The role of physical activity, malnutrition and sarcopenia for the prediction of acute exacerbations and the evolution of COPD assessment test (CAT) in patients with COPD

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects (clinical cohort study)
Risk Categorisation:	Category A
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PROTOCOL SIGNATURE FORM

Study Title	The role of physical activity, malnutrition and sarcopenia for the prediction of acute exacerbations and the evolution of COPD assessment test (CAT) in patients with COPD

The Project Leader has approved the protocol version 1.0 dated with 17.05.2018, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles of Good Clinical Practice.

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GLOSSARY OF ABBREVATIONS

AECOPD	*Acute exacerbations of COPD*
BASEC	*Business Administration System for Ethical Committees*
BIA	*Bioelectrical impedance analysis*
BMI	*Body mass index*
CAT	*COPD assessment test*
COPD	*Chronic obstructive pulmonary disease*
CRF	*Case report form*
CRP	*C-reactive protein*
DXA	*Dual-energy X-ray absorptiometry*
FEV1	*Forced expiratory volume in 1 second*
FFMI	*Fat free mass index*
FOPH	*Federal Office of Public Health*
FVC	*Forced vital capacity*
HGS	*Hand grip strength*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
SO	*Sarcopenic obesity*
THC	*Telehealth care*

1 BACKGROUND AND PROJECT RATIONALE

A low body mass index (BMI) has been described as an independent risk factor for mortality in subjects with chronic obstructive pulmonary disease (COPD), while the association was strongest in patients with severe COPD [1]. Additionally, weight loss in the course of the disease was associated with increased mortality [2].
A low fat free mass index (FFMI) was also associated with increased overall and COPD-related mortality, even in subjects with normal BMI [3]. FFMI seems to be a better predictor of disease severity regarding the degree of chronic dyspnea, forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC) ratio and stage of disease than BMI [4]. Patients with the constellation of abdominal obesity, normal weight and low muscle mass have an increased cardiometabolic risk [5]. FFMI also correlates with quality of life [6]. Sarcopenic obesity (SO) is associated with worse physical performance and higher systemic inflammatory burden compared with other body composition phenotypes in COPD [7]. Sarcopenia affects 15% of patients with stable COPD and impairs function and health status. Sarcopenia does not impact on response to pulmonary rehabilitation (PR), which can lead to a reversal of the syndrome in select patients [8]. Body composition evaluation is useful for the assessment of COPD patients referred to pulmonary rehabilitation and should be routinely performed [9]. A well-balanced diet is beneficial to all COPD patients, not only for its potential pulmonary benefits, but also for its proven benefits in metabolic and cardiovascular risk [10].
If our hypothesis proves to be true, the clinical consequence would be the need to systematically include nutritional assessment / therapy and other measures to reduce malnutrition and sarcopenia in the clinical routine of treating COPD patients to reduce overall risk of acute exacerbation of COPD (AECOPD) and improve quality of life.
The study is of risk category A since there are no relevant risks for participating patients (the study poses no additional risks to the patients compared to routine care).

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

The primary objective is to investigate the association between physical activity, malnutrition and sarcopenia and the occurrence of AECOPD / the evolution of the COPD assessment test (CAT) over 1 year in a cohort of COPD patients. We hypothesize that being malnourished and/or sarcopenic at baseline and a decline of FFMI over time is associated with an increased rate of AECOPD and an increased (or increasing) CAT score.

2.2 Primary and secondary endpoints

The primary endpoint is the rate of exacerbation depending on the explanatory variables FFMI, hand grip strength (HGS) and C-reactive protein (CRP), measured at baseline, after 6 and after 12 months. We will examine the correlation between the evolution of FFMI/HGS/CRP and the occurrence of AECOPD / the evolution of the CAT.
Secondary endpoints include further parameters from our COPD cohort, such as physical activity and further biochemical markers (e.g., protein, albumin, 25-OH vitamin D3), which will be analyzed by descriptive statistics (including cross-sectional and longitudinal analyses).

2.3 Project design

A national, monocentric, prospective, observational, exploratory cohort study.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

Inclusion: any patient with COPD GOLD stage B or higher giving written informed consent to participate. The study population will consist of our current telehealth care (THC) cohort of COPD patients as well as newly recruited COPD patients.

Exclusion: any patient who is unable to provide informed consent or to follow the trial procedures. Insufficient knowledge of the trial language is therefore a reason of exclusion.

3.2 Recruitment, screening and informed consent procedure

Patients will be mainly recruited from our established THC cohort of COPD patients [11] by dedicated study nurses of the Lungenzentrum St. Gallen at the Kantonsspital St. Gallen (phone calls and, if necessary, other channels of communication). New participating patients will also be acquired, namely through ongoing recruitment by the referring physicians in daily practice. All referred COPD patients will be screened systematically by our study nurses on a daily basis. Screening procedures for study inclusion involve routine daily practices. Eligible patients will be informed about the study through personal communication and, if willing to participate, provided with the dedicated informed consent sheet sent along with this proposal. Written informed consent is a prerequisite for study inclusion. No compensation payments will be distributed.

3.3 Study procedures

All patients will be followed using the THC procedure as previously described [11, 12]. Specifically, the CAT score is measured once per week and patients answer questions on a daily basis that aim at the early detection of AECOPD. The study duration is one year per patient.

In addition, we will measure body composition (e.g., FFMI and fat share) by direct segmental multi-frequency bioelectrical impedance analysis (BIA) and/or dual-energy X-ray absorptiometry (DXA), HGS (with a dynamometer) and biochemical parameters (e.g., CRP, protein, albumin, 25-OH vitamin D3). These measurements will take place at baseline and after 6 and 12 months. Furthermore, patients are provided with a pedometer to record step count and/or an accelerometer to record overall movement/distance traveled. This might be complemented by a standardized sit-to-stand physical test at each visit (baseline, 6 and 12 months). We will assess the nutritional status by standardized questionnaires (Nutritional Risk Screening [NRS] 2002; in case of malnutrition, “Nutritional Assessment” according to local guidelines) and provide nutritional support/therapy by professional personnel. In the final analysis, receipt of nutritional support/therapy will be one parameter stratified for. Nutritional parameters will be assessed at baseline and after 6 and 12 months. Schedule of assessment in appendix 1.

3.4 Withdrawal and discontinuation

Patients are withdrawn from the study by virtue of their own will at any time.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

A sample size of 85 patients is envisaged to be able to detect a significant association (expected correlation coefficient r=0.30) between ΔFFMI (1 year vs. baseline) and the patients' exacerbation rate with 80% power at a 5% significance level (two-sided).

The evolution of the FFMI will be analyzed using linear regression. The association between the FFMI and the occurrence of AECOPD will be evaluated using the Andersen-Gill formulation of the Cox proportional hazard model as well as joint modeling useful for the analysis of recurrent time-to-event data (exacerbation) with time-varying predictors (FFMI). The association between

FFMI and CAT will be estimated using linear mixed models or alternately generalized estimating equations.

4.2. Handling of missing data

The patients expected to be enrolled in the current study consist of patients from our previous THC cohort willing to participate in this extension study (approx. 100 patients). Assuming a dropout rate of 15% (including patients not willing to participate to the extension study as well as patients dropping out in the course of the study), we are expecting to enroll 85 patients in the study. Potential dropouts beyond 15% will not be replaced. If a patient withdraws her/his consent during the course of the study, no further data will be collected. However, data that have been collected before withdrawal will be used for the final analysis.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as the Project Leader.

5.2 Notification of safety and protective measures (HRO Art. 20)

The Project Leader and/or the sponsor are promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via Business Administration System for Ethical Committees (BASEC) of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Radiation

Not applicable.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project termination, the Ethics Committee is notified within 90 days. In the unlikely event that the trial is terminated prematurely, the Ethics Committee is notified within 15 days

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

(including a statement of the reasons for premature termination). Health-related data are anonymized upon trial termination.

5.7 Insurance

In the event of project-related damage or injuries, the liability of the Kantonsspital St. Gallen provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Refined prediction of AECOPD leading to timely intervention will positively influence the QoL of the individual study participant. Results from the study are thought to be generalizable among COPD patients. No incidental findings with immediate relevance to the study participant are expected to be made, and genetic findings are anyway precluded in this observational cohort study. The study design is perfectly suited to longitudinally track different clinical parameters and to assess the evolution of the CAT. The time effort that the participants have to take is absolutely reasonable.

6.2 Risk-Benefit Assessment

The study poses no additional risks to the patients compared to routine care. The patients can benefit from the study through earlier recognition of clinical deterioration, thus allowing for earlier therapeutic intervention and attenuation (or even prevention) of disease exacerbation.

6.3 Rationale for the inclusion of vulnerable participants

Not applicable.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The trial personnel are trained for all important trial aspects. For the purpose of quality assurance, audits or site visits may be performed by the Ethics Committee. Direct access to the source data and all project-related files and documents is granted on such occasions.

7.2 Data recording and source data

Trial data is recorded with paper Case Report Forms (CRF). At the end of the trial, all data is transferred to an electronic database for analysis. Source data according to section 2.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. The study nurse stores the subject identification list under closure. Data protection is warranted respecting the Swiss data protection legislation.

7.4 Retention and destruction of study data and biological material

All trial data, including documents necessary for patient identification and post-trial care, must be archived for a minimum of 10 years upon trial termination. All data are stored on a secure and regularly backed-up server provided by KSSG.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

This project is funded by the Lungenliga St. Gallen and internal funds from the KSSG. It is planned that results from the study are published in a peer-reviewed journal, possibly in an open access format. The planned authorship (first/last author) for the main publication (in case of different emerging publications) will be: Frank Rassouli and Maximilian Bösch as co-first authors, and Martin Brutsche as last author. There are no conflicts of interest to declare.

9 REFERENCES

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2. Human Research Act (HRA) http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf
3. Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html)
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Appendix 1: Schedule of assessments

Time (months)	***>-1 day***	***0***	***+6***	***+12***
	Information	*Screening*	*1st visit*	*2nd visit*
Oral and written information	*+*			
Written consent		*+*		
Check inclusion-/ exclusion criteria		*+*		
Medical history		*+*		
Participant characteristics		*+*		
CAT score		*+*	*+*	*+*
Procedures (FFMI, BIA, DXA, HGS, etc.)		*+*	*+*	*+*
Questionnaire (NRS)		*+*	*+*	*+*
Sampling		*+*	*+*	*+*
Data analysis			*+*	*+*