

BMJ Open Fatigue in patients with chronic obstructive pulmonary disease: protocol of the Dutch multicentre, longitudinal, observational *FAntasTIGUE* study

Yvonne M J Goërtz,¹ Milou Looijmans,² Judith B Prins,² Daisy J A Janssen,^{1,3} Melissa S Y Thong,⁴ Jeannette B Peters,² Chris Burtin,⁵ Yvonne Meertens-Kerris,⁶ Arnold Coors,⁷ Jean W M Muris,⁸ Mirjam A G Sprangers,⁴ Emiel F M Wouters,^{1,9} Jan H Vercoolen,² Martijn A Spruit^{1,5,9,10}

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ABSTRACT

Introduction Fatigue is the second most common symptom in patients with chronic obstructive pulmonary disease (COPD). Despite its high prevalence, fatigue is often ignored in daily practice. For this reason, little is known about the underlying determinants of fatigue in patients with COPD. The primary objectives of this study are 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, to evaluate the impact of exacerbation-related hospitalisations on fatigue and to better understand the association between fatigue and 2-year all-cause hospitalisation and mortality in patients with COPD. The secondary aim is to identify diurnal differences in fatigue by using ecological momentary assessment (EMA). This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of the possible strengths, weaknesses and clinical implications.

Methods and analysis A 2-year longitudinal, observational study, enrolling 400 patients with clinically stable COPD has been designed. Fatigue, the primary outcome, will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue). The secondary outcome is the day-to-day/diurnal fatigue, registered in a subsample (n=60) by EMA. CIS-Fatigue and EMA will be evaluated at baseline, and at 4, 8 and 12 months. The precipitating and perpetuating factors of fatigue (physical, psychological, behavioural and systemic) will be assessed at baseline and at 12 months. Additional assessments will be conducted following hospitalisation due to an exacerbation of COPD that occurs between baseline and 12 months. Finally, at 18 and 24 months the participants will be followed up on their fatigue, number of exacerbations, exacerbation-related hospitalisation and survival.

Ethics and dissemination This protocol was approved by the Medical research Ethics Committees United, Nieuwegein, the Netherlands (NL60484.100.17).

Trial registration number NTR6933; Pre-results.

Strengths and limitations of this study

- This study is a large, longitudinal, multicentre study evaluating a wide range of possible precipitating and perpetuating factors of mild to severe fatigue in patients with chronic obstructive pulmonary disease (COPD).
- The ecological momentary assessment data will give us more insight in the diurnal variations of fatigue.
- The longitudinal design enables to examine the association between fatigue, exacerbation-related hospitalisations and mortality and allows us to investigate whether the associations between fatigue and the explaining factors are temporary or fluctuate over time.
- The perpetuating and precipitating factors have been carefully selected; it is—however—possible that there are other factors that contribute to fatigue in COPD that will be missed.

INTRODUCTION

Fatigue, the subjective feeling of tiredness or exhaustion, is next to dyspnoea, the most common and distressing symptom in patients with chronic obstructive pulmonary disease (COPD).¹ It affects the ability to perform activities of daily living and impacts the patient's quality of life.^{2–3} Among patients with stable moderate to severe COPD, around 50% experiences mild to severe fatigue,⁴ which is significantly higher compared with elderly, non-COPD subjects.⁵ Nevertheless, despite its high prevalence and significant negative health consequences, fatigue remains often undiagnosed and, in turn, untreated.⁶ This might be due to the under-representation of fatigue questions in commonly used health status assessment tools.^{7–8} Moreover, relatively few studies have focused on the symptom fatigue and,



For numbered affiliations see end of article.

Correspondence to

Yvonne M J Goërtz;
yvonnegortz@ciro-horn.nl

therefore, little is known about the precipitating and perpetuating factors of mild to severe fatigue in patients with COPD. Consequently, specific interventions aimed at reducing COPD-related fatigue are lacking. A better insight into the underlying determinants will provide guidance for the development of personalised interventions for this important yet disregarded symptom in patients with COPD.⁹

Multiple precipitating factors are expected to play a role in the cause of COPD-related fatigue.⁹ It has been suggested that COPD-specific features are associated with fatigue, since the prevalence of fatigue is higher in patients with COPD compared with elderly control subjects.⁵ However, evidence suggests that fatigue is not related to the degree of airflow limitation.⁴ This indicates that the degree of airflow limitation may not be the primary underlying cause of mild to severe fatigue in patients with COPD. On the other hand, a COPD exacerbation precipitates mild to severe fatigue.^{5,10} However, the size of the impact of an exacerbation-related hospitalisation on fatigue remains to be clarified.

Next to precipitating factors, various physical, systemic, psychological and behavioural factors are assumed to perpetuate mild to severe fatigue in patients with COPD. Generally, studies report significant, weak to moderate associations between fatigue and health status, exercise performance, physical activity, functional impairments, sleep quality, symptoms of anxiety or depression and mood status.^{2,5,11–15} Moreover, research indicates that COPD is associated with low-grade systemic inflammation.¹⁶ Nonetheless, whether and to what extent low-grade systemic inflammation is related to fatigue needs to be further explored.

Thus, fatigue in COPD is a complex symptom, due to a combination of precipitating and perpetuating factors. To date, the above-mentioned factors have rarely been assessed comprehensively in one study in patients with COPD.¹⁷ Moreover, the role of sleep apnoea, comorbidities, medication and exacerbation-related hospitalisations are unknown. Therefore, we have designed a longitudinal, observational study, which evaluates a wide range of possible underlying factors of mild to severe fatigue in patients with COPD. This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of its possible strengths, weaknesses and clinical implications.

Objectives of this study

The primary objectives of the *FAntasTIGUE* study are:

1. To chart the course of fatigue in patients with COPD.
2. To identify physical, systemic, psychological and behavioural factors that precipitate and/or perpetuate fatigue in patients with COPD.
3. To identify the impact of exacerbation-related hospitalisations on fatigue and its perpetuating factors.
4. To better understand the association between baseline fatigue and 2-year all-cause hospitalisation and mortality in patients with COPD.

The secondary objective of this study is:

1. To identify diurnal differences in fatigue by augmenting traditional questionnaire data with ecological momentary assessment (EMA).

METHODS

The *FAntasTIGUE* study is a collaboration between CIRO (Horn, The Netherlands), Radboud University Medical Centre (Nijmegen, The Netherlands), Academic Medical Centre (Amsterdam, The Netherlands), Maastricht University Medical Centre (Maastricht, The Netherlands) and Hasselt University (Diepenbeek, Belgium). The consortium consists of members from various disciplines and backgrounds (eg, chest physicians, clinical psychologists, an elderly care specialist, a cardiologist, a general practitioner and researchers), to ensure necessary know-how to enable the successful completion of the project. Moreover, a patient advisory board is closely involved to advise and monitor the *FAntasTIGUE* project, by providing valuable insight from the patient perspective.

Patient and public involvement

Based on the input of patients with chronic lung disease, fatigue was prioritised as a research topic during the Netherlands Respiratory Society meeting (www.nationaalprogrammaalongonderzoek.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.

Study design

A 2-year longitudinal, observational study, enrolling patients with clinically stable COPD has been designed (figure 1). The assessments at baseline, 12 months and during the first 4 days of a possible exacerbation-related hospitalisation will be performed in a hospital setting. The remaining measurements at 4, 8, 18 and 24 months will take place at the patients' homes.

The primary outcome fatigue severity will be assessed with a questionnaire at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalisations and 2 weeks after discharge. The secondary outcome, day-to-day/diurnal variation in fatigue, will be registered using EMA in a subsample (n=60) at baseline, and at 4, 8 and 12 months. Selection is based on convenient sampling, a 'first-come, first-serve' approach. The precipitating and perpetuating factors of mild to severe fatigue in patients with COPD (physical, psychological, behavioural and systemic factors) will be assessed at baseline and at 12 months. 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 4 days of hospitalisation and 2 weeks after

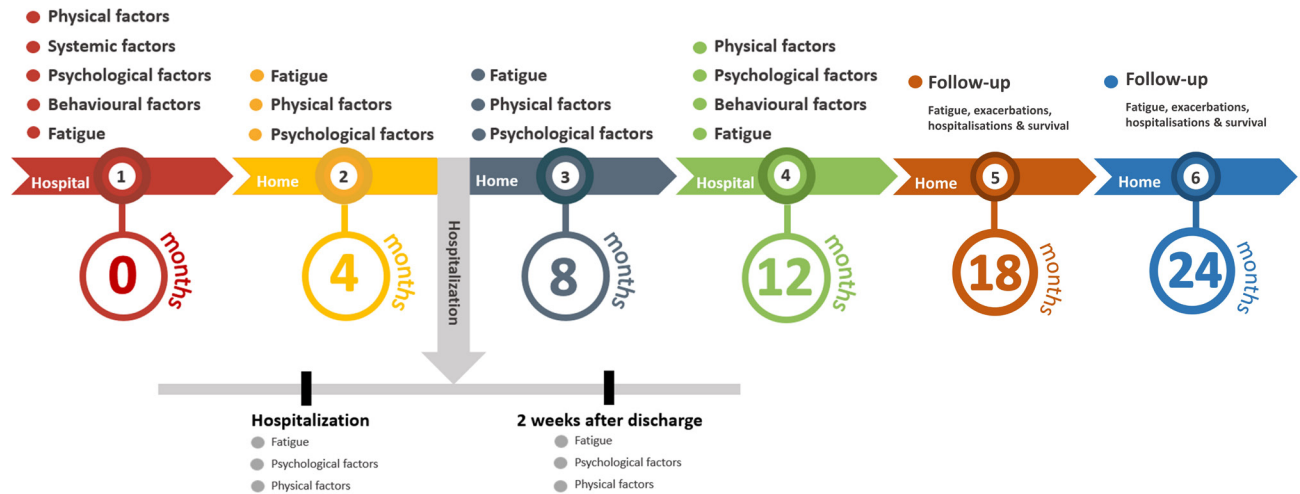


Figure 1 Timeline: measurements will be performed at baseline, and at months 4, 8 and 12. Additional measurements will be carried out when a non-elective, exacerbation-related hospitalisation occurs. Patients will be followed up at month 18 and 24.

discharge. At last, at 18 and 24 months the participants will be followed up on their fatigue, number of exacerbations, exacerbation-related hospitalisations and survival.

Eligibility criteria

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

1. A diagnosis of COPD according to the Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD, grade 1A–4D), with a postbronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio, $FEV_1/FVC < 0.7$.¹⁹
2. No exacerbation-related hospitalisation less than 4 weeks preceding enrolment.
3. No use of oral corticosteroids and/or antibiotics less than 4 weeks preceding enrolment.
4. 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.

Extra eligibility criteria for the EMA substudy are as follows:

1. Access to the internet at home (Wi-Fi).
2. Able to operate a smartphone/iPod.

Recruitment

Participants will be recruited at the outpatient clinics of the Department of Respiratory Medicine in Maastricht and the Department of Pulmonary Diseases in Nijmegen, and from the registration Network of Family Practices

(RNH) of Maastricht University.²⁰ Eligible patients from the outpatient clinics will be informed about the research by their physician during their pulmonary consultation and are asked if the investigator may contact them to provide detailed information. Patients recruited via the RNH network will receive a letter on behalf of their general practitioner introducing the research project. In case the patient agrees to participate, an appointment for the baseline assessment at the hospital will be made. Written informed consent will be obtained at the beginning of this visit.

OUTCOMES

Primary outcome

Fatigue severity will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue).²¹ The CIS-Fatigue consists of eight items scored on a seven-point Likert scale. The scores range from 8 (normal fatigue) to 56 (most severe fatigue). A score of 26 or lower indicates normal fatigue, scores between 27 to 35 indicate mild fatigue and a score of 36 or higher indicates severe fatigue. The CIS-Fatigue is a standardised and validated questionnaire that has been used in healthy subjects,^{22–24} and among various patient populations including COPD.^{21 25–27} The CIS-Fatigue will be administered at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalisations and 2 weeks after discharge.

Secondary outcome

Day-to-day/diurnal variations of fatigue will be measured in a subsample (n=60) with EMA.^{28 29} EMA involves repeated measurements of the participant's behaviour and context in vivo and in real time. In the current study, the participants will be given an iPod for the duration of the study with the EMA application (www.psymate.eu) installed. The participants will be prompted to answer questions about their fatigue, context and surroundings, eight times per day at random moments between 7:30 and 22:30 for five consecutive days at baseline, and at 4, 8 and 12 months. Patients will be given instructions to carry the device with them at all times for five consecutive days. Furthermore, they will be requested to fill out the questions immediately after the alert and to keep a normal day/night routine.

Explanatory factors

Table 1 provides an overview of the precipitating and perpetuating factors of mild to severe fatigue that will be assessed at baseline, and at months 4, 8, 12, 18 and 24, as well as during non-elective, exacerbation-related hospitalisations and 2 weeks after discharge.

Questionnaires will be completed via RadQuest in the home environment. RadQuest allows very simple online questionnaire completion. If, for any reason (eg, no PC or internet connection) it is not possible to fill out the questionnaires via RadQuest, the participant will receive a paper version. Regarding the systemic factors, we will collect blood at baseline to assess systemic high-sensitivity C-reactive protein, interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), IL-1 α , IL-1 β , IL-1-RA, IL-10, fibrinogen, leukocytes, cortisol, haemoglobin, glucose, thyroid function, renal function (creatinine), sodium, potassium, calcium, magnesium, vitamin B₁₂, vitamin 25(OH)D₃, liver function (aspartate aminotransferase and alanine aminotransferase), N-Terminal pro-Brain Natriuretic Peptide, blood sediment, antinuclear antibodies and DNA.

Sample size calculation

A total of 260 patients are needed to detect a medium to small effect size of 0.175 between factors (218 (2 groups with or without an exacerbation) or 264 (3 groups normal, mild or severe fatigue)) and a small effect within-between factors (222 (3 groups normal, mild or severe fatigue)), with a power of 90%, a significance level of 5% and an expected drop-out rate of 20%.³⁰ Nevertheless, as a rather large number of possible perpetuating and precipitating factors will be evaluated, it is decided to augment the sample size to 400 inclusions.

For EMA, a sample of 60 patients with each 160 observations (5 days with eight measurements, collected over four time points) ensures that the EMA analyses are adequately powered to detect differences in fatigue, based on a power of 0.8 and two-tailed significance of 0.05.³¹

Data management and statistical analysis

Missing data of questionnaires will be minimised using RadQuest, since items cannot be skipped. In case of missing data for other variables, the likeliness of this being missing at random will be assessed. If missing data are random, we will use appropriate imputation methods.³²

All statistical analyses will be performed using statistics software (SPSS V.25.0 for Windows). First, to characterise transitions over time in fatigue, we will use latent transition analysis.³³ Second, to identify the factors that precipitate and/or perpetuate fatigue in patients with COPD, mixed model analyses will be applied for continuous outcomes measures and generalised estimating equations for dichotomous outcomes measures. Third, to study the impact of exacerbation-related hospitalisations on fatigue and its perpetuating factors we will use mixed model analyses. Fourth, to better understand the extent to which baseline fatigue is related to 2-year all-cause hospitalisation and mortality, Cox proportional hazard models will be applied. At last, to identify whether there are diurnal differences in fatigue and what factors are associated with these variations, we will use hierarchical linear modelling as items are nested within moments and moments are nested within individuals. The responsiveness and sensitivity of the fatigue questionnaire versus EMA data are compared with effect sizes (Cohen's d) for the component of observed change derived from model parameters. A priori, a two-tailed p value of <0.05 is considered significant.

Ethics and dissemination

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subject Act (WMO). The study was registered on www.trialregister.nl on 8 January 2018. The results will be submitted for publication in peer-reviewed journals and will be presented at (inter)national conferences.

DISCUSSION

The *FantasTIGUE* study has been designed to identify the factors that perpetuate and/or precipitate mild to severe fatigue in patients with COPD. The novel findings will hopefully further guide the development of tailored interventions, which—in turn—will help to diminish the impact on daily life of this important yet ignored symptom.

Strengths

A major strength of the *FantasTIGUE* study is that a wide range of possible precipitating and perpetuating factors will be tested concurrently in one model of stable patients with COPD. Moreover, the *FantasTIGUE* study also examines the impact of an exacerbation-related hospitalisation on fatigue. This way, we aim to identify relevant factors that explain variance in fatigue. Another strength of this

Table 1 Overview outcome measurements

	Number (n)	0 month	4 months	8 months	12 months	18 months	24 months	Exacerbation-related hospitalisations*
Fatigue								
Subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue) ²¹	400	•	•	•	•	•	•	•
Ecological momentary assessment ^{28 29}	60	•	•	•	•			
Sociodemographic factors								
Gender	400	•						
Age	400	•						
Social-economic status ³⁴	400	•						
Marital status	400	•			•			
Survival status	400	•	•	•	•	•	•	
Physical factors								
Current medication	400	•			•			
Charlson Comorbidity Index ³⁵	400	•			•			
Symptoms checklist ³⁶	400	•			•			
Modified Medical Research Council (mMRC) dyspnoea scale ³⁷	400	•	•	•	•			•
Exacerbations last 4 or 6 months (as appropriate)	400	•	•	•	•	•	•	
All-cause hospitalisations	400	•	•	•	•	•	•	
Body mass index	400	•			•			
Waist circumference	400	•			•			
Bioelectrical impedance analyses ³⁸	400	•			•			
6 min Walk Test ³⁹	400	•			•			
Short Physical Performance Battery ⁴⁰	400	•			•			
Lower limb muscle function (MicroFet2 Wireless Hand-held Dynamometer) ⁴¹	400	•			•			
Hand grip strength ⁴²	400	•			•			
Lung function (postbronchodilator spirometry, whole-body plethysmography, and transfer factor for carbon monoxide)	400	•						
Peripheral arterial disease (Doplex D900, Huntleigh Healthcare, Cardiff, UK) ^{43 44}	400	•			•			
Resting cardiac echocardiography (Maastricht only)	200	•						
Resting ECG(Maastricht only)	200	•						
Retinal microcirculation ⁴⁵ (Maastricht only)	200	•						
Polysomnography (Maastricht only)	50	•						
Psychological factors								
Nijmegen Clinical Screening Instrument ⁴⁶	400	•			•			
COPD Assessment Test ⁸	400	•	•	•	•			•
Euroqol-5d-5L ⁴⁷	400	•			•			
Hospital Anxiety Depression Scale ⁴⁸	400	•	•	•	•			•
Montreal Cognitive Assessment ⁴⁹	400	•			•			

Continued

Table 1 Continued

	Number (n)	0 month	4 months	8 months	12 months	18 months	24 months	Exacerbation-related hospitalisations*
Qualitative experience of fatigue (KWAMOE) ⁵⁰	400	•			•			
Acceptance of Disease and Impairments Questionnaire ⁵¹	400	•			•			
Fatigue-related self-efficacy (Self-Efficacy-5) ⁵²	400	•			•			
Jacobsen Fatigue Catastrophising Scale ⁵³	400	•			•			
Fear of Progression Questionnaire ⁵⁴	400	•			•			
Patient Activations Measure ⁵⁵	400	•			•			
Activity Cognitions Instrument (self-developed questionnaire)	400	•			•			
Behavioural factors								
Smoking status	400	•			•			
Alcohol consumption	400	•			•			
Caffeine consumption	400	•			•			
Objectified physical activity (Actigraph GT9X Link, 3-axis activity monitor, sample frequency 30Hz) ⁵⁶	400	•			•			
Pittsburgh Sleep Quality Index ⁵⁷	400	•			•			
Epworth Sleepiness Scale ⁵⁸	400	•			•			
Causal Attribution List ⁵⁹	400	•			•			
Sickness Impact Profile ⁶⁰	400	•			•			
Social Support List, Interactions and Discrepancies ⁶¹	400	•			•			
Systemic factors								
Venous blood samples	400	•						

*Non-elective hospitalisations due to an exacerbation of COPD may occur at any moment after the start of the study. Those which occur between baseline and 12 months will result in additional measurements. Those which may occur between 12 and 24 months will not result in additional measurement.

COPD, chronic obstructive pulmonary disease, mMRC, modified Medical Research Council

study is the use of EMA to capture diurnal variations of fatigue in patients with COPD. In comparison with the usual web-based or paper-and-pencil questionnaires, data gathered via EMA are not subject to recall bias and provide us with a film of variations in the patient's fatigue in their natural environment rather than a snapshot. To our knowledge, this is the first study that uses EMA to evaluate fatigue in a population of patients with COPD. The information about the diurnal variations of fatigue will further help us to tailor interventions for reducing fatigue in patients with COPD. Moreover, EMA provides us with contextual information of factors that could precipitate or perpetuate fatigue. A methodological strength of this study is the longitudinal design. It enables us to examine the association between fatigue, exacerbation-related hospitalisations and mortality. Moreover, it allows us to investigate if the associations between fatigue and the precipitating and perpetuating factors are temporarily or can change over time. And last, the structure of the *FAntasTIGUE* consortium, including a steering committee

and a patient's advisory board, allows us to improve the research capacity, to share (academic) resources, to disseminate study results and to speed up future research.

Limitations

The present study may encounter the following limitations: first, despite the benefits of repeated measurements in longitudinal studies, higher drop-out rates are expected as disease progresses. This attrition could result in a biased sample, which may compromise the study's generalisability. To limit the loss to follow-up, we will minimise the burden as much as possible and keep close contact with the patients. The patient advisory board has been intimately involved in the design of the *FAntasTIGUE* project to balance patient burden and number of variables that needed to be assessed to identify the factors that perpetuate and/or precipitate mild to severe fatigue in patients with COPD. Second, the current study selection is based on convenience sampling. This may cause selection bias, since participants with a lack of motivation

and a higher disease burden are less likely to respond. We will try to prevent selection bias, by inviting all patients who are diagnosed with COPD either via their physician during consultation hour or via their own general practitioner. Third, together with the steering committee and patient advisory board, the perpetuating and precipitating factors that will be evaluated have been carefully selected. However, we still may miss other factors that potentially contribute to fatigue in COPD.

Clinical implications

The results of the *FAntasTIGUE* study will contribute to a better understanding of the physical, psychological, behavioural and systemic factors that precipitate and/or perpetuate fatigue in patients with COPD when studied concurrently. Furthermore, it will give us more insight in the diurnal variations of fatigue and the impact of exacerbations on fatigue. These findings will provide further guidance for the development of fatigue-reducing and coping interventions to improve the daily functioning of patients with COPD. This will be an important first step in the management of COPD-related fatigue.

Author affiliations

¹Department of Research and Education, Ciro, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands

²Department of Medical Psychology and Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

³Centre of Expertise for Palliative Care, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

⁴Department of Medical Psychology, Academic Medical Centre University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

⁵REVAL - Rehabilitation Research Center, BIOMED - Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

⁶Patient Advisory Board, Ciro, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands

⁷Patient Advisory Board, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

⁸Department of Family Medicine, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands

⁹Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

¹⁰NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

Contributors YMJG and ML are responsible for the recruitment, data collection and data analysis. JHV is the principal investigator of Radboud University Medical Centre. EFWM is the principal investigator of Maastricht University Medical Centre and MAS is the project leader. Together with DJAJ, MSYT, JBPe, CB, JWMM, MAGS and JBPr, they form the *FAntasTIGUE* consortium, and are responsible for the design, recruitment and interpretation of the results. YM and AC are members of the patient advisory board. All authors contributed to the writing of this manuscript, read and approved the final version of the manuscript.

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Competing interests Professor Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, GSK, Novartis and AstraZeneca outside the scope of this work.

Patient consent Not required.

Ethics approval Medical Research Ethics Committees United approved the study, Nieuwegein, the Netherlands, on 22 December 2017 (R17.036/NL60484.100.17).

Provenance and peer review Not commissioned; externally peer reviewed.

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