLQ) [51].
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) [52].
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale)
  [To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used [53], evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*®, Ellipta, Spiromax and Forspiro)].

All questionnaires will be used in validated Portuguese versions [47-52 54 55]. All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
  - Exacerbation history.
  - Years of diagnosis.

    - Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)[45]
    - COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)[46].
- Social class according to Graffar classification (Portuguese version)[56].
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese[57].
- Frailty state in elderly, using a self-reported instrument in Portuguese [58].
- Cognitive function using Montreal Cognitive Assessment (MOCA)in Portuguese [59]
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.)..
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical Analysis

The hypothesis testing approach will be the following:

Null hypothesis: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Alternative hypothesis: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Data will be analysed using the *STATA Statistical Package*© software.

Test statistic for primary outcome: Dichotomous data will be analysed with a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and both arms will be compared using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses.

Test statistic for secondary outcomes: Continuous data will be analysed using parametric tests, such as T test for comparison of mean values and dichotomous data will be analysed using Chi-square test. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature [60]. As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Missing data will be treated as missing completely at random. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device

type, as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.
An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 [61].

Study Setting
The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of Asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each health care facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.
All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines, and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline
Study protocol final version: August 2017
Ethics consent and scientific academic authorisation: December 2017
Clinical administrative authorisations: first semester of 2018
Multicentre team gathering: first semester of 2018
Beginning of recruitment: second semester of 2018
End of recruitment: second semester of 2019
Data analysis and dissemination: during 2020

Patient and Public Involvement
No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

DISCUSSION

This study is innovative because it includes exclusively elderly patients with Asthma or COPD, addressing a specific placebo device education programme, alone, without any other aspects, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.
This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group ("usual care") will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group ("usual care") participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting). Using usual care as the comparator arm also brings some limitations to consider, because it is not a perfect comparator due to its nature. It is not sufficient for good patient outcomes and it is not standardized. This aspect is due, for instance, to the fact that patients on usual care can receive interventions on inhaler education and self-management tools from other uncontrolled sources. To overcome that we will retrospectively query patients in this arm and their own family doctor for any type of interventions that may have been delivered during the study period.

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available – INCA device[62]. Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide, and also in Portuguese [52]. Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of asthma and COPD patients. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardization of all procedures of intervention and it will be provided ahead by the coordination team of the study.

ETHICS AND DISSEMINATION

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.
Every participant will sign a written consent form (Appendix I). We decided to use "usual care" as the main comparator instead of another intervention method, since all interventional methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. We thus believe that comparing with other education methods would minimise the effect detection of our teach-to-goal placebo-device intervention. Moreover, all of the randomised studies that included mostly elderly patients also used "usual care" as a comparator, which will be important when comparing them with our results. However, we highlight the fact that those studies did not use the same age criteria as we are using, since they also included non-elderly adult patients in their samples. In addition, they did not just focus on inhaler teaching, since they provided additional sessions with other program elements, such as self-management care. There is, thus, insufficient evidence about the efficacy of inhaler education as an isolated intervention, and for that reason, our approach will be novel and will significantly contribute towards clarifying those issues.
A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.
Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Health Care Service Number (eg. *Name FirstSurname SecondSurname*, 123456789 -------> code "NF89").
The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.
The results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary health care and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to the elaboration of this protocol in every stage of its design and writing. TM elaborated the first draft of the study, JCS and LTB gave inputs to all necessary design adjustments, and all authors have carried out final revisions of the manuscript.

COMPETING INTERESTS STATEMENT

Dr. Correia-de-Sousa reports competing interests from Harvard Medical School, during the conduct of the study, as scientific support. He also reports from Boheringer Ingelheim and from AstraZeneca outside the submitted work, and all these fees were received by a non-profit organisation to be used in CME and research.
The remaining authors declare only from Harvard Medical School, during the conduct of the study, as scientific support.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
This work was developed without any funding support or financial source. The academic affiliation of this protocol is the Life and Health Sciences Research Institute (ICVS)/3B's at University of Minho and the Faculty of Health Sciences at the University of Beira Interior in Portugal.
This work was prepared with scientific support from Harvard Medical School, in accordance with the Portuguese Clinical Scholarship Research Training Program.

ACKNOWLEDGMENTS

The authors endorse acknowledgment to Prof. Jonh Groarke, from the Harvard Medical School, for his important scientific support and input in reviewing the final version of this manuscript.

DATA ACESS

All data from the trial will be kept in a safe place of the principal investigator`s institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

FIGURE LEGENDS

Figure 1 – Study design diagram.

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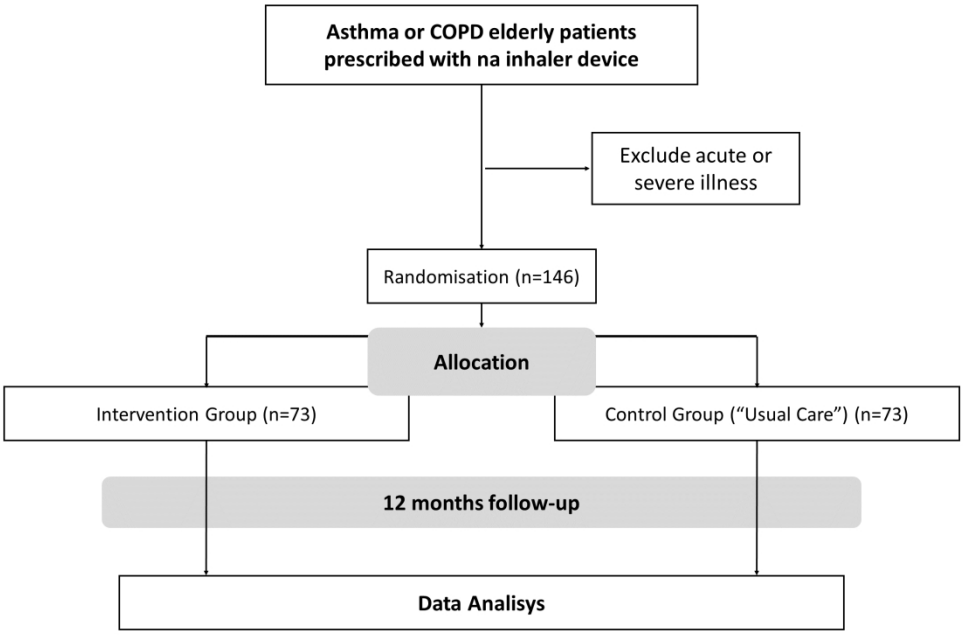

Figure 1 - Study Design Diagram

APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.

Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.

A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.

A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.

O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.

O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional**]**
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente**]**
Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio

Reporting checklist for protocol of a clinical trial (SPIRIT).

Instructions to authors

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	NA

		ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug	9

		tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5,8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5,8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6,9

		trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6,9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10,11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10,11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Apx.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA