PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The PEP-CoV protocol: a PEP flute-selfcare randomised controlled trial to prevent respiratory deterioration and hospitalisation in early Covid-19
AUTHORS	Mollerup, Annette; Larsen, Sofus; Bennetzen, Anita; Henriksen, Marius; Simonsen, Mette; Weis, Nina; Kofod, Linette; Heitmann, Berit

VERSION 1 – REVIEW

REVIEWER	Fan, Xiaoyun First Affiliated Hospital of Anhui Medical University
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	This is an interesting study adding relevant intervention means about preventing respiratory deterioration in Covid-19 with the use of PEP flute. Unfortunately, there are some important concerns that should be addressed before: 1. Page 5 of the text (line 23-39), The benefit evidence used by PEP is insufficient, so we can supplement some of the related studies on PEP and lung diseases, so that the function of PEP may be more convincing; in addition, there is no need to elaborate too much on the specific contents of the relevant studies. 2. Page 6 of the text (line 8-11) CAT is used to evaluate COPD, the author is now used to evaluate COVID-19 may not be very rigorous, COVID-19 's patients may not be sensitive to CAT, although the author mentioned the previous study in Page 11 of the text (line 19-24), but the evidence is insufficient and the data is too old. 3. Page 7 of the text (line 33-35) There is no detailed explanation in the exclusion criteria to exclude COVID-19 patients with other underlying diseases, including heart failure or asthma, which can cause symptoms such as dyspnea, chest tightness, etc. 4. Whether the standard treatment mentioned on page 12 is the same as the standard care mentioned on page 9, or whether the Danish health authorities recommend standard treatment or standard care. In addition, it is hoped that the author can make the each section concise and to the point, and it is better to list the data in the form of graphs or tables.

REVIEWER	Xie, Min Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
REVIEW RETURNED	28-Mar-2021

GENERAL COMMENTS	This article described the protocol of a randomized controlled trial for PEP used in COVID-19 patients. The protocol is complete and clear. The ethics was granted properly. It would be interesting to have the result public. There are several concerns as below. 1. The mean CAT score is 12.8 at interim analysis, which indicate the population are relative mild cases. PEP flute may be more effective in severe cases than mild cases. It would be interesting to see whether PEP flute take effect in mild COVID-19 patients. 2. PEP flute is wildly used in airway clearance and rehabilitation for the patients with respiratory disease. According to the protocol, the patients included in this clinical trial would be recorded for the self-reported comorbidity without chest image test or pulmonary function test. The incomplete baseline characteristics, no matter of pulmonary or extra-pulmonary condition would diminish the significance of the results in this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Xiaoyun Fan, First Affiliated Hospital of Anhui Medical University Comments to the Author:
Dear authors,
This is an interesting study adding relevant intervention means about preventing respiratory deterioration in Covid-19 with the use of PEP flute. Unfortunately, there are some important concerns that should be addressed before:

Thank you, Dr. Xiaoyun Fan, for your kind remarks and the relevant comments, which we have addressed below.

1. Page 5 of the text (line 23-39), The benefit evidence used by PEP is insufficient, so we can supplement some of the related studies on PEP and lung diseases, so that the function of PEP may be more convincing; in addition, there is no need to elaborate too much on the specific contents of the relevant studies.

The text in subsection: Background and rationale (line 118-131 in clean version) has been revised and supplemented with relevant references (new ref 10 and ref 12) and the content of the individual studies have been shortened.

2. Page 6 of the text (line 8-11) CAT is used to evaluate COPD, the author is now used to evaluate COVID-19 may not be very rigorous, COVID-19 's patients may not be sensitive to CAT, although the author mentioned the previous study in Page 11 of the text (line 19-24), but the evidence is insufficient and the data is too old.

Thank for your comments. We are aware that the CAT may not be the ideal instrument for measuring symptoms of COVID-19. However, the CAT is already translated to Danish and is widely used as a telemonitoring instrument for self-report of symptoms like those of COVID-19. We will consider this potential issue related to internal validity very thoroughly in the interpretation of our results. The text in subsection ‘Study objectives and hypotheses’ (lines 146-147, clean version), in the subsection ‘Primary outcome’ (lines 262-265, clean version) and in the section ‘Potential outcomes and impact’ has been revised (lines 376-378, clean version).

3. Page 7 of the text (line 33-35) There is no detailed explanation in the exclusion criteria to exclude COVID-19 patients with other underlying diseases, including heart failure or asthma, which can cause symptoms such as dyspnea, chest tightness, etc.

The text in subsection 'Trial population and eligibility criteria' (lines 192-194, clean version) and in the subsection 'Secondary outcomes' (lines 289-291, clean version) has been elaborated as regards comorbidity.

4. Whether the standard treatment mentioned on page 12 is the same as the standard care mentioned on page 9, or whether the Danish health authorities recommend standard treatment or standard care.

Thank you for highlighting this unclarity. We have rephrased the term to 'Usual care' which now should be consistently used throughout the manuscript. We have elaborated the text in the subsection 'Usual care' (lines 245-248, clean version). The Danish Health Authorities recommend selfcare, which we define as part of usual care. The text in Table 1 has been revised accordingly.

In addition, it is hoped that the author can make the each section concise and to the point, and it is better to list the data in the form of graphs or tables.

Reviewer: 2
Dr. Min Xie, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology Comments to the Author:
This article described the protocol of a randomized controlled trial for PEP used in COVID-19 patients. The protocol is complete and clear. The ethics was granted properly. It would be interesting to have the result public. There are several concerns as below.

Thank you, Dr. Min Xie, for the kind comments. We have addressed your concerns below.

1. The mean CAT score is 12.8 at interim analysis, which indicate the population are relative mild cases. PEP flute may be more effective in severe cases than mild cases. It would be interesting to see whether PEP flute take effect in mild COVID-19 patients.

Yes, it will be interesting to analyse the data. The overall aim of the trial is to explore the effectiveness of PEP as preventive measure, thus in early-stage disease. Recruitment is in a population of individuals at home at baseline. In severe cases, we would assume that they would already be hospitalized. This trial is in a Public Health setting which challenges how to recruit eligible and consenting participants. We expect the large sample size and the RCT design to compensate for this.

2. PEP flute is wildly used in airway clearance and rehabilitation for the patients with respiratory disease. According to the protocol, the patients included in this clinical trial would be recorded for the self-reported comorbidity without chest image test or pulmonary function test. The incomplete baseline characteristics, no matter of pulmonary or extra-pulmonary condition would diminish the significance of the results in this study.

Yes, it would have been nice to have chest image test or other objective measures at baseline. However, this was not deemed feasible in this Public Health setting and because of SARS-CoV-2-societal restrictions (lines 373-378, clean version). Comorbidity, if diagnosed, will be established through highly reliable register data from the Danish National Patient Registry giving way for subgroup analysis.