BMJ Open

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation among SARS-CoV-2 infected individuals with Covid-19 symptoms

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050582
Article Type:	Protocol
Date Submitted by the Author:	01-Mar-2021
Complete List of Authors:	Mollerup, Annette; Copenhagen University Hospital, The Parker Institute, Frederiksberg Larsen, Sofus; Copenhagen University Hospital, The Parker Institute, Frederiksberg Bennetzen, Anita; Copenhagen University Hospital, The Parker Institute, Frederiksberg Henriksen, Marius; Copenhagen University Hospital, The Parker Institute, Frederiksberg Simonsen, Mette; Copenhagen University Hospital, Department of Neuro-Medicine, Bispebjerg Weis, Nina; Copenhagen University Hospital, Department of Infectious Diseases, Hvidovre; University of Copenhagen, Department of Clinical Medicine, Faculty of Health and Medical Science Kofod, Linette; Copenhagen University Hospital, Department of Physio- and Occupational Therapy and PMR-C, Hvidovre Heitmann, Berit; Copenhagen University Hospital, The Parker Institute, Research Unit for Dietary Studies, Frederiksberg; University of Copenhagen, Section for General Practice, Department of Public Health
Keywords:	COVID-19, PREVENTIVE MEDICINE, PUBLIC HEALTH, RESPIRATORY MEDICINE (see Thoracic Medicine), Clinical trials < THERAPEUTICS, INFECTIOUS DISEASES

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Title:

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation among SARS-CoV-2 infected individuals with Covid-19 symptoms

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Word count: 4225

Keywords: SARS-CoV-2 infection, Covid-19, selfcare, public health, randomised controlled trial

ABSTRACT

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in Covid-19

Introduction

Infection with severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2) may progress to severe pulmonary disease Covid-19. Currently, patients admitted to hospital because of Covid-19 have better prognosis than during the first period of the pandemic due to improved treatment. However, the overall societal susceptibility of being infected makes it pivotal to prevent severe courses of disease to avoid high mortality rates and collapse of the health care systems. Positive expiratory pressure (PEP) selfcare is used in chronic pulmonary disease and has been shown to prevent pneumonia in a high-risk cohort of leukaemia patients. The PEP-CoV trial examines the effectiveness on respiratory symptoms and need of hospital admission by regular PEP flute-use among non-hospitalised individuals with confirmed SARS-CoV-2 infection and Covid-19 symptoms.

Methods and analysis

In this randomised controlled trial, we hypothesise that daily PEP flute usage as add-on to usual care is superior to usual care as regards symptom severity measured by the COPD Assessment Test (CAT) at 30-day follow-up (primary outcome) and hospital admission through register data (secondary outcome). We expect to recruit 400 individuals for the trial. Participants in the intervention group receive a kit of 2 PEP flutes and adequate resistances and access to instruction videos. A telephone hotline offers possible contact to a nurse. The 8-item CAT-score measures cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms, sleep quality and vigour. The CAT-score is measured daily in both intervention and control arms by surveys prompted through text messages.

Ethics and dissemination

The study was registered prospectively at www.clinicaltrials.gov on August 27, 2020 (NCT04530435). Ethical approval was granted by the local Health Research Ethics Committee (Journal number: H-20035929) July 23, 2020. Enrolment of participants began October 6, 2020. Results will be published in scientific journals.

Keywords

SARS-CoV-2 infection, Covid-19, selfcare, public health, randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study

- Using a randomised design, this study addresses an important evidence gap in the SARS-CoV-2 pandemic; how to mobilise the individual's selfcare to prevent respiratory deterioration in Covid-19 with the use of a simple, cheap and accessible intervention, thus potentially avoid hospitalisation.
- This study is a niche project between a public health intervention and disease prevention in a clinical setting which may challenge a warranted non-selective recruitment as recruitment awaits the initiative from eligible participants.
- Due to the type of intervention, blinding of the participants and treatment providers is not feasible.
- Covid-19 is a novel disease and this study is explorative when using self-reported measurements from COPD-treatment i.e. the CAT-score as an outcome variable. In the absence of objectively measured values like oxygen saturation or body temperature as outcome variables, this calls for attention when discussing the results of the trial.
- There is a risk of contamination across arms as participants can acquire the PEP flute as over-the-counter medical equipment.

INTRODUCTION

The pandemic infection with severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2) may result in non-specific symptoms like fever, fatigue and dyspnoea or it may progress to severe pulmonary disease Corona Virus Disease 2019 (Covid-19). Mid-January 2021 as reported by WHO, the worldwide number of people dying because of Covid-19 exceeded two million. Over time, we learn more about this new disease e.g. reports of a median time from symptom onset to development of pneumonia of approximately 5 days[1]. Covid-19 seems to damage the respiratory system due to an overreaction of the immune system with individual risk profiles of age and comorbidity[2]. This may lead to acute respiratory distress syndrome (ARDS) and in these cases, the median time from symptom onset to severe hypoxemia and intensive care unit (ICU) admission has been reported to be approximately 7-12 days[1]. At a median follow-up period of 79 days among ICU-patients, mortality was reported to be 37 % in a Danish nationwide study. Hence, the Covid-19 disease burdens the health care systems even in countries without any restrictions as to ICU-admission in times of a pandemic[3].

At present, the disease trajectory is not easy to predict[1], and little is known of any measures or medication to alter the course of early-stage disease i.e. to prevent the need of hospitalisation and critical care. The PEP-CoV trial will investigate the effect of PEP flute-selfcare on respiratory deterioration and hospital admission among non-hospitalised individuals with Covid-19 symptoms. If PEP flute-selfcare proves to be effective, it will be easy to implement as a public health intervention also in a global context. In the trial, participants have confirmed SARS-CoV-2 infection by positive PCR swab test and Covid-19 symptoms at study entry hence, although no medical examination has been conducted, they are considered to be Covid-19 cases according to WHO Covid-19 case definitions[4].

Background and rationale

Recent evidence suggests a poor prognosis whenever the Covid-19 disease has become so severe that hospital admission is needed. A large observational cohort study from UK found that within a minimal follow-up time of two weeks 26 % of patients admitted to acute care hospitals had died[5]. Among patients in need of critical care facilities and/or receiving mechanical ventilation, the proportion of fatal outcome was 32 % and 37 % respectively. In the pandemic waves, health care systems face an imminent threat of collapse because of an overload of Covid-19 cases. The prognosis of having a severe course of disease due to Covid-19 is better now than in the first period of the pandemic because of improvements in treatment. Antiviral treatment with remdesivir[6] and dexamethasone[7] appears to have moderate effects. However, both treatments are administered only in cases when the patient is hospitalised and in need of oxygen. In the overall population, all are at risk of being infected and this overall societal susceptibility makes prevention of severe courses of disease pivotal to the health care system.

A variety of symptoms have been observed in patients with Covid-19. The study by Docherty et al. refers to clusters of symptoms on admission i.e. musculoskeletal symptoms (myalgia, joint pain, headache, and fatigue); enteric symptoms (abdominal pain, vomiting, and diarrhoea); and a mucocutaneous cluster[5]. However, the most common symptom cluster involves respiratory symptoms i.e. cough, sputum and shortness of breath, accompanied by fever. When critically ill, the intensive care treatment includes mechanical ventilation with high oxygenation and positive end expiratory pressure (PEEP). PEEP increases functional residual capacity and reduces the work of breathing. The use of positive expiratory pressure has been highlighted as very important measures to avoid a critical course administered as continuous positive airway pressure (CPAP) by face masks[8] or by use of a helmet[9]. However, this treatment is for hospitalised patients. Positive expiratory pressure (PEP) is used in selfcare in chronic inflammatory pulmonary diseases like chronic obstructive pulmonary disease (COPD) as an airway clearance technique (ACT) because of the possible beneficial effects on lung function. ACT appears to be safe and the PEP flute has been shown to be as effective as other ACTs[10]. However, little is known of the potential effects of PEP flute other than those related to COPD. In one small randomised controlled trial (RCT) among patients with acute myeloid leukaemia, lung training with PEP flute at least twice daily alongside daily spirometry was superior to daily spirometry only in preventing pneumonia[11]. The trial reported 25 incidences of X-ray-verified pneumonia throughout the study period affecting six patients from the intervention group with daily PEP-training and 17 patients from the control group. The difference in first pneumonia incidence between intervention versus control group was significant with an incidence per 1000 days of 2.17 versus 6.52 respectively ($p = 0.021$). The authors suggested a causal effect of mechanically supported inflation of the alveoli and loosening of secretions by PEP use, that may have prevented atelectasis and lower tract infection and concluded, that in this high-risk cohort of patients progression to manifest x-ray-verified lung infiltrates were hindered by PEP flute use without any adverse events[11].

Most current research on SARS-CoV-2 and Covid-19 relates to screening measures, vaccine development and optimising hospital treatment i.e. the bottom and top ends of a pyramid which depicts the relationship between populational size, setting and treatment options (Fig. 1). It is likely that we have this pandemic for several years until we have reached a high level of immunity in the population either by natural spread of the disease or via an efficient vaccination programme and measures are needed to help the SARS-CoV-2 infected individual at home to overcome the course of disease with less symptoms and strain. Based on the hypothesis that the regular use of a PEP flute may prevent the progression of respiratory symptoms in non-hospitalised individuals with SARS-CoV-2 infection, a PEP flute intervention, feasible for home use, may prevent prolonged disease courses, long-term sequelae and costly hospital admissions.

> Insert Figure 1 <

Study objectives and hypotheses

The aim of the present study is to explore the effectiveness on respiratory symptoms by regular use of PEP among SARS-CoV-2 infected, non-hospitalised individuals with Covid-19 symptoms. The primary objective is to examine the effect of PEP flute use on self-reported change in COPD Assessment Test (CAT) score during 30 days of follow-up. We hypothesise that PEP flute use has positive effects on self-reported respiratory symptoms such as dyspnoea, coughing and perceived mucus clearance through beneficial effects on lung function and airway clearance. Secondly, we expect a lower rate of hospitalisation and use of antibiotics in the intervention group as compared to the usual care group, the latter in case of a bacterial superinfection.

METHODS

Trial design and setting

The PEP-CoV trial is designed as a randomised, controlled, open-label trial with two parallel groups and consecutive inclusion. The trial is investigator-initiated and hosted by the Parker Institute, a part of Copenhagen University Hospital Bispebjerg-Frederiksberg. The participants are recruited from the Capital Region and Region Zealand in Denmark (in total, approximately 2.7 million citizens). The trial registration data set is displayed in Table 1.

Patient and Public Involvement

Ideation of the trial intervention was based upon anecdotal evidence of a PEP flute's beneficial effects in a single case of Covid-19. Personal communication with Covid-19 convalescents has contributed to the designing process of the study. However, due to the ongoing pandemic crisis further patient and public involvement in the research process has not been feasible.

Table 1

Table 1 WHO trial registration data set	
Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov NCT04530435
Date of registration in primary registry	27 august, 2020
Secondary identifying numbers	Danish Data Protection Agency (P-2020-879) Health Research Ethics (H-20035929)
Sources of monetary or material support	The Danish Innovation Fund (0211-00023B) and the Danish Nursing Council (grant number: n/a)
Sponsor	The Parker Institute, Copenhagen, Denmark
Contact for public queries	Annette Mollerup, PhD (annette.mollerup@regionh.dk) The Parker Institute Copenhagen University Hospital Bispebjerg-Frederiksberg Ndr. Fasanvej 57, 2000 Frederiksberg, Denmark +45 38163102
Contact for scientific queries	Annette Mollerup, PhD (annette.mollerup@regionh.dk)
Public title	Covid-19: symptoms and respiratory selfcare [in Danish: COVID-19 sygdom: symptomer og vejrtrækningsøvelser]
Scientific title	PEP flute-selfcare to prevent respiratory deterioration and hospitalisation among Covid-19 patients: a randomised trial (acronym: The PEP-CoV trial)
Countries of recruitment	Denmark
Health condition(s)	Adults aged 18 or older with a positive SARS-CoV-2 test and symptoms of COVID-19
Intervention	Active comparator: daily use of PEP flute and daily self-monitoring of symptoms for 30 days as add-on to usual care Comparator: daily self-monitoring of symptoms and usual care as recommended by the Danish Health Authorities (self-quarantine, sufficient intake of liquid especially in case of high body temperature, over-the-counter symptom relieving medication)
Key inclusion and exclusion criteria	Inclusion criteria: 1. Aged 18 years or older 2. Positive SARS-CoV-test 3. Symptoms of Covid-19 according to the COVIDmeter; at least one respiratory symptom (cough, sneezing, shortness of breath, chest pain, running nose) and one general symptom 4. Access to use a smartphone 5. Can reply to a questionnaire in Danish (sent on email, text-message or via telephone interview) as assessed by the investigator 6. Given informed consent Exclusion criteria: 1. Any condition or impairment that, in the opinion of the investigator, makes a potential participant unsuitable for participation or which obstruct participation, such as psychiatric disorders, individuals, habitually using a PEP flute, participation in other clinical Covid-trials or persons living in the same household as existing participants in the trial 2. Hospitalized patients or nursing home residents
Study type	Interventional, open-label trial with randomisation to two parallel groups Primary purpose: prevention of respiratory deterioration of symptoms and hospitalisation
Data of first enrollment	October 2020
Target sample size	400
Recruitment status	Recruiting
Primary outcome	Day 30 COPD Assessment Test score (CAT-score) (modified for the present study)
Key secondary outcomes	1. Hospital admissions on Day 30, Day 90 and Day 180 2. Use of antibiotics in case of superinfection 3. Number of participants with serious adverse events (SAE) during the 30-day intervention period 4. Compliance assessment

PEP, positive expiratory pressure; COVID-meter, the Danish Health Authority surveillance of symptoms reported by the public to a designated website; CAT, COPD Assessment Tool consisting of eight items on a scale from 0-5: cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms (because of actual self-quarantine, modified for the present study from feeling safe at leaving home despite symptoms), sleep quality and vigour

The study duration is six months and the primary endpoint is CAT-score after 30 days of active intervention. Follow-ups of CAT-scores are also planned at 90- and 180-days post-baseline. The study's enrolment, intervention and assessments schedules according to SPIRIT Guidelines[12] are outlined in Table 2.

Table 2

Table 2 Schedule for study enrolment, intervention and assessments					
Activity/assessment	**Recruitment**	**Enrolment**	**Follow-up$_{30days}$**	**Follow-up$_{90days}$**	**Follow-up$_{180days}$**
Time point	**T_{-1}**	**T_0**	**T_1**	**T_2**	**T_3**
Pre-screening (positive PCR-test)	x				
Information to e-Boks	x				
Informed e-consent		x			
Eligibility screening		x			
Baseline questionnaire		x			
Randomisation/group allocation		x			
Video guides		x			
PEP flute deliverance		x (+3 days)			
Self-report of symptoms CAT)		x (+1 day) ----------	x (day 30)		
Intervention group: PEP-usage		x (+1 day) ----------	x (day 30)		
Compliance assessment		x (+1 day) ----------	x (day 30)		
Outcome assessment			x	x	x
Baseline/outcome variables*					
Age, sex (register data)	x				
Symptoms within last week		x	x	x	x
Cohabitation		x			
Education		x			
Health literacy (two dimensions)		x			
Profession, employment		x			
Self-rated health (one item)		x	x	x	x
Weight, height		x			
Smoking, alcohol		x			
Comorbidity self-reported		x			
Comorbidity (register data)			x		
CAT-score		x	x	x	x
Hospital admission (register data)			x		x
Medication (register data)			x		x
Death (register data)			x		x
Serious adverse event			As needed throughout protocol		

*All baseline and outcome variables are collected as questionnaire data unless stated otherwise

Trial population and eligibility criteria

To avoid unnecessary spread of the SARS-CoV-2, any contact i.e. oral information, consent and screening is provided over phone and by use of secured electronic communication via the public 'Digital Post' system (electronic mailbox for letters from Danish authorities) administered by the platform 'e-Boks' (https://www.e-boks.com/danmark/en). This system is linked to the individual's Personal Identification number – a national identification number, which is part of the personal information stored in the Danish Civil Registration System. Daily information of positive results from the SARS-CoV-2 PCR-tests are provided from the Departments of Microbiology at Copenhagen University Hospitals Rigshospitalet, Hvidovre Hospital and Herlev Hospital, which covers the overall Capital Region, and the Department of Microbiology, Slagelse Hospital, covering the entire Region Zealand. Based upon these data, individuals eligible for study participation receive study information and invitation electronically via e-Boks. The individual may then contact the project directly via e-mail or phone or leave a phone number for a subsequent call from the data collectors (AM and ASB).

The inclusion/exclusion criteria for the trial are described in Table 1. A variety of symptoms has been associated to Covid-19[5,13] and early Danish reports indicated that the most frequent self-reported respiratory symptoms in Covid-19 (n = 308) were cough (71%) and shortness of breath (54 %)[14]. However, recent findings have suggested that approximately three quarters of people with SARS-CoV-2 infection are asymptomatic on the day of the test[15]. As the rationale for the potential effect of a PEP flute in a course of SARS-CoV-2 infection and Covid-19 involves the progression of respiratory symptoms, at least one reported respiratory symptom is required at enrolment. A screening manual has been developed and questions of symptoms according to the COVIDmeter[16] are posed after given consent (Table 2).

Randomisation and blinding

The participants reply to a telephone-administered baseline questionnaire before randomisation. Subsequently, the participant is randomly allocated to treatment or control arm using an appropriate statistical software embedded in REDCap, an online web-based clinical trial management application (Vanderbilt University, Nashville, TN, USA)[17]. The computer-generated random allocation is then unknown to the investigator and data collectors. As mortality prognosis to Covid-19 is higher in men and elderly[5], the allocation is based upon permuted random blocks and 1:1 stratified for the conditions sex and age (< 60 and ≥ 60 years). Sex is determined through the unique Danish personal identification number as a binary variable.

As this is an 'open-label' trial neither the health professionals delivering the interventions, nor the participants are blinded to treatment allocation. Statistical analyses will be conducted blinded to the intervention group.

Trial intervention

The trial intervention is the regular use of a PEP flute in combination with standard care. A set of two PEP flutes and three airway resistances (equivalent to a resistance of 10-20 cm H_2O) are delivered to the participants who are advised to use the PEP flute at least three times daily. Ideally, each session consists of 10-15 breaths (for approximately 1 minute) repeated twice with the participant sitting at an upright position. Two video guides (Fig. 2) are sent to the participant by e-Boks; one with instructions as to the rationale and how to use the PEP flute including how to choose the suitable resistance; the other with instruction of hygienic maintenance, advised to be daily because of a manifest SARS-CoV-2 infection.

> Insert Figure 2 <

The use of a PEP flute is considered safe for even the weakest patient with lung disease[18]. The participants are instructed in using the flute with a pressure of approximately 10 cm H_2O. If a person blows with full power, they might reach a pressure of approximately 50 cmH_2O, whereas coughing generates a pressure in

the lungs of 80-120 cm H_2O[19]. The participants will be advised to stop the PEP flute session in case of any discomfort. Even among patients acutely ill with leukaemia and having neutropenia, no adverse events were detected related to PEP-usage[11]. Despite this, the participants in the intervention group are encouraged to inform the project manager in case of any adverse event during the trial via the designated hotline or by e-mail.

Participants are advised to continue use of PEP in the active intervention period of 30 days or at least for as long as they still have respiratory symptoms. They receive daily text-messages administered as an automated service by Twilio Inc. to prompt their reporting of CAT-scores by links to a questionnaire in REDCap. Also, they are asked to report their present choice of airway resistance as well as the number of PEP flute sessions the previous day. These daily self-reports constitute assessment of treatment adherence.

Standard of care

As selfcare in Covid-19, the Danish Health Authorities recommends a sufficient intake of liquid especially in case of high body temperature; potential use of paracetamol when having myalgia, headache and fever; and a throat lozenge in case of sore throat. Otherwise, the citizen with a positive SARS-CoV-2 test is requested to perform self-quarantine and to pay special attention to hygiene and cleaning maintenance. The participants in the usual care group also receive daily text-messages to prompt their reporting of CAT-scores by links to the electronic questionnaire.

To avoid attrition of the trial due to early recovery of symptoms, the project manager will contact the participants in both allocation groups by phone or text message approximately on day 15 to ask about their health condition and to answer to any potential concerns of continued participation in the trial.

Measurements

Data is collected both through questionnaires (primary outcome) and as register data (see Table 2). With consideration to the participants' possibly affection with sickness at inclusion point, the questionnaire at baseline is deliberately delimited. The participants are asked about educational/professional background as health care professionals have both higher incidence of Covid-19 and are presumably better qualified to conduct disease selfcare than lay persons. Health literacy will be measured by the two dimensions 'Understanding' and 'Engagement' (five items each) derived from the multi-dimensional Health Literacy Questionnaire (HLQ™) and validated in a Danish general population survey[20]. The 'Understanding' dimension covers 'understanding health information well enough to know what to do', whereas 'Engagement' covers 'the ability to actively engage with healthcare providers'[20]. In addition to abovementioned topics, the participants are asked one single item of self-rated health (on a five-point Likert scale) and a few questions about smoking and alcohol habits.

Primary outcome

The CAT-score is based on a validated questionnaire designed to evaluate symptoms in COPD patients[21]. The CAT-scale is free of use by curtesy of GlaxoSmithKline and is widely used in COPD-treatment both as a tele-monitoring tool and to stratify the patients into groups based upon the severity of symptoms. Even among the patients in the most unstable phase of COPD, daily self-report of CAT is considered quick and easy for patients to use[22]. The latter is important to ensure adequate data collection among the participants in the present trial. The eight items in the scale cover symptoms of cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms (modified for the present study from feeling safe at leaving home despite symptoms), sleep quality and vigour. The eight items sum up to a range of 0-40 with higher scores indicating more symptom impairment. Although validated for COPD-use, the CAT-scale is considered useful in the present study because several of the items (dyspnoea, cough, fatigue, sputum and pleuritic chest pain) previously have been used as outcome variables in pneumonia studies[23] and Covid-19 convalescents report long term breathlessness, chest pain and fatigue[24]. Based upon anecdotal evidence, a single course of Covid-19 revealed changes in CAT-score from CAT=5 prior to onset of symptoms to a peak of CAT=31 and a CAT=14 after a total of 40 days (personal communication).

Although the change in CAT-score from baseline to follow-up at day 30 is the primary outcome, the CAT-score as repeated daily measurements throughout the active intervention period of 30 days is supposed to contribute to a more thorough understanding of how the individual symptoms may intercorrelate and at what point a potential effect of the PEP-flute intervention may initiate and peak.

Secondary outcomes

The secondary outcomes are comparison between the intervention group and the usual care group of the number of hospital admissions and use of antibiotics during the follow-up period. Moreover, number of participants with serious adverse events (SAEs) during the 30-day intervention period will be evaluated. Finally, potential sub-group effects by sex, age, comorbidity and body mass index (BMI) at study entry will be explored for all outcomes as various conditions and comorbidities such as diabetes, hypertension and other chronic diseases have been pointed out as prognostic risk factors[5].

Statistical plan and data analysis

Both intention-to-treat and per-protocol analyses will be performed. The intention-to-treat population consists of all randomised participants irrespective of whether the participant received study intervention or whether the participant complied to the study protocol in the treatment group to which the participant was assigned at randomisation. The per-protocol population is defined as participants with a baseline measure of primary outcome and a follow-up measure of primary outcome at the primary assessment call (day 30). As regards the intervention group, participants fulfil the per-protocol criteria if they have complied to the PEP

flute-intervention for as long as respiratory symptoms are still reported in the CAT-score. These data are accessible through the daily self-reports. Participants in the usual care group fulfil the per-protocol criteria if they have no major protocol violations i.e. have not reported the use of a PEP-flute or treatment related to the respiratory system from a physiotherapist.

A statistical analysis plan that describes the details of the planned statistical analyses will be produced before last patient's last visit i.e. 30-day follow-up. Assessments of changes from baseline and construction of confidence intervals (CI) for continuous measures will be based on analysis of covariance (ANCOVA) including group as the main factor and baseline measure of outcome as covariate. Superiority will be claimed if the computed 95% CI of the estimated group difference in primary outcome does not include 0 in the ITT population. All statistical test will be two-sided and statistical significance will be claimed if the computed p-value is < 0.05.

Interactions between intervention status and baseline participant groupings i.e. sex and age will be prioritised as a priori subgroup analyses for the primary and secondary outcomes.

Determination of sample size according to the primary outcome i.e. the self-reported symptom CAT-score was based upon reported symptom scores in a previous study of community-acquired pneumonia[23]. On a 0-100 value scale (higher values indicate more symptoms), the mean symptom score at time of diagnosis was 51.7 (SD 20.1). We used these scores as reference. Hence, we assumed the mean CAT-score in the PEP-CoV-trial at baseline to be 20.0 (SD 10.0). A minimal clinical reported difference (MCID) of 2.0 on the CAT-scale has been reported from clinical studies of COPD rehabilitation[25]. Based on this MCID; the assumed mean CAT-score at baseline; a significance level of 5 % and a power of 0.8, we have estimated a need of including $n > 141$ in each group. With consideration to potential dropouts in a heterogenous sample, we assess that inclusion of 200 participants in each intervention arm will be an adequate number. A mitigation strategy has been developed to be executed in case of recruitment problems. An interim analysis showed that the mean CAT = 12.8 (SD 12.5) at baseline after recruiting 109 participants. No other interim analyses are planned. At present, the prevalence of hospital admission in Denmark is approximately 6 % and as such, we should expect 30 participants being hospitalised during the active intervention period of 30 days. However, we have not estimated sample size based upon hospital admission as outcome variable.

ETHICS AND DISSEMINATION

The use of PEP flute is considered a low risk intervention with no expected side effect. Since the interventions will be delivered in combination with standard treatment and we will be closely monitoring potential side effects, we anticipate no ethical issues. The intervention is considered justifiable in a health research ethics perspective. Ethical approval has been granted by the local Health Ethics Committee (Journal number: H-20035929). The Danish Data Protection Agency has approved conduct of the trial (Capital

Region: P-2020-879). An inquiry about the study has been directed to the Danish Medicines Agency, because the PEP flute is classified as a medical device. No approval from the Agency is needed since the flute is used for a purpose within the CE-classification (Agency reference number: 2020051572). It has not been a requirement to compose a data monitoring committee. The trial is exploratory with a design that needs to adapt according to how the pandemic develops and the governmental countermeasures e.g. as regards testing and restrictions. The trial is internally monitored, evaluated and adjusted accordingly.

Prior to screening, all potential trial participants are informed, both orally and in writing, about the purpose of this trial, its process and potential risks, as well as costs and benefits of participation. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing an e-consent form before trial participation can take place.

Protocol deviations and adverse events (AEs) are recorded by the data collectors (AM and ASB). The principal investigator and project manager (AM) monitor and do follow-up of possible AEs and serious adverse events (SAEs) throughout the study. These procedures are qualified by use of templates from the Danish GCP-units[26].

POTENTIAL OUTCOMES AND IMPACT

The PEP-CoV project is an innovative project niched between screening / prevention through vaccine and hospitalisation / critical illness treatment. This is an important area that, to the best of our knowledge, has received limited attention from both research and Health Authorities. Coronavirus will continue to be present for the next several years. Thus, many people will become infected by the virus and develop Covid-19 and as a worldwide response to the pandemic, we need to focus upon selfcare. The PEP-CoV trial aims to prevent serious lung disease and possibly shorten the course of the disease with the use of a simple, cheap and accessible intervention, a PEP flute.

It is difficult to estimate how many hospitalisations among the group of people having Covid-19 could have avoided by the individual's use of a PEP flute. However, a PEP flute including postal deliverance costs approximately 10 €; a regular hospital bed costs around 1000 € a day, whereas an ICU-bed usually costs 2.-5.000 € a day. The PEP flute-selfcare intervention is feasible and easy to use. If it proves to be effective, it will be easy to implement as a public health intervention. This may result in less sick leave and less strain for the individual and the family. Moreover, potentially less severe courses of Covid-19 will reduce the overall burden of the health care system and the society whereby we can ensure continued normal high activity in the health care system. Handling the PEP flute as a selfcare tool during quarantine in one's own home may contribute to a sense of mastery and coping to potentially impact the course of disease through selfcare. These latter perspectives may be explored subsequently in a qualitative study design.

According to the ethical approval, the trial is obliged to recruit by a single invitation letter only, sent to the individual's official e-Boks and then await a request for further contact from the eligible participant. Many people check their e-Boks only occasionally. Other eligible participants may feel too sick to overcome this task. Hence, a large sample of individuals tested positive for SARS-CoV-2 will be invited to the trial with only very few to ask for contact. This may challenge a non-selective recruitment although the inclusion criteria are fewer than in many other randomised controlled trials.

Although warranted, it is not possible to deliver a placebo PEP flute-intervention. Thus, blinding of the patients and treatment providers is not feasible. Because the Covid-19 is a novel disease, this study is explorative in relation to using self-reported measurements from COPD-treatment i.e. the CAT-score as the primary outcome variable. In the design process, it was considered to add objective measures like oxygen saturation, body temperature and/or infectious biomarkers as outcome variables. However, the quarantine restrictions made this choice not feasible and the subsequent implementation of potential positive findings in a public health context advocated for the opt-out of objective measures. However, this issue calls for attention in the later discussion of the results of the trial.

There is a risk of contamination across arms as participants can acquire the PEP flute as over-the-counter medical equipment. The participants are asked at follow-up, if they have used a PEP flute and/or have received any physiotherapeutic treatment. As data will be analysed both as regards intention-to-treat and per-protocol, this will be directed in the interpretation of the results.

Trial status

At submission of this manuscript, recruitment to the trial is ongoing with a total of 375 participants enrolled. The protocol was first prospectively registered www.ClinicalTrials.gov (NCT04530435) on August 27, 2020. No amendments have been made to the protocol (version 3.0 July 14, 2020) since recruitment of the first participant. Minor amendments have been made to the registration December 16, 2020, with clarification of outcome measurements (general and respiratory symptoms). Recruitment was started on October 6, 2020 and the first participant was enrolled on this date as well. Data of test-positive individuals are provided from the beforementioned four microbiological departments. Recruitment was initiated based upon data from only one of the departments in the Capital Region to ensure feasibility of the data management process. One by one the other departments were enrolled and since end of October, we have obtained data of all individuals with tests analysed by the regional microbiological departments of the two regions.

Authors' contributions

AM forwarded the idea and MKS gathered the project team. AM, MKS, SCL, MH, LMK, NW and BLH all contributed to the study conception and design. AM is the project manager. LMK steered the production of instruction videos. ASB steered the setup of data management system supervised by MH. AM and ASB both

handle recruitment, data collection, deliverance of intervention and assessment of all participants. AM handles the hotline and request of advice from participants including any adverse events. MH developed the allocation sequence. SCL manages data and statistical analysis. NW has the medical responsibility in conduct of the trial and BLH is project lead. AM drafted the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors will contribute to the subsequent publication of findings according to the guidelines set forth by the International Committee of Medical Journal Editors. No professional writers will part of the reporting and publication of the results from the PEP-CoV trial.

Competing interests

None of the authors declared any conflict of interest.

Acknowledgments

By sharing their experiences of disease course, the Covid-19 convalescents are both acknowledged for valuable contributions to the trial design.

Funding

This work was supported by Innovation Fund Denmark (grant number 0211-00023B) and a grant (unnumbered) from the Danish Nursing Council. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation. The funders have no role in the design, conduct, collection of data, analysis, writing, or reporting of the trial.

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LEGENDS

Figure 1: Relationship between population/setting and level of care/treatment options of SARS-CoV-2 and Covid-19. Upwards arrows indicate disease trajectory and higher level of care accordingly (to the left) and add-ons of treatment options (right side). Abbreviations: PEEP, positive end expiratory pressure; FiO2, inspired oxygen fraction; NIV, non-invasive ventilation; ECMO, extracorporeal membrane oxygenation; CPAP, continuous positive airway pressure

Figure 2: Still-photos from instruction videos about PEP flute usage and hygienic maintenance.
In details, 2a: how to use the PEP flute; 2b: how to assemble the three parts of the flute correctly; 2c: how to choose the suitable resistance, and 2d: how to perform hygienic maintenance of the PEP flute. Both videos including the shown subtitles in Danish are produced by the Department of Communication at Copenhagen University Hospital Hvidovre

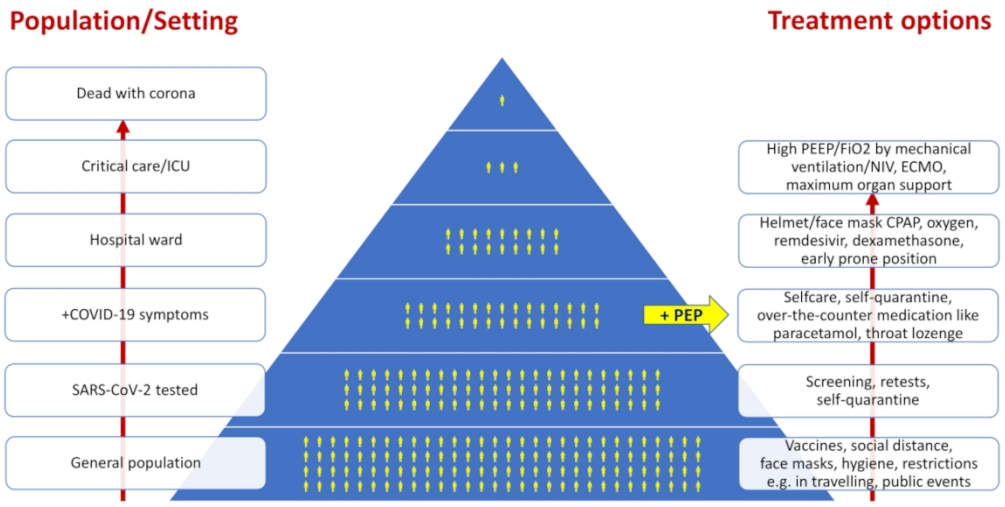

Figure 1: Relationship between population/setting and level of care/treatment options of SARS-CoV-2 and Covid-19. Upwards arrows indicate disease trajectory and higher level of care accordingly (to the left) and add-ons of treatment options (right side). Abbreviations: PEEP, positive end expiratory pressure; FiO_2, inspired oxygen fraction; NIV, non-invasive ventilation; ECMO, extracorporeal membrane oxygenation; CPAP, continuous positive airway pressure

190x107mm (300 x 300 DPI)

Figure 2: Still-photos from instruction videos about PEP flute usage and hygienic maintenance. In details, 2a: how to use the PEP flute; 2b: how to assemble the three parts of the flute correctly; 2c: how to choose the suitable resistance, and 2d: how to perform hygienic maintenance of the PEP flute. Both videos including the shown subtitles in Danish are produced by the Department of Communication at Copenhagen University Hospital Hvidovre

190x107mm (300 x 300 DPI)

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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

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

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 + 7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	7 + 15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 + 14-15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 + 7
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 ultimate authority over any of these activities	15

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

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)	13-15
Introduction			
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	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	6
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)	6-7

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Methods: Participants, interventions, and outcomes

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	6-7
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)	7-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
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)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	10

		monitoring adherence (eg, drug tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
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	7 + 10-12
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)	8
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	12

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8 + 13
Methods: Assignment of interventions (for controlled trials)			
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	9
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	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 + 15

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9 + 14
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	n/a: Open-label trial with no blinding
Methods: Data collection, management, and analysis			
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	10-12

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

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	10-12
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	9-12
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	11-12: A statistical analysis plan will be amended the protocol
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Will be described in the statistical analysis plan
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)	Will be described in the statistical analysis plan

Methods:

Monitoring

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	13
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	12
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	10-11 + 13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7 + 12: The trial is approved
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)	13-14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13: Ethical approval is needed in case of qualitative evaluation
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 + 12-13

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7 + 15
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	7 + 15: The trial is initiated and sponsored by the research institution
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	12-15: The trial has ethical approval and insurance via the research organisation
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	2 + 12-15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a: Documents in Danish and public access is not planned

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a: Documentation in Danish; not suitable for international publication
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	n/a: No specimens are collected

Notes:

- 17b: n/a: Open-label trial with no blinding
- 20a: 11-12: A statistical analysis plan will be amended the protocol
- 20b: Will be described in the statistical analysis plan
- 20c: Will be described in the statistical analysis plan
- 24: 7 + 12: The trial is approved
- 26b: 14: Ethical approval is needed in case of qualitative evaluation
- 29: 7 + 15: The trial is initiated and sponsored by the research institution
- 30: 12-15: The trial has ethical approval and insurance via the research organisation
- 31c: n/a: Documents in Danish and public access is not planned

- 32: n/a: Documentation in Danish; not suitable for international publication

- 33: n/a: No specimens are collected This checklist was completed on 17. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in early Covid-19

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050582.R1
Article Type:	Protocol
Date Submitted by the Author:	14-May-2021
Complete List of Authors:	Mollerup, Annette; Copenhagen University Hospital, The Parker Institute, Frederiksberg; University College Copenhagen, The Bachelor of Science in Nursing Programme, The Danish Deaconess Community Frederiksberg Larsen, Sofus; Copenhagen University Hospital, The Parker Institute, Frederiksberg Bennetzen, Anita; Copenhagen University Hospital, The Parker Institute, Frederiksberg Henriksen, Marius; Copenhagen University Hospital, The Parker Institute, Frederiksberg Simonsen, Mette; Copenhagen University Hospital, Department of Neuro-Medicine, Bispebjerg Weis, Nina; Copenhagen University Hospital, Department of Infectious Diseases, Hvidovre; University of Copenhagen, Department of Clinical Medicine, Faculty of Health and Medical Science Kofod, Linette; Copenhagen University Hospital, Department of Physio- and Occupational Therapy and PMR-C, Hvidovre Heitmann, Berit; Copenhagen University Hospital, The Parker Institute, Research Unit for Dietary Studies, Frederiksberg; University of Copenhagen, Section for General Practice, Department of Public Health
Primary Subject Heading:	Global health
Secondary Subject Heading:	Public health, Respiratory medicine, Infectious diseases
Keywords:	COVID-19, PREVENTIVE MEDICINE, PUBLIC HEALTH, RESPIRATORY MEDICINE (see Thoracic Medicine), Clinical trials < THERAPEUTICS, INFECTIOUS DISEASES

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The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in early Covid-19

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Word count: 4367

Keywords: SARS-CoV-2 infection, Covid-19, selfcare, public health, randomised controlled trial

ABSTRACT

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in early Covid-19

Introduction

Infection with severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2) may progress to severe pulmonary disease Covid-19. Currently, patients admitted to hospital because of Covid-19 have better prognosis than during the first period of the pandemic due to improved treatment. However, the overall societal susceptibility of being infected makes it pivotal to prevent severe courses of disease to avoid high mortality rates and collapse of the health care systems. Positive expiratory pressure (PEP) selfcare is used in chronic pulmonary disease and has been shown to prevent pneumonia in a high-risk cohort of leukaemia patients. The PEP-CoV trial examines the effectiveness on respiratory symptoms and need of hospital admission by regular PEP flute-use among non-hospitalised individuals with confirmed SARS-CoV-2 infection and Covid-19 symptoms.

Methods and analysis

In this randomised controlled trial, we hypothesise that daily PEP flute usage as add-on to usual care is superior to usual care as regards symptom severity measured by the COPD Assessment Test (CAT) at 30-day follow-up (primary outcome) and hospital admission through register data (secondary outcome). We expect to recruit 400 individuals for the trial. Participants in the intervention group receive a kit of 2 PEP flutes and adequate resistances and access to instruction videos. A telephone hotline offers possible contact to a nurse. The 8-item CAT-score measures cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms, sleep quality and vigour. The CAT-score is measured daily in both intervention and control arms by surveys prompted through text messages.

Ethics and dissemination

The study was registered prospectively at www.clinicaltrials.gov on August 27, 2020 (NCT04530435). Ethical approval was granted by the local Health Research Ethics Committee (Journal number: H-20035929) July 23, 2020. Enrolment of participants began October 6, 2020. Results will be published in scientific journals.

Keywords

SARS-CoV-2 infection, Covid-19, selfcare, public health, randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study

- Using a randomised design, this study addresses an important evidence gap in the SARS-CoV-2 pandemic; how to mobilise the individual's selfcare to prevent respiratory deterioration in Covid-19 with the use of a simple, cheap and accessible intervention, thus potentially avoid hospitalisation.
- This study is a niche project between a public health intervention and disease prevention in a clinical setting which may challenge a warranted non-selective recruitment as recruitment awaits the initiative from eligible participants.
- Due to the type of intervention, blinding of the participants and treatment providers is not feasible.
- Covid-19 is a novel disease and this study is explorative when using self-reported measurements from COPD-treatment i.e. the CAT-score as an outcome variable. In the absence of objectively measured values like oxygen saturation or body temperature as outcome variables, this calls for attention when discussing the results of the trial.
- There is a risk of contamination across arms as participants can acquire the PEP flute as over-the-counter medical equipment.

INTRODUCTION

The pandemic infection with severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2) may result in non-specific symptoms like fever, fatigue and dyspnoea or it may progress to severe pulmonary disease Corona Virus Disease 2019 (Covid-19). Mid-January 2021 as reported by WHO, the worldwide number of people dying because of Covid-19 exceeded two million. Over time, we learn more about this new disease e.g. reports of a median time from symptom onset to development of pneumonia of approximately 5 days.[1] Covid-19 seems to damage the respiratory system due to an overreaction of the immune system with individual risk profiles of age and comorbidity.[2] This may lead to acute respiratory distress syndrome (ARDS) and in these cases, the median time from symptom onset to severe hypoxemia and intensive care unit (ICU) admission has been reported to be approximately 7-12 days.[1] At a median follow-up period of 79 days among ICU-patients, mortality was reported to be 37 % in a Danish nationwide study. Hence, the Covid-19 disease burdens the health care systems even in countries without any restrictions as to ICU-admission in times of a pandemic.[3]

At present, the disease trajectory is not easy to predict,[1] and little is known of any measures or medication to alter the course of early-stage disease i.e. to prevent the need of hospitalisation and critical care. The PEP-CoV trial will investigate the effect of PEP flute-selfcare on respiratory deterioration and hospital admission among non-hospitalised individuals with Covid-19 symptoms. If PEP flute-selfcare proves to be effective, it will be easy to implement as a public health intervention also in a global context. In the trial, participants have confirmed SARS-CoV-2 infection by positive PCR swab test and Covid-19 symptoms at study entry hence, although no medical examination has been conducted, they are considered to be Covid-19 cases according to WHO Covid-19 case definitions.[4]

Background and rationale

Recent evidence suggests a poor prognosis whenever the Covid-19 disease has become so severe that hospital admission is needed. A large observational cohort study from UK found that within a minimal follow-up time of two weeks 26 % of patients admitted to acute care hospitals had died.[5] Among patients in need of critical care facilities and/or receiving mechanical ventilation, the proportion of fatal outcome was 32 % and 37 % respectively. In the pandemic waves, health care systems face an imminent threat of collapse because of an overload of Covid-19 cases. The prognosis of having a severe course of disease due to Covid-19 is better now than in the first period of the pandemic because of improvements in treatment. Antiviral treatment with remdesivir and dexamethasone appears to have moderate effects. [6, 7] However, both treatments are administered only in cases when the patient is hospitalised and in need of oxygen. In the overall population, all are at risk of being infected and this overall societal susceptibility makes prevention of severe courses of disease pivotal to the health care system.

A variety of symptoms have been observed in patients with Covid-19. The study by Docherty et al. refers to clusters of symptoms on admission i.e. musculoskeletal symptoms (myalgia, joint pain, headache, and fatigue); enteric symptoms (abdominal pain, vomiting, and diarrhoea); and a mucocutaneous cluster.[5] However, the most common symptom cluster involves respiratory symptoms i.e. cough, sputum and shortness of breath, accompanied by fever. When critically ill, the intensive care treatment includes mechanical ventilation with high oxygenation and positive end expiratory pressure (PEEP). PEEP increases functional residual capacity (FRC) and reduces the work of breathing. The use of positive expiratory pressure (PEP) has been highlighted as very important measures to avoid a critical course administered as continuous positive airway pressure (CPAP) by face masks or by use of a helmet.[8, 9] However, this treatment is for hospitalised patients. PEP is used as selfcare in chronic inflammatory pulmonary diseases like chronic obstructive pulmonary disease (COPD) despite the lack of robust evidence. In an RCT, PEP therapy as add-on to usual medical care had only minor effects among inpatients with acute exacerbation of COPD. The intervention led to more rapidly improved dyspnoea following discharge but had no impact on subsequent exacerbations and hospitalisations.[10] Little is known of the potential effects of PEP as selfcare in pneumonia prevention. Among patients with leukaemia, PEP alongside daily spirometry was superior to daily spirometry to prevent pneumonia (first pneumonia incidence per 1000 days 2.17 versus 6.52, $p = 0.021$, intervention group and control group respectively).[11] The mechanically supported inflation of the alveoli and loosening of secretions by PEP presumably prevented manifest lung infiltrates without any adverse events.[11] Among several effects, use of PEP can increase FRC and tidal volume, decrease hyperinflation and improve airway clearance.[12] Moreover, in both healthy subjects and patients undergoing surgery, increased gas exchange and decreased atelectasis have been reported after PEP usage.[12] Analogously, PEP may have beneficial effects on the progression of symptoms in the Covid-19 trajectory. Airway Clearance Techniques (ACT) appear to be safe and the PEP flute has shown as effective as other ACTs.[13]

Most current research on SARS-CoV-2 and Covid-19 relates to screening measures, vaccine development and optimising hospital treatment i.e. the bottom and top ends of a pyramid which depicts the relationship between populational size, setting and treatment options (Fig. 1). It is likely that we have this pandemic for several years until we have reached a high level of immunity in the population either by natural spread of the disease or via an efficient vaccination programme and measures are needed to help the SARS-CoV-2 infected individual at home to overcome the course of disease with less symptoms and strain. Based on the hypothesis that the regular use of a PEP flute may prevent the progression of respiratory symptoms in non-hospitalised individuals with SARS-CoV-2 infection, a PEP flute intervention, feasible for home use, may prevent prolonged disease courses, long-term sequelae and costly hospital admissions.

> Insert Figure 1 <

Study objectives and hypotheses

The aim of the present study is to explore the effectiveness on respiratory symptoms by regular use of PEP among SARS-CoV-2 infected, non-hospitalised individuals with Covid-19 symptoms. The primary objective is to examine the effect of PEP flute use on self-reported symptoms during 30 days of follow-up. We hypothesise that PEP flute use has positive effects on self-reported respiratory symptoms such as dyspnoea, coughing and perceived mucus clearance through beneficial effects on lung function and airway clearance. Secondly, we expect a lower rate of hospitalisation and use of antibiotics in the intervention group as compared to the usual care group, the latter in case of a bacterial superinfection.

METHODS

Trial design and setting

The PEP-CoV trial is designed as a randomised, controlled, open-label trial with two parallel groups and consecutive inclusion. The trial is investigator-initiated and hosted by the Parker Institute, a part of Copenhagen University Hospital Bispebjerg-Frederiksberg. The participants are recruited from the Capital Region and Region Zealand in Denmark (in total, approximately 2.7 million citizens). The trial registration data set is displayed in Table 1.

Patient and Public Involvement

Ideation of the trial intervention was based upon anecdotal evidence of a PEP flute's beneficial effects in a single case of Covid-19. Personal communication with Covid-19 convalescents has contributed to the designing process of the study. However, due to the ongoing pandemic crisis further patient and public involvement in the research process has not been feasible.

Table 1

Table 1 WHO trial registration data set	
Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov NCT04530435
Date of registration in primary registry	27 august, 2020
Secondary identifying numbers	Danish Data Protection Agency (P-2020-879) Health Research Ethics (H-20035929)
Sources of monetary or material support	The Danish Innovation Fund (0211-00023B) and the Danish Nursing Council (grant number: n/a)
Sponsor	The Parker Institute, Copenhagen, Denmark
Contact for public queries	Annette Mollerup, PhD (annette.mollerup@regionh.dk) The Parker Institute Copenhagen University Hospital Bispebjerg-Frederiksberg Ndr. Fasanvej 57, 2000 Frederiksberg, Denmark +45 38163102
Contact for scientific queries	Annette Mollerup, PhD (annette.mollerup@regionh.dk)
Public title	Covid-19: symptoms and respiratory selfcare [in Danish: COVID-19 sygdom: symptomer og vejrtrækningsøvelser]
Scientific title	PEP flute-selfcare to prevent respiratory deterioration and hospitalisation among Covid-19 patients: a randomised trial (acronym: The PEP-CoV trial)
Countries of recruitment	Denmark
Health condition(s)	Adults aged 18 or older with a positive SARS-CoV-2 test and symptoms of COVID-19
Intervention	Active comparator: daily use of PEP flute and daily self-monitoring of symptoms for 30 days as add-on to usual care Comparator: daily self-monitoring of symptoms and usual care including selfcare recommended by the Danish Health Authorities (self-quarantine, sufficient intake of liquid especially in case of high body temperature, over-the-counter symptom relieving medication)
Key inclusion and exclusion criteria	Inclusion criteria: 1. Aged 18 years or older 2. Positive SARS-CoV-test 3. Symptoms of Covid-19 according to the COVIDmeter; at least one respiratory symptom (cough, sneezing, shortness of breath, chest pain, running nose) and one general symptom 4. Access to use a smartphone 5. Can reply to a questionnaire in Danish (sent on email, text-message or via telephone interview) as assessed by the investigator 6. Given informed consent Exclusion criteria: 1. Any condition or impairment that, in the opinion of the investigator, makes a potential participant unsuitable for participation or which obstruct participation, such as psychiatric disorders, individuals, habitually using a PEP flute, participation in other clinical Covid-trials or persons living in the same household as existing participants in the trial 2. Hospitalized patients or nursing home residents
Study type	Interventional, open-label trial with randomisation to two parallel groups Primary purpose: prevention of respiratory deterioration of symptoms and hospitalisation
Data of first enrollment	October 2020
Target sample size	400
Recruitment status	Recruiting
Primary outcome	Day 30 COPD Assessment Test score (CAT-score) (modified for the present study)
Key secondary outcomes	1. Hospital admissions on Day 30, Day 90 and Day 180 2. Use of antibiotics in case of superinfection 3. Covid-19 symptoms Day 30, Day 90 and Day 180 4. CAT-score Day 90 and Day 180 5. Number of participants with serious adverse events (SAE) during the 30-day intervention period 6. Compliance assessment

PEP, positive expiratory pressure; COVID-meter, the Danish Health Authority surveillance of symptoms reported by the public to a designated website; CAT, COPD Assessment Tool consisting of eight items on a scale from 0-5: cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms (because of actual self-quarantine, modified for the present study from feeling safe at leaving home despite symptoms), sleep quality and vigour

The study duration is six months and the primary endpoint is CAT-score after 30 days of active intervention. Follow-ups of CAT-scores are also planned at 90- and 180-days post-baseline. The study's enrolment, intervention and assessments schedules according to SPIRIT Guidelines are outlined in Table 2.[14]

Table 2

Table 2 Schedule for study enrolment, intervention and assessments					
Activity/assessment	**Recruitment**	**Enrolment**	**Follow-up$_{30days}$**	**Follow-up$_{90days}$**	**Follow-up$_{180days}$**
Time point	**T_{-1}**	**T_0**	**T_1**	**T_2**	**T_3**
Pre-screening (positive PCR-test)	x				
Information to e-Boks	x				
Informed e-consent		x			
Eligibility screening		x			
Baseline questionnaire		x			
Randomisation/group allocation		x			
Video guides		x			
PEP flute deliverance		x (+3 days)			
Self-report of symptoms (CAT)		x (+1 day) ---------- x (day 30)			
Intervention group: PEP-usage		x (+1 day) ---------- x (day 30)			
Compliance assessment		x (+1 day) ---------- x (day 30)			
Outcome assessment			x	x	x
Baseline/outcome variables*					
Age, sex (register data)	x				
Symptoms within last week		x	x	x	x
Cohabitation		x			
Education		x			
Health literacy (two dimensions)		x			
Profession, employment		x			
Self-rated health (one item)		x	x	x	x
Weight, height		x			
Smoking, alcohol		x			
Comorbidity self-reported		x			
Comorbidity (register data)			x		
CAT-score		x	x	x	x
Hospital admission (register data)			x		x
Medication (register data)			x		x
Death (register data)			x		x
Serious adverse event		As needed throughout protocol			

*All baseline and outcome variables are collected as questionnaire data unless stated otherwise

Trial population and eligibility criteria

To avoid unnecessary spread of the SARS-CoV-2, any contact i.e. oral information, consent and screening is provided over phone and by use of secured electronic communication via the public 'Digital Post' system (electronic mailbox for letters from Danish authorities) administered by the platform 'e-Boks' (https://www.e-boks.com/danmark/en). This system is linked to the individual's Personal Identification number – a national identification number, which is part of the personal information stored in the Danish Civil Registration System. Daily information of positive results from the SARS-CoV-2 PCR-tests are provided from the Departments of Microbiology at Copenhagen University Hospitals Rigshospitalet, Hvidovre Hospital and Herlev Hospital, which covers the overall Capital Region, and the Department of Microbiology, Slagelse Hospital, covering the entire Region Zealand. Based upon these data, individuals eligible for study participation receive study information and invitation electronically via e-Boks. The individual may then contact the project directly via e-mail or phone or leave a phone number for a subsequent call from the data collectors (AM and ASB).

The inclusion/exclusion criteria for the trial are described in Table 1. The exclusion criteria are deliberately few to reflect the target population and promote a highly scalable Public Health implementation given a successful intervention. Various symptoms have been associated to Covid-19[5,15] and early Danish reports indicated that the most frequent self-reported respiratory symptoms in Covid-19 (n = 308) were cough (71%) and shortness of breath (54 %).[16] However, recent findings have suggested that approximately three quarters of people with SARS-CoV-2 infection are asymptomatic on the day of the test.[17] As the rationale for the potential effect of a PEP flute in a course of SARS-CoV-2 infection and Covid-19 involves the progression of respiratory symptoms, at least one reported respiratory symptom is required at enrolment. A screening manual has been developed and questions of symptoms according to the COVIDmeter[18] are posed after given consent (Table 2).

Randomisation and blinding

The participants reply to a telephone-administered baseline questionnaire before randomisation. Subsequently, the participant is randomly allocated to treatment or control arm using an appropriate statistical software embedded in REDCap, an online web-based clinical trial management application (Vanderbilt University, Nashville, TN, USA).[19] The computer-generated random allocation is then unknown to the investigator and data collectors. As mortality prognosis to Covid-19 is higher in men and elderly,[5] the allocation is based upon permuted random blocks and 1:1 stratified for the conditions sex and age (< 60 and ≥ 60 years). Sex is determined through the unique Danish personal identification number as a binary variable.

As this is an 'open-label' trial neither the health professionals delivering the interventions, nor the participants are blinded to treatment allocation. Statistical analyses will be conducted blinded to the intervention group.

Trial intervention

The trial intervention is the regular use of a PEP flute in combination with usual care. A set of two PEP flutes and three airway resistances (equivalent to a resistance of 10-20 cm H_2O) are delivered to the participants who are advised to use the PEP flute at least three times daily. Ideally, each session consists of 10-15 breaths (for approximately 1 minute) repeated twice with the participant sitting at an upright position. Two video guides (Fig. 2) are sent to the participant by e-Boks; one with instructions as to the rationale and how to use the PEP flute including how to choose the suitable resistance; the other with instruction of hygienic maintenance, advised to be daily because of a manifest SARS-CoV-2 infection.

> Insert Figure 2 <

The use of a PEP flute is considered safe for even the weakest patient with lung disease.[20] The participants are instructed in using the flute with a pressure of approximately 10 cm H_2O. If a person blows with full power, they might reach a pressure of approximately 50 cmH_2O, whereas coughing generates a pressure in the lungs of 80-120 cm H_2O.[21] The participants will be advised to stop the PEP flute session in case of any discomfort. Even among patients acutely ill with leukaemia and having neutropenia, no adverse events were detected related to PEP-usage.[11] Despite this, the participants in the intervention group are encouraged to inform the project manager in case of any adverse event during the trial via the designated hotline or by e-mail.

Participants are advised to continue use of PEP in the active intervention period of 30 days or at least for as long as they still have respiratory symptoms. They receive daily text-messages administered as an automated service by Twilio Inc. to prompt their reporting of CAT-scores by links to a questionnaire in REDCap. Also, they are asked to report their present choice of airway resistance as well as the number of PEP flute sessions the previous day. These daily self-reports constitute assessment of treatment adherence.

Usual care

As selfcare in Covid-19, the Danish Health Authorities recommend sufficient intake of liquid especially in case of high body temperature; potential use of paracetamol when having myalgia, headache and fever; and a throat lozenge in case of sore throat. Otherwise, the citizen with a positive SARS-CoV-2 test is requested to perform self-quarantine and to pay special attention to hygiene and cleaning maintenance. The participants in the usual care group also receive daily text-messages to prompt their reporting of CAT-scores by links to the electronic questionnaire.

To avoid attrition of the trial due to early recovery of symptoms, the project manager will contact the participants in both allocation groups by phone or text message approximately on day 15 to ask about their health condition and to answer to any potential concerns of continued participation in the trial. As part of the trial information, the participants in both groups are advised to contact their general practitioner, the Covid-19-specific clinics or the emergency medical services, if needed, as they would otherwise do if not participating in the trial.

Measurements

Data is collected both through questionnaires (primary outcome) and as register data (see Table 2). With consideration to the participants' possibly affection with sickness at inclusion point, the questionnaire at baseline is deliberately delimited. The participants are asked about educational/professional background as health care professionals have both higher incidence of Covid-19 and are presumably better qualified to conduct disease selfcare than lay persons. Health literacy will be measured by the two dimensions 'Understanding' and 'Engagement' (five items each) derived from the multi-dimensional Health Literacy

Questionnaire (HLQ™) and validated in a Danish general population survey.[22] The 'Understanding' dimension covers 'understanding health information well enough to know what to do', whereas 'Engagement' covers 'the ability to actively engage with healthcare providers'.[22] In addition to abovementioned topics, the participants are asked one single item of self-rated health (on a five-point Likert scale) and a few questions about smoking and alcohol habits.

Primary outcome

In the design phase of the trial, a valid Covid-19 symptom severity scale for outpatients was lacking and emphasis was on the feasibility of the individual self-reporting symptoms while being sick with Covid-19. The COPD Assessment Test (CAT) is a validated questionnaire designed to evaluate symptoms in COPD patients.[23] The CAT is free of use by curtesy of GlaxoSmithKline and is widely used both as a tele-monitoring tool and to stratify the patients into groups based upon the severity of symptoms. Even among the patients in the most unstable phase of COPD, daily self-report of CAT is considered quick and easy for patients to use.[24] The latter is important to ensure adequate data collection among the participants in the present trial. The eight items in the scale cover symptoms of cough, sputum, chest pain, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms (modified for the present study from feeling safe at leaving home despite symptoms), sleep quality and vigour. The eight items sum up to a range of 0-40 with higher scores indicating more symptom impairment. Although not validated for Covid-19 trials, the CAT-scale is considered useful in the present study because several of the items (dyspnoea, cough, fatigue, sputum and pleuritic chest pain) previously have been used as outcome variables in pneumonia studies[25] and Covid-19 convalescents report long term breathlessness, chest pain and fatigue.[26] Based upon anecdotal evidence, a single course of Covid-19 revealed changes in CAT-score from CAT=5 prior to onset of symptoms to a peak of CAT=31 and a CAT=14 after a total of 40 days (personal communication).

Although the change in CAT-score from baseline to follow-up at day 30 is the primary outcome, the CAT-score as repeated daily measurements throughout the active intervention period of 30 days is supposed to contribute to a more thorough understanding of how the individual symptoms may intercorrelate and at what point a potential effect of the PEP-flute intervention may initiate and peak.

Secondary outcomes

The secondary outcomes are comparison between the intervention group and the usual care group of the number of hospital admissions and use of antibiotics during the follow-up period. Presence of Covid-symptoms day 30/90/180 and the CAT at day 90/180 will be assessed. Moreover, number of participants with serious adverse events (SAEs) during the 30-day intervention period will be evaluated. Finally, potential sub-group effects by sex, age, comorbidity and body mass index (BMI) at study entry will be explored for all outcomes as various conditions and comorbidities such as diabetes, hypertension and other

chronic diseases have been pointed out as prognostic risk factors.[5] Register data of diagnosed comorbidity will also be valuable in the interpretation of symptoms like dyspnoea and chest tightness which may be overlaps between an underlying disease like heart failure and the present course of Covid-19.

Statistical plan and data analysis

Both intention-to-treat and per-protocol analyses will be performed. The intention-to-treat population consists of all randomised participants irrespective of whether the participant received study intervention or whether the participant complied to the study protocol in the treatment group to which the participant was assigned at randomisation. The per-protocol population is defined as participants with a baseline measure of primary outcome and a follow-up measure of primary outcome at the primary assessment call (day 30). As regards the intervention group, participants fulfil the per-protocol criteria if they have complied to the PEP flute-intervention for as long as respiratory symptoms are still reported in the CAT-score. These data are accessible through the daily self-reports. Participants in the usual care group fulfil the per-protocol criteria if they have no major protocol violations i.e. have not reported the use of a PEP-flute or treatment related to the respiratory system from a physiotherapist.

A statistical analysis plan that describes the details of the planned statistical analyses will be produced before last patient's last visit i.e. 30-day follow-up. Assessments of changes from baseline and construction of confidence intervals (CI) for continuous measures will be based on analysis of covariance (ANCOVA) including group as the main factor and baseline measure of outcome as covariate. Superiority will be claimed if the computed 95% CI of the estimated group difference in primary outcome does not include 0 in the ITT population. All statistical test will be two-sided and statistical significance will be claimed if the computed p-value is < 0.05.

Interactions between intervention status and baseline participant groupings i.e. sex and age will be prioritised as a priori subgroup analyses for the primary and secondary outcomes.

Determination of sample size according to the primary outcome i.e. the self-reported symptom CAT-score was based upon reported symptom scores in a previous study of community-acquired pneumonia.[25] On a 0-100 value scale (higher values indicate more symptoms), the mean symptom score at time of diagnosis was 51.7 (SD 20.1). We used these scores as reference. Hence, we assumed the mean CAT-score in the PEP-CoV-trial at baseline to be 20.0 (SD 10.0). A minimal clinical reported difference (MCID) of 2.0 on the CAT-scale has been reported from clinical studies of COPD rehabilitation.[27] Based on this MCID; the assumed mean CAT-score at baseline; a significance level of 5 % and a power of 0.8, we have estimated a need of including $n > 141$ in each group. With consideration to potential dropouts in a heterogenous sample, we assess that inclusion of 200 participants in each intervention arm will be an adequate number. A mitigation strategy has been developed to be executed in case of recruitment problems. An interim analysis

showed that the mean CAT = 12.8 (SD 12.5) at baseline after recruiting 109 participants. No other interim analyses are planned. At present, the prevalence of hospital admission in Denmark is approximately 6 % and as such, we should expect 30 participants being hospitalised during the active intervention period of 30 days. However, we have not estimated sample size based upon hospital admission as outcome variable.

ETHICS AND DISSEMINATION

The use of PEP flute is considered a low risk intervention with no expected side effect. Since the interventions will be delivered in combination with standard treatment and we will be closely monitoring potential side effects, we anticipate no ethical issues. The intervention is considered justifiable in a health research ethics perspective. Ethical approval has been granted by the local Health Ethics Committee (Journal number: H-20035929). The Danish Data Protection Agency has approved conduct of the trial (Capital Region: P-2020-879). An inquiry about the study has been directed to the Danish Medicines Agency, because the PEP flute is classified as a medical device. No approval from the Agency is needed since the flute is used for a purpose within the CE-classification (Agency reference number: 2020051572). It has not been a requirement to compose a data monitoring committee. The trial is exploratory with a design that needs to adapt according to how the pandemic develops and the governmental countermeasures e.g. as regards testing and restrictions. The trial is internally monitored, evaluated and adjusted accordingly.

Prior to screening, all potential trial participants are informed, both orally and in writing, about the purpose of this trial, its process and potential risks, as well as costs and benefits of participation. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing an e-consent form before trial participation can take place.

Protocol deviations and adverse events (AEs) are recorded by the data collectors (AM and ASB). The principal investigator and project manager (AM) monitor and do follow-up of possible AEs and serious adverse events (SAEs) throughout the study. These procedures are qualified by use of templates from the Danish GCP-units.[28]

POTENTIAL OUTCOMES AND IMPACT

The PEP-CoV project is an innovative project niched between screening / prevention through vaccine and hospitalisation / critical illness treatment. This is an important area that, to the best of our knowledge, has received limited attention from both research and Health Authorities. Coronavirus will continue to be present for the next several years. Thus, many people will become infected by the virus and develop Covid-19 and as a worldwide response to the pandemic, we need to focus upon selfcare. The PEP-CoV trial aims to prevent serious lung disease and possibly shorten the course of the disease with the use of a simple, cheap and accessible intervention, a PEP flute.

It is difficult to estimate how many hospitalisations among the group of people having Covid-19 could have avoided by the individual's use of a PEP flute. However, a PEP flute including postal deliverance costs approximately 10 €; a regular hospital bed costs around 1000 € a day, whereas an ICU-bed usually costs 2.-5.000 € a day. The PEP flute-selfcare intervention is feasible and easy to use. If it proves to be effective, it will be easy to implement as a public health intervention. This may result in less sick leave and less strain for the individual and the family. Moreover, potentially less severe courses of Covid-19 will reduce the overall burden of the health care system and the society whereby we can ensure continued normal high activity in the health care system. Handling the PEP flute as a selfcare tool during quarantine in one's own home may contribute to a sense of mastery and coping to potentially impact the course of disease through selfcare. These latter perspectives may be explored subsequently in a qualitative study design.

According to the ethical approval, the trial is obliged to recruit by a single invitation letter only, sent to the individual's official e-Boks and then await a request for further contact from the eligible participant. Many people check their e-Boks only occasionally. Other eligible participants may feel too sick to overcome this task. Hence, a large sample of individuals tested positive for SARS-CoV-2 will be invited to the trial with only very few to ask for contact. This may challenge a non-selective recruitment although the inclusion criteria are fewer than in many other randomised controlled trials.

Although warranted, it is not possible to deliver a placebo PEP flute-intervention. Thus, blinding of the patients and treatment providers is not feasible. Because the Covid-19 is a novel disease, this study is explorative in relation to using self-reported measurements from COPD-treatment i.e. the CAT-score as the primary outcome variable. In the design process, it was considered to add objective measures like oxygen saturation, body temperature and/or infectious biomarkers as outcome variables. However, the quarantine restrictions made this choice not feasible and the subsequent implementation of potential positive findings in a public health context advocated for the opt-out of objective measures. However, these issues of both the CAT as outcome measure and the lack of objective measures call for attention in the later discussion of the results of the trial.

There is a risk of contamination across arms as participants can acquire the PEP flute as over-the-counter medical equipment. The participants are asked at follow-up, if they have used a PEP flute and/or have received any physiotherapeutic treatment. As data will be analysed both as regards intention-to-treat and per-protocol, this will be directed in the interpretation of the results.

Trial status

At submission of this manuscript, recruitment to the trial is ongoing with a total of 375 participants enrolled. The protocol was first prospectively registered www.ClinicalTrials.gov (NCT04530435) on August 27, 2020. No amendments have been made to the protocol (version 3.0 July 14, 2020) since recruitment of the first participant. Minor amendments have been made to the registration December 16, 2020, with

clarification of outcome measurements (general and respiratory symptoms). Recruitment was started on October 6, 2020 and the first participant was enrolled on this date as well. Data of test-positive individuals are provided from the beforementioned four microbiological departments. Recruitment was initiated based upon data from only one of the departments in the Capital Region to ensure feasibility of the data management process. One by one the other departments were enrolled and since end of October, we have obtained data of all individuals with tests analysed by the regional microbiological departments of the two regions.

Authors' contributions

AM forwarded the idea and MKS gathered the project team. AM, MKS, SCL, MH, LMK, NW and BLH all contributed to the study conception and design. AM is the project manager. LMK steered the production of instruction videos. ASB steered the setup of data management system supervised by MH. AM and ASB both handle recruitment, data collection, deliverance of intervention and assessment of all participants. AM handles the hotline and request of advice from participants including any adverse events. MH developed the allocation sequence. SCL manages data and statistical analysis. NW has the medical responsibility in conduct of the trial and BLH is project lead. AM drafted the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors will contribute to the subsequent publication of findings according to the guidelines set forth by the International Committee of Medical Journal Editors. No professional writers will be part of the reporting and publication of the results from the PEP-CoV trial.

Competing interests

None of the authors declared any conflict of interest.

Acknowledgments

By sharing their experiences of disease course, the Covid-19 convalescents are both acknowledged for valuable contributions to the trial design.

Funding

This work was supported by Innovation Fund Denmark (grant number 0211-00023B) and a grant (unnumbered) from the Danish Nursing Council. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation. The funders have no role in the design, conduct, collection of data, analysis, writing, or reporting of the trial.

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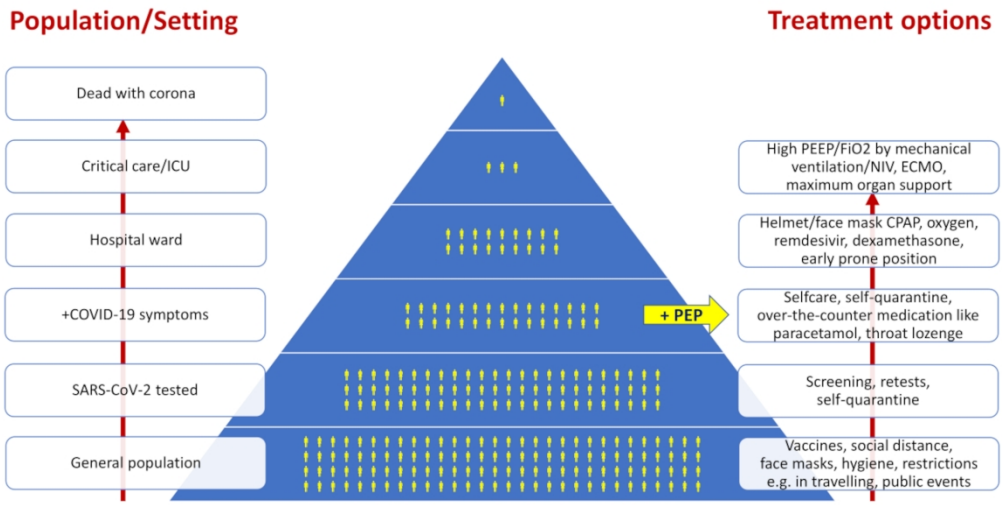
LEGENDS

Figure 1: Relationship between population/setting and level of care/treatment options of SARS-CoV-2 and Covid-19. Upwards arrows indicate disease trajectory and higher level of care accordingly (to the left) and add-ons of treatment options (right side). Abbreviations: PEEP, positive end expiratory pressure; FiO2, inspired oxygen fraction; NIV, non-invasive ventilation; ECMO, extracorporeal membrane oxygenation; CPAP, continuous positive airway pressure

Figure 2: Still-photos from instruction videos about PEP flute usage and hygienic maintenance.
In details, 2a: how to use the PEP flute; 2b: how to assemble the three parts of the flute correctly; 2c: how to choose the suitable resistance, and 2d: how to perform hygienic maintenance of the PEP flute. Both videos including the shown subtitles in Danish are produced by the Department of Communication at Copenhagen University Hospital Hvidovre



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190x107mm (300 x 300 DPI)

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The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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

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

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 + 7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	7 + 15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 + 14-15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 + 7
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 ultimate authority over any of these activities	15

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

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)	13-15
Introduction			
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	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	6
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)	6-7

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Methods: Participants, interventions, and outcomes			
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	6-7
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)	7-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
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)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	10

		monitoring adherence (eg, drug tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
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	7 + 10-12
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)	8
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	12

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8 + 13
Methods:			
Assignment of interventions (for controlled trials)			
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	9
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	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 + 15

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9 + 14
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	n/a: Open-label trial with no blinding
Methods: Data collection, management, and analysis			
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	10-12

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

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	10-12
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	9-12
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	11-12: A statistical analysis plan will be amended the protocol
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Will be described in the statistical analysis plan
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)	Will be described in the statistical analysis plan

Methods:

Monitoring

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	13
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	12
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	10-11 + 13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7 + 12: The trial is approved
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)	13-14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13: Ethical approval is needed in case of qualitative evaluation
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 + 12-13

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7 + 15
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	7 + 15: The trial is initiated and sponsored by the research institution
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	12-15: The trial has ethical approval and insurance via the research organisation
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	2 + 12-15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a: Documents in Danish and public access is not planned

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Documentation in Danish; supplementary file
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	n/a: No specimens are collected

Notes:

- 17b: n/a: Open-label trial with no blinding
- 20a: 11-12: A statistical analysis plan will be amended the protocol
- 20b: Will be described in the statistical analysis plan
- 20c: Will be described in the statistical analysis plan
- 24: 7 + 12: The trial is approved
- 26b: 14: Ethical approval is needed in case of qualitative evaluation
- 29: 7 + 15: The trial is initiated and sponsored by the research institution
- 30: 12-15: The trial has ethical approval and insurance via the research organisation
- 31c: n/a: Documents in Danish and public access is not planned
- 32: n/a: Documentation in Danish; not suitable for international publication

The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in SARS-CoV-2 infected individuals with Covid-19 symptoms

- 33: n/a: No specimens are collected The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 17. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai