Contents

1. Hypothesis

The number of admissions with Worsening in Chronic Obstructive Pulmonary Disease (F-COPD) can be reduced by a multifactorial differentiated preventive optimization effort given in continuation of current admission.

1.1 Background

COPD is a chronic and potentially life-threatening disease in which a chronic inflammatory condition leads to varying degrees of breathing resistance as well as destruction of lung tissue (alveoli) with the formation of emphysema. COPD is characterized by permanent and most often decreasing lung function and is manifested by respiratory distress, coughing, and airway mucus [1]. F-COPD is associated with significant physiological impairment, and increasing inflammation of the respiratory tract, due to several factors including viruses, bacteria, tobacco smoke and air pollution [2].

Exacerbations of the disease will often lead to contact with a doctor, outpatient clinic, emergency room, or hospitalization [1]. F-COL leads to increased morbidity and mortality [2, 3]. Figures from the National Patient Register show that the number of admissions with COPD has increased from 2013-2017 respectively. from 19,117 to 22,556, which corresponds to an increase of 18% [4]. 17,000 admissions are registered annually with F-KOL as action diagnosis. This corresponds to 2% of all somatic admissions in Denmark [1]. Furthermore, a citizen with COPD has on average 3 times more hospital admissions than the general population [5]. Some COPD patients suffer from repeated exacerbations of their disease [6].

These are large amounts used in the treatment of patients with COPD. The National Board of Health states in an inventory an annual cost of DKK 1,290 million. DKK for treatment and care of COPD patients [1], and the Health Data Agency states in an equivalent statement an amount annually of DKK 8,500 million. DKK for COPD patients' medications and contacts with the health service [5].

In Denmark, 163,000 people live with COPD [5], approx. 16,000 of these are very ill due to multiple comorbidities. This group is averaged 8 times more frequently than those without comorbidities [5]. Cardiovascular diseases are frequent and important co-morbidities to COPD. These include ischemic heart disease, heart failure, arrhythmias, peripheral vascular disease, and hypertension [7]. Heart failure and COPD at the same time provide a diagnostic and therapeutic challenge. This is because the two modes affect and aggravate each other. Both diseases are systemic with potentially overlapping pathophysiological processes. It is therefore important that the diagnosis and treatment of heart failure is optimized in COPD patients [8].

As the mean life expectancy increases, the number of patients with chronic disorders also increases [9]. The incidence rate of COPD increases with age [1], and patients with COPD more often suffer from several chronic diseases at the same time as age-matched controls [9].

Initially, the inflammatory process in patients with F-COPD has been perceived as homogeneous primary neutrophil, but recent studies have shown that both the inflammation [10, 11] but also the etiology [12-14] are heterogeneous. It has been shown that a subset of patients with F-COL have eosinophilic inflammation [15]. This particular subgroup has an increased risk of being hospitalized with a severe exacerbation of their COPD [16], but at the same time they have a good therapeutic effect of inhaled corticosteroid (ICS) [17-19].

A meta-analysis from 2007 examined how several factors influenced the risk of re-admissions with F-COP. The factors that were found to significantly increase the risk of re-admissions were, for example, treatment with high accumulated dose of oral corticosteroid (P value = 0.006, OR = 1.55, 95% CI [1.13; 2.11,]), admission time over 5 days, status as care home resident, previous admissions within 1 year (P value = 0.0001), Dyspnea grade 2,3 and 4, and increased PaCO2 (P value = 0.025, OR = 1.04, 95% CI = [1.01; 1.08]). In addition, they found that low FEV1 is associated with increased risk of re-admission, high-dose systemic corticosteroid therapy is associated with shorter time for re-admission and long-term use increases the risk of re-admission [2].

A study from 2006 examined the effectiveness of an "integreted care program" on the number of re-admissions for COPD patients. The intervention consisted, among other things, of patient education and adoption go to a special nurse via a web-based call center. In the study, there was a significant reduction in re-admissions to the intervention group [20]. An additional study, which highlighted the differences between control and intervention groups, found that the patient's knowledge about COPD was significantly different. This could potentially explain the reduced number of admissions, as these patients can more clearly identify a worsening (P value = <0.001) and thus initiate treatment early (P value = 0.036) [21].

Studies have shown that there is a correlation between low BMI and severe COPD. It is estimated that underweight people are more prone to emphysema. COPD patients with a high BMI have a better prognosis than patients with low BMI [22].

Few studies have evaluated the effect of the influenza vaccine on the number of exacerbations of COPD. However, they find a significant reduction in the total number of exacerbations in vaccinated subjects compared to those receiving placebo [7].

To our knowledge, it has not before been investigated what effect a multifactorial medical optimization effort will have on the number of admissions with F-COPD. The intervention will consist of several sub-elements, each of which has documented effect on the reduction of the number of admissions for this patient group, including the influenza vaccine [7, 23, 24], pneumococcal vaccine [25, 26], ICS [17-19], physically. exercise [27-29], smoking cessation [30], weight optimization by dietician [31], diagnosis and treatment of diabetes mellitus [32], cardiac clearance and optimization [8, 33], N-acetylcysteine (high-dose mucolytic therapy) [34], Roflumilast [35, 36], inhaled corticosteroid by eosinophilic inflammation and COPD [17-19, 37], azithromycin [34, 38], hemilitic (LTOT) [39] and home-NIV [40].

1.2 Purpose

The purpose of the study is to investigate whether or not

1. A targeted medical optimization effort can reduce the number of admissions with F-COP within 12 months.
2. The effort can reduce the 12-month mortality.
3. The effort gives the patient a better understanding of his illness, and thus is able to act more quickly on symptoms of a worsening
4. The intervention can increase the overall health, measured by CAT, SF-36 and HADS, in the individual patient.
5. The effort can increase overall health, measured by standard blood tests, HS-CRP, eosinophilic granulocytes, Lp-PLA2, blood pressure, ECG, 6 min walking test, spirometry, MRC, smoking status, prednisolone consumption, BMI and pulse oximetry.
6. The effort can lead to a reduced consumption of corticosteroid in the individual patient.

2. Search strategy

The literature for this study has been searched in the database PubMed.

A combination of the following keywords has been sought: COPD, chronic obstructive lung disease, readmitted, readmitting, exacerbation, BMI, smoking cessation, ICS, NIV, Roflumilast, LTOT, rehabilitation, Eosinophils, influenza vaccine, and pneumoccal vaccine.

3. Method

The study is an open-label randomized multicenter intervention study designed to investigate the effect of a multifactorial medical intervention on the number of hospitalizations in patients with exacerbation in their COPD, compared to conventional treatment.

This study will be conducted as a prospective, open-label, randomized intervention study in patients with worsening of their COPD. It is expected that 718 patients will be included in the project during 24 months. 359 patients are allocated to each of the two groups (the intervention group and the control group) using stratified blood randomization, ensuring equal distribution of patients at the site and age.

Patients will be randomized to one of the following two treatment groups:

a) Control group:
   - Conventional treatment
b) intervention group:
   - Influenza and pneumococcal vaccine, physical exercise, ICS for eosinophilic granulocytes> 0.3x109 / L, dietician, smoking cessation aid, N-acetylcysteine, Roflumilast, Azithromycin, treatment optimization of diabetes mellitus and cardiac dysfunction, home and HIV

Both patient groups continue their usual COPD treatment, but the intervention group is offered a structured course with treatment of any co-morbidities that may affect COPD.
The program will be completed with a PhD student as coordinator.

3.1 Recruitment, inclusion and centers

At each center, consecutive screening of patients admitted with F-COPD is performed. Patients admitted with F-COPD will be assessed either at the Joint Emergency Reception or at the pulmonary medicine department in relation to inclusion and exclusion criteria. If a patient is considered suitable, the person concerned will be invited to participate in the project, and informed consent will be obtained after oral and written participant information. The pulmonary medical officer at each center helps with inclusion.

Inclusion of 718 patients is expected to be distributed almost equally at the four centers over 18 months: 180 patients from the Lung Medicine Department at Gentofte Hospital, 179 patients from the Lung Medicine Department at Bispebjerg Hospital, 180 patients from the Lung and Infectious Medicine Department at Hillerød Hospital and 179 patients from the Lung Medicine Department at Hvidovre Hospital. An experimental officer has been appointed at each of the four departments who will be responsible for teaching staff, inclusion of patients and data collection. The trial managers at Hillerød, Bispebjerg and Hvidovre hospital are members of the board of the study.

3.2 Inclusion criteria

- Patients which is hospitalized with deterioration in COPD as a primary diagnosis.

- Spirometry-verified and specialist-assessed COPD (defined as FEV1 / FVC ≤ 70%)

- GOLD Class C or D

3.3 Exclusion criteria

• Expected lifetime less than 30 days

• Severe deterioration requiring invasive ventilation or intensive care

• Severe mental illness that is not controlled with medication

• Persons who are detained under the Act on the use of coercion in psychiatry

• People with dementia

• Severe linguistic problems or inability to give informed informed consent

• Pregnancy or breast-feeding

3.4 Randomization

Randomization to conventional treatment or the multifactorial medical effort, respectively, will occur by a computer-generated randomization sequence. Patients are divided equally between the two arms using the randomization program REDCap. Here, inclusion and exclusion criteria are entered, and the system will not allow to randomize participants who do not meet the inclusion criteria.

3.5 Clinical tests and data collection.

This chart illustrates the information to be obtained, as well as the clinical tests to be performed at the various follow-ups during the test period. This applies to both the control and intervention group.

	Baseline	Follow-ups			
Visit	1	2	3	4	5
Weeks	0	4	12	25	52
Days	0	30	90	187	365
Interval allowed		± 7 days	± 7 days	± 7 days	± 7 days
Informed consent	X				
Inklusion/exclusion	X				
Urine-hCG)[1]	X				
No. of acute admissions with COPD exacerbation within 12 months	X				
MDI – Depression screening	X				
MMSE – Dementia screening					
CT-scanning – Screening for lung cancer	X				
Spirometry (FVC, FEV_1)	X	X	X	X	X

Dyspnea scale (MRC)	X	X	X	X	X
Blood pressure	X	X	X	X	X
Smoking status (Smoker, previous S, Never S. Pack Years)	X	X	X	X	X
Prednisolone use	X	X	X	X	X
ECG	X		X	X	X
Echocardiography[2]	X				
CAT (COPD Assessment Test)	X	X	X	X	X
SF-36 (Self assessed)	X	X	X	X	X
HADS (Depr + anxiety)	X	X	X	X	X
6MWT	X	X	X	X	X
Pulse oximetry	X	X	X	X	X
BMI	X	X	X	X	X
Biochemistry:					
WBC + differential count	X	X	X	X	X
Glucosis + HbA1c	X	X	X	X	X
Liver: (ALAT, Albumine, ASAT, bilirubin, amylase, alcaline phosphatase, coagulation factors II, VII and X)	X	X	X	X	X
Kidney (K+, Na+, urea, creatinine)	X	X	X	X	X
Heart (BNP/pro-BNP, CK-MB, troponin I/T)	X	X	X	X	X
CRP, D-dimer + LDH	X	X	X	X	X
TSH	X	X	X	X	X
Haemoglobine + Platelets	X	X	X	X	X
INR	X	X	X	X	X
Biobank (Serum + Plasma)	X	X	X	X	X
Endpoints:					
Admissions		X	X	X	X
No days admitted		X	X	X	X
Self-reported illness		X	X	X	X
Visits to GP		X	X	X	X

[1]All women of childbearing age (<55 years).
[2]Echocardiography will be performed unless there is one available less than 3 months old.

3.6 Intervention

Intervention will consist of 6 items.

1. Inhalation therapy.

It must be ensured that patients receive the optimal inhalation therapy for their COPD. All patients in the intervention group should receive inhalation therapy unless intolerance to the active substances develops. At baseline, it is determined whether the patients have an eosinophilic inflammation. Only patients with eosinophilic inflammation as well as self- or doctor-reported asthma will receive ICS treatment. First choice preparation will be either Oladoterol/Tiotropium or Indacaterol/Glycopyrronium. The patients who qualify for ICS treatment will receive Trimbow as the first choice drug.

2. Supplemental COPD treatment

Roflumilast: If indicated, treatment with roflumilast will be tried for one month. A novel introduction strategy recently published will be used to reduce gastro-intestinal side effects.

Acetylcysteine: Patients will be offered this, if indicated.

NIV: All patients will be tested for nocturnal respiratory acidosis. If this is present, they will be referred for nocturnal "home" Non-Invasive Ventilation (NIV)

Long Term Oxygen Therapy (LTOT): All patients will be tested for de-saturation in rest (<7.4 KPa oxygen pressure). If so, they will be offered LTOT.

3. Infection prophylaxis

All patients in the intervention group will receive influenza and pneumococcal vaccination if they have not already received the current vaccine. These are maintained throughout the entire intervention period with the latest vaccines.

Patients who have frequent admissions (> 3 yearly) will receive Azithromycin prophylactically. Arrhythmias, QT interval> 450mm as well as hearing loss are all contraindications for treatment and will be excluded before the start of treatment. A dose of 250 mg is given 3x weekly t. The treatment is reassessed every 3-6 months.

4. Smoking cessation

All patients in the intervention group will receive advice on smoking cessation. They will Get rid of smoking cessation material, the number for the smoking cessation line and offers for the discharge of pharmacological aids such as nicotine substitution, bupropion, and varenicline.

5. Training and rehabilitation

Physiotherapist based training will be provided for all patients in the intervention group.

6. Optimization of comorbidity treatment

All patients will be tested for the following:

- HbA1c
- Echocardiography, unless one is available that are less than 3 months old.
- Depression screening by MDI.

If indication is found for optimizing of know treatment or start of new treatment this will be provided according to current treatment guides.

7. Patient education and support.

All patients will receive patient training and materials on COPD.

Patients with a BMI < 18,5 or > 25 will receive guidance from a dietitian.

This chart illustrates the actions of the multifactorial medical intervention received by the intervention group. At the same time, the control group must register which treatment they receive during the test period.

Days	0-90	90-187	187-365
LAMA/LABA[1] (always)	X	X	X

ICS if eosinophils > 0,3x10^9/l	X	X	X
ICS if asthma[2]	X	X	X
Roflumilast (if indicated)	X	X	X
N-Acetylcystein (if indicated)	X	X	X
Home-NIV (if indicated)	X	X	X
Long term oxygen treatment (LTOT) (if indicated) (tested)	X	X	X
Influenza vaccine	X		
Pneumococcal vaccine	X		
Azithromycin (if indicated)	X	X	X
Smoking Cessation Programme[3]	X		
Fysisk træning ved fysioterapeut	X	X	X
Optimized cardiological treatment	X	X	X
Optimized diabetic treatment	X	X	X
Patient Education	X		
Dietitian if BMI < 18,5 og > 25	X		

[1]All patients with patient or doctor reported asthma will receive ICS treatment.

[2]All patients receive LAMA / LABA treatment unless intolerance to the active substances occurs.

[3]Help for smoking cessation by delivery of smoking cessation material, number for the smoking cessation hotline and offer for prescription of pharmacological aids (eg varenicline or nicotine replacement)

3.7 Research plan and data collection

Inclusion of patients, data collection, processing, statistical analysis and publication of the data material will be carried out by a doctor, PhD student in collaboration with supervisors and COP: TRIN's other members. The randomized trial has begun with inclusion of patients from 1. February 2020 and the last patient is expected to be included no later than 1. September 2021. Data collection ceases 1. September 2022. A nurse and the PhD student will be responsible for blood sampling and examinations at day 0 and at the one, three, six and twelve months follow-ups respectively. Decisions of a medical nature will, as a rule, only be delegated to a doctor (cf. section 7 (4) of the GCP Order).

In addition, an agreement is entered into with the GCP unit at the University of Copenhagen in order to monitor the trial at the four centers.

Information from patient records is passed before consent to identify suitable patients for recruitment. The on-call physician at each of the 4 recruitment centers asks potential subjects whether they want to hear more about the trial. If they so wish, the supervising doctor will contact one of the trial officers at the department who will inform the patient about the study. Thus, no other information will be retrieved from the patient's record before consent. The consent will give trial managers, the GCP and any control authority directly access to obtain information in the patient's journal, including electronic journal, regarding the patient's health conditions, diagnoses and medication, and for control purposes, including self-control, quality control and monitoring. Collected data will be treated confidentially by the staff associated with the project. Data collected after consent is given will be reported in Case Report Forms (CRF) specifically for each patient. Here, demographic data, health status, current illnesses, current medication, hospital admissions, study results and which interventions have been carried out before and during the follow-up

period are recorded. This information must be used to answer the project's hypotheses regarding the patient's state of health and the number of admissions with exacerbations. CRF is kept in locked archives for the departments involved for 15 years. Data in CRF is entered by the lead investigator at each center, or the local project nurses working with COPD research.

3.8 Establishment of research biobank

A research biobank is set up with blood samples for patients with F-COPD, who are included in the project. All participants receive blood samples by inclusion at one, three, six and twelve months follow-up. The biobank may be used for blood samples, plasma and serum samples. A total of 100 ml of blood will be withdrawn from each patient from inclusion to completion at 12 months of follow-up. All blood samples are frozen down to -80 ° C. The freezers are in locked rooms on each of the four lung medicine departments for analysis before the end of the project. The samples are kept in anonymous form. The biobank will expire at 1. February 2035. This research biobank will be used to answer the project's hypotheses. Excess biological material will be transferred to a biobank for future research (see below).

The analyzes consist of standard blood test studies for health status assessment: Hgb, leukocytes + differential count, platelets, HDL, LDL, cholesterol, glucose, HbA1c, liver (ALT, AST, albumin, bilirubin, amylase, alkaline phosphatase, coagulation factors II, VII and X, INR), kidney numbers (K +, Na +, urea, creatinine), heart markers (BNP / pro-BNP, CK_MB, troponin I / T), CRP, D-dimer, LDH, TSH, T3, and T4. In addition, it is analyzed for HS-CRP, Lp-PLA2 and Eosinophilic granulocytes.

Permission is sought from the Danish Data Protection Agency for the establishment of a research biobank, with the aim of benefiting future COPD research. This biobank for future research projects will be used to clarify the following hypothesis: 1) Biomarkers for lung damage can accurately ("diagnostic accuracy studies") determine whether a COPD patient has, or will soon have, a worsening in COPD disease (COPD exacerbation) , 2) Biomarkers from metabolic processes in patients with COPD who can improve understanding of disease development (pathogenesis) at COPD, 3) The severity of the role of co-morbidities in disease development at COPD and worsening in COPD. Biomarkers collected during the project will be stored locked and in anonymous form, cf. the applicable rules. The biobank can only be used for other research projects if a separate approval is submitted by the Danish National Committee on Health Research Ethics and the Danish Data Protection Agency. Furthermore, each participant must sign a separate informed consent for their material to be stored.

4. Statistical considerations and power calculation

With conventional alfa of 0.05 and power of 0.8 and expected reduction in re-admittance to hospital from 40% (National Danish Data from “DR-KOL” registry, thus expected in control arm) to 30%, Group-sequential design and O´Brien-Fleming method and two interim analyses, **718** patients will be needed.

Interim data assessments will be made by an independent Data and Safety Monitoring Board (DSMB). Data on primary and secondary efficacy measures will be used for this. DSMB will review the protocol, monitor the guideline, evaluate the experiment with regard to recruiting participants, participant's risk and, based on interim analyzes, make recommendations to the investigators on whether the study program should continue or be terminated. In addition, DSMB may at any time require an extraordinary interim analysis.

4.1 Endpoints

Primary endpoint:

- Number of admissions or death within 12 months.

Secondary Endpoints:

- Number of days admitted within 12 months
- Number of sick days within 12 months
- Number of visits to own doctor within 12 months
- Change in lung function (ΔFEV1) from baseline, as well as in one, three, six, and twelve months follow-up.
- 365 days mortality (access via patient record)
- Antibiotic-demanding infections within 180 days after index deterioration in COPD (approach via patient record and questionnaire)
- The period between index deterioration in COPD and the next deterioration in COPD (approach via patient record and questionnaire)
- COPD Assessment Test (CAT) at baseline and at one, three, six, and twelve months follow-up
- MRC degree at baseline, and at one, three, six, and twelve months follow-up

4.2 Stage II

Assessment of outcome over the longer term than 12 months will occur in a stage II of the study. The study will move to stage II after the intervention. In Stage II, the endpoints below will be assessed by 2, 3 and 5 years. The results of these assessments will be published separately.

Long Term Assessment Endpoints:

- Number of admissions. To be assessed at 24, 36 and 48 months
- Mortality. To be assessed at 12, 24, 36 and 48 months

After completing the intervention in this study, the primary and secondary short-term endpoints will be analyzed. Then a post-conditional strength calculation is made that will be at argue whether more patients are required to be recruited to stage II of the PERISKOP project.

Stage II of the study is not yet fully planned. This part of the study will be reviewed by addition to the Danish National Committee on Health Research Ethics when this becomes relevant.

This does not change the fact that the primary results of this study will be analyzed and published after the 12-month follow-up period of the 718 planned patients is completed.

Stage II of this study will result in an expected recruitment of an additional approx. 500 patients in an observational manner (no interventions).

4.3 Data analysis

Data is processed and analyzed in SAS version 9.4.

5. Risks, incidents and side effects

In blood sampling, there is a small risk of infection or blood accumulation at the site of injection. In addition, the study may be associated with discomfort in connection with insertion of the needle.

In the case of influenza vaccination, local reactions (soreness) may occur at the site of injection and, less frequently, general malaise, fever and muscle pain, which usually resolve within 1-2 days without treatment. Pneumococcal vaccination may give rise to fever and local reaction in the form of redness, swelling and soreness at the injection site. After vaccination, irritability, vomiting, diarrhea and decreased appetite are also seen.

X-rays associated with CT scan of the thorax correspond to 9 mSv per scan. This must be compared with a background radiation of approx. 4 mSv per. years in Denmark. Statistically, the risk of getting cancer after one CT scan is very small and ranges from 1 in 10,000 to 1 in 1,000 (0,1-0,01%). In rare cases, the contrast agent (Iomeron®) may cause serious side effects.

Iomeron® has the following side effects cf. pro.medicin.dk

Common (1-10%) - Heat sensation

Uncommon (0.1-1%) - Dyspnea, Hypertension, Dizziness, Erythema

Rare (0.01-0.1%) - Bradycardia, Hypotension, Ventricular Extrasystole, Back Pain, Ridility.

Azithromycin has the following side effects, see pro.medicin.dk:

Very common (> 10%) - Abdominal pain, diarrhea, flatulence, and nausea.

Common (1-10%) - Powerlessness, Decreased appetite, Vomiting, Disturbances in taste, Agranulocytosis, Reduced serum bicarbonate, Arthralgia, Headache, Paresthesia, Dizziness, Skin itching, Skin rash and Visual disturbances.

Uncommon (0.1-1%) - Pain, hepatitis, Oral candidiasis, dyspnea, pneumonia, edema, eosinophilia, leukopenia, neutropenia, increased serum bicarbonate, Hyperchloridæmi, hyperglycemia, Hyperkalemia, Hypernatraemia, hypokalaemia, hyponatraemia, arthritis, back pain , Nervousness, somnolence, facial edema, dermatitis, photosensitivity, candidiasis, infections, metrorrhagia, kidney pain, testicular disease, vaginitis, hearing loss, and tinnitus.

Rare (0.01-0.1%) - Cholestasis, Liver Impact, Agitation, Acute Generalized Exanthemous Pustulose *, Allergic Reactions *, Angioedema *, and Hypersensitivity.

* In case of allergic reactions, Azithromycin should be discontinued.

Acetylcysteine has the following side effects, cf. pro.medicin.dk:

Very common (> 10%) - Diarrhea and Nausea

Uncommon (0.1-1%) - Abdominal pain and bronchospasm.

Rare (0.01-0.1%) - Angioedema.

Roflumilast has the following side effects, cf. pro.medicin.dk:

Very common (> 10%) - Decreased appetite, weight loss, abdominal pain, diarrhea, nausea, headache and insomnia.

Uncommon (0.1-1%) - Muscle weakness, Anxiety, Dizziness, Tremor and Hypersensitivity.

Rare (0.01-0.1%) - Hematocrit, Gynecomastia, Depression, Nervousness, Angioedema and Respiratory Infection.

The pharmacological excipients for smoking cessation have no documented serious side effects, rarely releasing the convulsions when using bupropion.

An adverse reaction (AR) is defined as any adverse and undesirable reaction to a test drug regardless of dose. Since the trial drugs are well-known and used for approved indication, and since the study is only interested in the medicinal long-term effects of the drugs, only side effects not mentioned in the respective product summary of the test drug are recorded.

An adverse event: AE is defined as any undesirable event in a subject in a clinical trial after treatment with a drug, without necessarily being related to this treatment and the adverse event. The following events are expected for patients with COPD and will therefore not be recorded as adverse events: Cough, respiratory mucus, shortness of breath, wheezing, chest tightness, palpitations, lower abdominal swelling, agitation, anxiety, sleep disturbances, joint swelling, fatigue, anxiety, sleep disturbances, joint swelling, fatigue, anxiety, sleep disturbances, mourning, fatigue, dizziness, sleep disturbances, mourning, fatigue, dizziness, sleep disturbances, mourning, not clinically significantly increased infection parameters.

A severe or severe adverse reaction (event: SAR / SAE) is defined as an event or adverse event which, irrespective of dose, results in death, is life-threatening, involves hospitalization or hospitalization, results in significant or persistent disability or incapacity. or leads to a congenital anomaly or malformation. See. above, F-KOL should not be registered as SAE.

Investigator must report all serious events (Serious Adverse Events) to sponsors as soon as possible. Sponsors must ensure that all information about SUSAR's (Suspected Unexpected Serious Adverse Reaction), which is fatal or life-threatening, is recorded and reported to the Danish Medicines Agency and NVK within 7 days after the sponsor has become aware of a suspected adverse reaction. Within 8 days of the report, the sponsor must inform the Danish Medicines Agency and the NVK about the sponsors and investigator's follow-up to the report. All other SUSARs must be reported to the Danish Medicines Agency and NVK no later than 15 days after the sponsor has gained knowledge of these. At the same time, the investigators are informed at the other centers.

All incidents and registered side effects are reported at the end of the trial in a final report to the National Board of Health (SST). All serious suspected events / side effects should be recorded annually and a report on the safety of the subjects d must be prepared. The serious side effects must also be stated in the final report to SST.

6. Exclusion from and interruption of trial

If the attending physician at a center deems it necessary (medical risk, safety risk, or other circumstances), the subject may at any time take the subject out of the investigation. However, this must be done in agreement with the coordinating investigator. The coordinating investigator can be contacted 24 hours a day.

In this case, the researcher must be informed immediately and the possibilities for the further treatment must be discussed with the subject. Likewise, a subject may at any time withdraw his consent to participate in the trial. It will not have any consequences for the further treatment.

Since the study is not a drug trial, the incidence of adverse events is not a sufficient reason for discontinuation of the study.

7. Financial matters

This study is the Investigator initiated project. Initiator of the project is the steering committee for the COP: STEP. The project is budgeted for DKK 6,011,265. This includes salaries for one PhD student, enrollment of PhD students at the University of Copenhagen, project nurse for data collection, performance of laboratory work and diagnostic tests, creation and maintenance of database / website, CRF, and medical expenses. The trial is financed partly by the participating lung medicine departments. At the same time as the recruitment will be applied for additional coverage of expenses from different funds. Scientific ethics committee will be informed regularly as funding from funds is achieved. At the same time, the participant information will be updated.

The members of the project group have no financial interest in the problem examined. The study is not supported by pharmaceutical companies or other organizations of economic interest in the study.

7.1. Remuneration

Participants will not receive a fee for participation.

8. Availability of Information

It is the board's conviction that knowledge sharing creates more and better scientific results. Requests for knowledge sharing from other groups will be submitted to the Steering Committee, and if the hypothesis to be examined is not planned to be examined by our group, we will allow the use of our data. However, it should be emphasized that data can be used for a particular purpose, not for future purposes in general. This is categorized by the Steering Committee with a view to maintaining a sound testing of hypotheses with a relevant scientific content.

9. Publication of test results

The experiment is part of minimum 2 PhD theses (several substudies, biobank, cohort gathered) . The results of the trial will be published regardless of whether they are positive, negative or inclusive. Publication in international high-impact peer-reviewed scientific journals is expected. When published in a journal, the results will also be made accessible at www.coptrin.dk .

10. Scientific ethics statement

A worsening of COPD is extremely unpleasant for patients, as it often causes increased dyspnoea, coughing, sputum and anxiety. Patients suffer from a psychological burden of hospitalization, while acute exacerbation of COPD is associated with significant morbidity and mortality. The financial burden for society according to the treatment of F-COP is significant. Therefore, there is a great deal of interest both at the patient and community level to reduce the number of admissions in connection with F-COPD.

The beneficial effects of the various parts of the intervention are well documented, and therefore the subjects are not exposed to unnecessary risk when participating in the project. The results of the research project, on the other hand, could potentially contribute to promoting the current treatment of patients with COPD so as to avoid hospitalization, as well as the discomfort that comes with an F-COPD, and that society thus saves significantly on financial resources.

The research project is carried out according to the Helsinki Declaration and is implemented in accordance with the rules of the Personal Data Act and the Health Act. The patients can withdraw their consent at any time and withdraw from the research project without this having any consequence for their current or future treatment.

In the event that significant information on the individual's health condition occurs during the trial, this will be provided in writing both orally to the subject concerned, unless this has unambiguously denied this in advance in the signed consent statement.

11. Informed consent

Participation in the experiment is voluntary. Informed consent is obtained from the participants of the trial, in particular, Executive Order No. 1083 of 15 September 2017 on information and consent to participation in health science research projects, as well as on notification and supervision of health science research projects. The subjects are recruited during admission to the pulmonary medicine department at the four centers. The on-call doctor asks potential subjects if they want information about the study. If desired, a physician on duty will contact one of the investigators who inform the patient about the study. Participant information is given both orally and in writing on the day of admission, and the patient then has a reflection period of min. 24 hours. The patient may possibly bring an adherent to the next interview, where the consent declaration is signed, if the patient will participate in the study. The conversations take place undisturbed in one of the department's talk rooms arranged for this. The right to confidants will appear in the participant information. As the patients are often hospitalized for more than one day, information about the study as well as obtaining a signature of the consent declaration will take place during admission.

The trial responsible doctor will not always be available and since samplesize is limited, a group of Investigators will be set up at all centers, who work under the experimental manager. These will assist in

the recruitment of subjects. All Investigators will be doctors with GCP education and experience in treating lung diseases. 17 Subjects are protected in accordance with the Data Protection Regulation and the Data Protection Act. It is the responsibility of the investigators to ensure that the data protection rules are complied with in connection with processing personal data in the project. The trial is notified, via the joint notification in the region, to the Regional Committee on Health research Ethics, the Danish Health Authority and the Danish Data Protection Agency.

12. Information on compensation or compensation schemes

Patients who believe that they have suffered injury can apply for compensation, cf. Consolidated Act No. 1113 of 7 November 2011 on Access to Compensation and Compensation in the Health Service.

13. References

1. Flachs EM, E.L., Koch MB, Ryd JT, Dibba E, Skov-Ettrup L, Juel K. Statens Institut for Folkesundhed, Syddansk Universitet., Sygdomsbyrden i Danmark – sygdomme. 2015, Sundhedsstyrelsen: København.

2. Bahadori, K. and J.M. FitzGerald, Risk factors of hospitalization and readmission of patients with COPD exacerbation--systematic review. Int J Chron Obstruct Pulmon Dis, 2007. 2(3): p. 241-51.

3. Soler-Cataluna, J.J., et al., Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax, 2005. 60(11): p. 925-31.

4. Landspatientregisteret. [cited 2018 November 11.]; Available from: http://www.esundhed.dk/sundhedsregistre/LPR/Sider/LPR01_Tabel.aspx?rp:A_Soegeord=&rp:D_Aar=2012%7C%7C%7C2013&rp:C_Koen=-1%7C%7C%7C1%7C%7C%7C2&rp:C_Alder=-1&rp:B_Diagnose=9644.

5. Afdeling for Sundhedsanalyser, L.o.S., Borgere med KOL - kontaktforbrug i sundhedsvæsenet og medicinforbrug. 2016, Sundhedsdatastyrelsen.

6. Hurst, J.R., et al., Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med, 2010. 363(12): p. 1128-38.

7. GOLD. 2018; Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.

8. Hawkins, N.M., et al., Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail, 2009. 11(2): p. 130-9.

9. Divo, M.J., C.H. Martinez, and D.M. Mannino, Ageing and the epidemiology of multimorbidity. Eur Respir J, 2014. 44(4): p. 1055-68.

10. Bhowmik, A., et al., Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax, 2000. 55(2): p. 114-20.

11. Saetta, M., et al., Airway eosinophilia in chronic bronchitis during exacerbations. Am J Respir Crit Care Med, 1994. 150(6 Pt 1): p. 1646-52.

12. Papi, A., et al., Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med, 2006. 173(10): p. 1114-21.

13. Seemungal, T., et al., Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2001. 164(9): p. 1618-23.

14. Sethi, S. and T.F. Murphy, Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med, 2008. 359(22): p. 2355-65.

15. Saha, S. and C.E. Brightling, Eosinophilic airway inflammation in COPD. Int J Chron Obstruct Pulmon Dis, 2006. 1(1): p. 39-47.

16. Vedel-Krogh, S., et al., Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med, 2016. 193(9): p. 965-74.

17. Cheng, S.L., Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis, 2018. 13: p. 2775-2784.

18. Barnes, N.C., et al., Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J, 2016. 47(5): p. 1374-82.

19. Pavord, I.D., et al., Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax, 2016. 71(2): p. 118-25.

20. Casas, A., et al., Integrated care prevents hospitalisations for exacerbations in COPD patients. Eur Respir J, 2006. 28(1): p. 123-30.

21. Garcia-Aymerich, J., et al., Effects of an integrated care intervention on risk factors of COPD readmission. Respir Med, 2007. 101(7): p. 1462-9.

22. Lim, J.U., et al., Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis, 2017. 12: p. 2465-2475.

23. Hovden, A.O., R.J. Cox, and L.R. Haaheim, Influenza: the virus and prophylaxis with inactivated influenza vaccine in "at risk" groups, including COPD patients. Int J Chron Obstruct Pulmon Dis, 2007. 2(3): p. 229-40.

24. Sehatzadeh, S., Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review. Ont Health Technol Assess Ser, 2012. 12(3): p. 1-64.

25. Tomczyk, S., et al., Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep, 2014. 63(37): p. 822-5.

26. Walters, J.A., et al., Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 2017. 1: p. Cd001390.

27. Lalmolda, C., et al., Effect of a rehabilitation-based chronic disease management program targeting severe COPD exacerbations on readmission patterns. Int J Chron Obstruct Pulmon Dis, 2017. 12: p. 2531-2538.

28. Maddocks, M., et al., Rehabilitation following hospitalization in patients with COPD: can it reduce readmissions? Respirology, 2015. 20(3): p. 395-404.

29. Puhan, M.A., et al., Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality -- a systematic review. Respir Res, 2005. 6: p. 54.

30. Borglykke, A., et al., The effectiveness of smoking cessation groups offered to hospitalised patients with symptoms of exacerbations of chronic obstructive pulmonary disease (COPD). Clin Respir J, 2008. 2(3): p. 158-65.

31. Ferreira, I.M., et al., Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 2012. 12: p. Cd000998.

32. Mannino, D.M., et al., Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J, 2008. 32(4): p. 962-9.

33. Kaushal, M., et al., Chronic obstructive pulmonary disease and cardiac comorbidities: A cross-sectional study. Lung India, 2016. 33(4): p. 404-9.

34. Wedzicha, J.A., et al., Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J, 2017. 50(3).

35. Shen, L.F., et al., Effect of roflumilast on chronic obstructive pulmonary disease: a systematic review and meta-analysis. Ir J Med Sci, 2018. 187(3): p. 731-738.

36. Martinez, F.J., et al., Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet, 2015. 385(9971): p. 857-66.

37. Watz, H., et al., Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med, 2016. 4(5): p. 390-8.

38. Ni, W., et al., Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. PLoS One, 2015. 10(3): p. e0121257.

39. Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis. Ont Health Technol Assess Ser [Internet] March 2012 [cited 12 7]; 1-64]. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_LTOT_March.pdf.

40. Duiverman, M.L., Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? ERJ Open Res, 2018. 4(2).