PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	FOOTPRINTS® study protocol: rationale and methodology of a 3-year longitudinal observational study to phenotype patients with COPD
AUTHORS	Crapo, James; Gupta, Abhya; Lynch, David; Vogel-Claussen, Jens; Watz, Henrik; Turner, Alice; Mroz, Robert; Janssens, Wim; Ludwig-Sengpiel, Andrea; Beck, Markus; Langellier, Bérengère; Ittrich, Carina; Risse, Frank; Diefenbach, Claudia

VERSION 1 – REVIEW

REVIEWER	Alexandru Corlateanu Department of Respiratory Medicine, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Moldova
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	Thank you for inviting me to review this manuscript which representing the study protocol: FOOTPRINTS® study: rationale and methodology of a 3-year longitudinal observational study to phenotype patients with COPD. it is now obvious that no single parameter can describe the complexity of COPD and a more holistic approach should be used in clinical practice. The recognition of major prognostic and therapeutic patient subgroups may lead to a more personalised approach to each patient and also provides data to the omics in COPD to uncover the pathogenetic background of this diversity and develop new targeted treatments. The manuscript is easy to read and all data, and conclusions will present huge interest with impact on clinical practice.

REVIEWER	Roberto Benzo Mayo Clinic, USA
REVIEW RETURNED	24-Aug-2020

GENERAL COMMENTS	The protocol is well describe and the objectives are clear. the study may add some understanding on disease progression. However current smokers are not included which may limit that value of the conclusions. I am not sure how much the readers will be interested in reading this protocol .

REVIEWER	Susumu Sato Kyoto University, Japan
REVIEW RETURNED	11-Oct-2020

GENERAL COMMENTS	This article is a kind of protocol paper which authors intended to investigate prospectively patients with COPD and subjects with

	smoking history but no airflow limitation, then will monitor their clinical courses including blood samples to evaluate their biomarkers. This study looks quite interesting and there are not so many problems in the study protocol, I am also willing to see their results soon. I would like to point out several concerns in the present protocol, and the manuscript. In the introduction section, they mentioned that “A1AT deficiency (A1ATD) is the only underlying gene defect that has been identified as a cause for COPD.” I would suggest that other potential gene defects which are associated with pulmonary emphysema, such as fibrillin-1 or other gene abnormalities associated with Marfan syndrome, or Ehlers-Danlos syndrome. Moreover, there are several reports which showed potential biomarkers in COPD, such as elastin degradation products, or desmosine. In inclusion and exclusion criteria, how about past experience of A1AT augmentation therapy, and how about past history of diagnosis of asthma in childhood. Why don’t you evaluate physical activities directory or indirectory in these subjects? They did not mention the calibration of the CT machine. It is required that routine calibration of CT machine using specific phantom, such as COPDGene study used.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments	Response
Reviewer 1	
Thank you for inviting me to review this manuscript which representing the study protocol: FOOTPRINTS® study: rationale and methodology of a 3-year longitudinal observational study to phenotype patients with COPD. It is now obvious that no single parameter can describe the complexity of COPD and a more holistic approach should be used in clinical practice. The recognition of major prognostic and therapeutic patient subgroups may lead to a more personalised approach to each patient and also provides data to the omics in COPD to uncover the pathogenetic background of this diversity and develop new targeted treatments. The manuscript is easy to read and all data, and conclusions will present huge interest with	Thank you for your positive comments.

Reviewer comments	Response
impact on clinical practice.	
Reviewer 2	
The protocol is well describe and the objectives are clear. The study may add some understanding on disease progression.	Thank you for your positive comments. We have outlined our responses to your additional comments below.
1. However current smokers are not included which may limit that value of the conclusions.	Current smokers were not included in the study due to the large extent to which smoking cessation can affect outcome measures, particularly measurements of lung density. Given that disease progression occurs despite smoking cessation, ex-smokers were considered to be a more suitable population for the study. We have now updated the justification for excluding current smokers to include lung density as an example and added supporting references (Discussion; page 24). *Note that current smokers were not included because smoking cessation can cause high variability in outcomes, particularly lung density measurements.[52,53] Given that disease progression occurs despite smoking cessation, ex-smokers were considered to be a more appropriate population.*

Reviewer comments	Response
2. I am not sure how much the readers will be interested in reading this protocol.	We hope that the FOOTPRINTS® study, which aims to address key unmet needs in our understanding of different COPD phenotypes, as well as our knowledge of disease biomarkers will be of interest to readers. Here we provide a detailed summary of the rationale for the ongoing study and the study methodology, presenting its strengths in the context of other longitudinal biomarker studies. Given that few such studies have been conducted thus far, we would suggest that the study design, methodology and biomarker assessments will be of interest. As noted by reviewer 1, we envisage that the findings of this study will be of significant interest and may impact upon clinical practice. In addition, our findings may provide a model for future clinical trials of emphysema.
Reviewer 3	
This article is a kind of protocol paper which authors intended to investigate prospectively patients with COPD and subjects with smoking history but no airflow limitation, then will monitor their clinical courses including blood samples to evaluate their biomarkers. This study looks quite interesting and there are not so many problems in the study protocol, I am also willing to see their results soon. I would like to point out several concerns in the present protocol, and the manuscript.	Thank you for your positive comments. We have outlined our responses to your detailed comments below.
1. In the introduction section, they mentioned that “A1AT deficiency (A1ATD) is the only underlying gene defect that has been identified as a cause for COPD.” I would suggest that other potential gene defects which are associated with pulmonary emphysema, such as fibrillin-1 or	Thank you for raising this point. The statement on A1AT deficiency has now been updated to acknowledge other potential gene defects associated with emphysema and a reference has been added for this,[1] as below (Introduction; page 5): *Although a number of gene defects have been associated with emphysema,[7] A1AT deficiency (A1ATD) is the most*

Reviewer comments	Response
other gene abnormalities associated with Marfan syndrome, or Ehlers-Danlos syndrome.	*well established as a cause for COPD.[8]*
2. Moreover, there are several reports which showed potential biomarkers in COPD, such as elastin degradation products, or desmosine.	In response to your comment on other biomarkers, we have updated paragraph 3 of the Introduction (page 6) to include additional details on the potential biomarkers in COPD that have been identified in previous studies: *When quantified, levels of NE, PR3 or their specific elastin degradation products have been associated with poorer disease outcomes in patients with COPD, such as incidence of exacerbations and higher risk of mortality.[11-13] Other proteases and biomarkers, including desmosine, fibrinogen and C-reactive protein, have also been associated with poorer disease outcomes in patients with COPD.[13-15]*
3. In inclusion and exclusion criteria, how about past experience of A1AT augmentation therapy, and how about past history of diagnosis of asthma in childhood.	Thank you for raising these points. We can confirm that past A1AT augmentation therapy was not permitted and that past history of asthma includes that which is documented during childhood. The 'Inclusion and exclusion criteria' section on page 9 have now been updated to clarify this: *Participants were excluded if any of the following were applicable:* • *Any prior, current or planned A1AT augmentation therapy.* • *Documented history of asthma, including during childhood.*

Reviewer comments	Response
4. Why don't you evaluate physical activities directory or indirectory in these subjects?	To assess physical activity performance, the 6-minute walk test is being conducted at visits 1, 2, 6 and 7. This is listed in the summary of biomarker assessments provided in Table 2 under 'Clinical parameters/assessments', and is also described in the 'Data Collection and management' section (Methods and Analysis; page 16). In addition, we have now added this to Figure 1.
5. They did not mention the calibration of the CT machine. It is required that routine calibration of CT machine using specific phantom, such as COPDGene study used.	The CT scanners were calibrated according to the routine procedures used locally. However, COPDGene® phantoms were used before the first patient scan and then bi-monthly to monitor the stability of each CT scanner. The manuscript has now been updated to include this in the 'Planned analyses and assessments' section (Methods and Analysis; page 14). *A COPDGene® phantom [26] is being used before the first patient scan and then bi-monthly to monitor the stability of CT measurements for each scanner.*

VERSION 2 – REVIEW

REVIEWER	Susumu Sato Kyoto University Hospital, Japan.
REVIEW RETURNED	06-Dec-2020

GENERAL COMMENTS	I do not have more comments.