PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Fatigue in patients with Chronic Obstructive Pulmonary Disease: protocol of the Dutch multicentre, longitudinal, observational FAntasTIGUE study
AUTHORS	Goërtz, Yvonne; Looijmans, Milou; Prins, Judith; Janssen, Daisy; Thong, Melissa S. Y.; Peters, Jeannette; Burtin, Chris; Meertens-Kerris, Yvonne; Coors, Arnold; Muris, Jean; Sprangers, Mirjam; Wouters, Emiel; Vercoulen, Jan; Spruit, Martijn

VERSION 1 – REVIEW

REVIEWER	Marc Miravitlles Hospital Vall d'Hebron Barcelona, Spain
REVIEW RETURNED	03-Feb-2018

GENERAL COMMENTS	Thanks for giving me the opportunity to review this manuscript describing an interesting protocol to evaluate fatigue in COPD. The manuscript is informative and well written. There are only a few aspects that should be improved: 1. The description of the objectives in the abstract is very different to the description provided in the introduction (page 7). 2. Inclusion criteria: please specify range of lung function values (pre or post-bronchodilator) and smoking habits. Will you accept never smokers in the study? Any age restriction? Any exclusion due to comorbidities? The criteria in general should be more clearly explained.

REVIEWER	Matthew Maddocks King's College London
REVIEW RETURNED	05-Feb-2018

GENERAL COMMENTS	Goertz and colleagues present a protocol for a novel and interesting study, which will provide much needed data on fatigue in COPD and hopefully raise the profile of this neglected symptom. The protocol is informative and clear. The authors provide a rationale for their design choices. There is an extensive battery of secondary outcome measures, but I note the use of adaptive/electronic questionnaires that will ensure missing data is minimized. A few specific comments: The sample size makes no mention of moderate fatigue, whereas the exposure of interest appears to be moderate-to-severe fatigue. I appreciate this is presented as an example of a 3-group

	classification, but the change in terminology was noted. The timing of the peri-hospitalisation measure is stated as the 'first days of…' If this time point has been operationalised it would be useful to specify more clearly. A key strength of the prospective design is that is enables you to assess the 'temporality' of associations between fatigue and your outcomes. The key points under strengths and limitations (page 3 in footnote), and the strengths in the discussion (page 12) could specify this more clearly. Under secondary outcomes use of an iPod is stated – do you mean iPad ?

REVIEWER	Maciek Godycki-cwirko Medical University of Lodz. Poland
REVIEW RETURNED	13-Feb-2018

GENERAL COMMENTS	Good choice of the topic, very well addressed

VERSION 1 – AUTHOR RESPONSE

Editorial Requirements:

- Please revise your title to include the study location.
    - Pag. 1: We have revised the title into: Fatigue in patients with Chronic Obstructive Pulmonary Disease: protocol of the Dutch multicentre, longitudinal, observational FAntasTIGUE study.

- Please remove the conclusions section, as this is not part of journal format for protocol articles.
    - Pag. 14: The conclusion section has been removed.

- You have cited reference number 33 to 66 in table 1 prior to reference number 29 which makes your citations incorrect. Please review again your main document and ensure that all references will be cited and will appear in ascending order.
    - We have revised the references throughout the complete manuscript, they appear now in ascending order.

- We have implemented an additional requirement to all articles to include 'Patient and Public Involvement' statement within the main text of your main document.
    - Page 5/6: We added information on the patient and public involvement.

Patient and public involvement

Based on the input of patients with chronic lung disease, fatigue was prioritized as a research topic during the Netherlands Respiratory Society (NRS) meeting (www.nationaalprogrammalongonderzoek.nl).[18] As stated, patient representatives

are full members of the FAntasTIGUE consortium, and have an active role in the decision process. The patient advisory board has been involved in setting up the proposal, in reviewing the study design before submission to the ethical committee, and in discussing the schedules of assessment. After completion of the study, the patient advisory board will also be asked to be involved in the development of post-trial communication.

Reviewer(s) Reports:

Reviewer: 1

Thanks for giving me the opportunity to review this manuscript describing an interesting protocol to evaluate fatigue in COPD. The manuscript is informative and well written. There are only a few aspects that should be improved.

First of all, we would like to thank the reviewer – Marc Miravitlles- for his feedback on this manuscript. We have taken the suggestions to heart and have revised the following:

C1 The description of the objectives in the abstract is very different to the description provided in the introduction (page 7).

R1 For consistency, the objectives in the abstract are aligned with the objectives in the introduction.

The primary ~~aim~~ objectives of this study are~~is~~ to chart the course of fatigue in patients with COPD, to identify the physical, systemic, psychological, and behavioural factors that precipitate and perpetuate fatigue in patients with COPD, ~~. Moreover, the secondary aim is~~ to evaluate the impact of exacerbation-related hospitalizations on fatigue, and to better understand the association between fatigue and 2-year all-cause hospitalization and mortality in patients with COPD. Moreover, the secondary aim is to identify diurnal differences in fatigue by using Ecological Momentary Assessment (EMA).

By adding these objectives, we exceeded the word limit (300 words). Therefore, we had to make some minor changes in the abstract.

C2 Inclusion criteria: please specify range of lung function values (pre or post-bronchodilator) and smoking habits. Will you accept never smokers in the study? Any age restriction? Any exclusion due to comorbidities? The criteria in general should be more clearly explained.

R2 We have elaborated on the inclusion criteria.

To be eligible, a subject must meet the following criteria:

i. A diagnosis of COPD according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD, grade 1A to 4D), with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio, $FEV_1/FVC < 0.07$;[18]
ii. No exacerbation-related hospitalization less than 4 weeks preceding enrolment;
iii. No use of oral corticosteroids and/or antibiotics less than 4 weeks preceding enrolment;
iv. Provided written informed consent.

Patients lacking a sufficient understanding of the Dutch language and/or participating in concurrent intervention studies will be excluded. There are no age or smoking status restrictions, as well as no exclusion based on comorbidities or the use of long term oxygen therapy.

Reviewer: 2

Goertz and colleagues present a protocol for a novel and interesting study, which will provide much needed data on fatigue in COPD and hopefully raise the profile of this neglected symptom. The protocol is informative and clear. The authors provide a rationale for their design choices. There is an extensive battery of secondary outcome measures, but I note the use of adaptive/electronic questionnaires that will ensure missing data is minimized. A few specific comments:

We are grateful to reviewer 2 – Matthew Maddocks- for his feedback and we will now react to the suggestions provided:

C1 The sample size makes no mention of moderate fatigue, whereas the exposure of interest appears to be moderate-to-severe fatigue. I appreciate this is presented as an example of a 3-group classification, but the change in terminology was noted.

R1 For consistency in terminology, moderate fatigue has been changed into mild fatigue (throughout the complete manuscript). This is in accordance with the terminology used by the developers of the CIS-Fatigue checklist (normal, mild, severe fatigue, respectively).

C2 The timing of the peri-hospitalisation measure is stated as the 'first days of…' If this time point has been operationalised it would be useful to specify more clearly.

R2 In order to specify the time of the hospitalization measure, the following is added:

a. Pag. 6: The assessments at baseline, 12 months, and during the first four days of a possible exacerbation-related hospitalization will be performed in a hospital setting.
b. Pag. 6: Also, when patients are admitted to the hospital between baseline and 12 months due to an exacerbation of COPD, some tests will be repeated during the first four days of hospitalization, and to weeks after discharge.

C3 A key strength of the prospective design is that is enables you to assess the 'temporality' of associations between fatigue and your outcomes. The key points under strengths and limitations (page 3 in footnote), and the strengths in the discussion (page 12) could specify this more clearly.

R3 The strength "to investigate whether the associations between fatigue and the explaining factors are temporarily or fluctuate over time" has been added to the pages:

c. Pag 3: The longitudinal design enables to examine the association between fatigue, exacerbation-related hospitalizations and mortality and allows us to investigate whether the associations between fatigue and the explaining factors are temporarily or fluctuate over time.

d. Pag. 13: It enables us to examine the association between fatigue, exacerbation-related hospitalizations and mortality. Moreover, it allows us to investigate if the associations between fatigue and the precipitating and perpetuating factors are temporarily or can change/fluctuate over time.

C4 Under secondary outcomes use of an iPod is stated – do you mean iPad ?

R4 In the current study an iPod (not an Ipad) will be used for Ecological Momentary Assessment.

Reviewer: 3

Please leave your comments for the authors below

Good choice of the topic, very well addressed

We would like to thank reviewer 3 for his feedback on this manuscript and the compliments.

VERSION 2 – REVIEW

REVIEWER	Marc Miravitlles Hospital Vall d'Hebron. Spain
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	My queries have been addressed by the authors