The CODEX-P Trial
[CopD EXacerbation and Pulmonary hypertension Trial]

Copenhagen19/NOV/2020, v. 2 .2

PROTOCOL

Organization: COP:TRIN -Chronic Obstructive Pulmonary Disease Trial Network: http://www.coptrin.dk

Research questions:

→ In patients with exacerbation of Chronic Obstructive Pulmonary Disease (COPD), identification of a subgroup of patients with elevated pressure in the pulmonary circulation (COPD-PH) and targeted pharmacological treatment of the condition can shorten the hospital stay and improve survival ←

This study is part of COPTRIN's (http://www.coptrin.dk) cluster of studies for personal medicine within Chronic Obstructive Pulmonary Disease, a strategy that so far also counts:

- **"TARGET-ABC" (reduction of antibiotic side effects in chronic lung infections), approved, funded by DFF, started in 2017.**
- **"CORTICO-COP" (biomarker-guided reduction of systemic adrenal cortex hormone treatment), approved, funded by DFF and the Regions' Medicines Fund, started in August 2016.**
- **”ProBe-COVID” with patients who are admitted acutely and who have a positive test for 2019-nCoV and symptoms similar to COVID-19 disease, treatment with corona-virus-inhibiting substance hydroxychloroquine and azithromycin lead to shorter hospital stays and fewer hospital admissions, ongoing study.**
- **-” COPERNICOS” biomarker-guided reduction of inhaled steroid in patients with COPD, starting in November 2020.**

Time schedule:

November 2020 - October 2023 (incl. initiation, study period and completion/publication).

Coordinating investigator:

Ema Rastoder, MD, PhD- student, Research Unit, Department of Pulmonary Medicine, Herlev-Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup, tel.: 38 67 35 13

Supervisors:

Jens-Ulrik Jensen, professor of respiratory medicine, and research leading senior consultant, PhD.
Pulmonary Medicine Section, Dept. C, Herlev & Gentofte Hospital, Hellerup &
ICU Division, CHIP (Center of Excellence for Health, Immunity and Infections), Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, tel.: 35 45 57 57.

Jørn Carlsen, senior consultant, associate professor, D.M.Sc.
Clinic of Cardiology, sect. 2142, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen

Pradeesh Sivapalan, MD, PhD Resp. Trainee, Post Doc Section of Respiratory Medicine, Herlev-Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup, tel.: 38 67 35 13.

Partner:

Tor Bjerring-Sørensen, associate professor, PhD, Department of Cardiology, Gentofte Hospital.

Kasper Hasseriis Andersen, MD, PhD-student, Clinic of Cardiology, Rigshospitalet
Department of Cardiology, section 2142, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen

Rasmus Lykke Marvig, M.Sc., PhD, Center for Genomic Medicine, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø

Malene Rohr Andersen, M.Sc., PhD, Clinical Biochemistry Department, Gentofte Hospital, Kildegårdsvej 28, 2900 Herlev

Experimental centers:

1st Department of Pulmonary Medicine, Gentofte hospital, Kildegårdsvej 28, 2900 Hellerup

Primary investigator: Coordinating investigator, Ema Rastoder MD, PhD-student.

The COPTRIN network makes it possible to expand to the following centers:

Department of Pulmonary Medicine, Bispebjerg hospital, Bispebjerg Bakke 23, 2400 Copenhagen.

Primary investigator: Helle Frost Andreassen, leading senior consultant, PhD.

Department of Pulmonary and Infectious Diseases, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød.

Primary investigator: Thyge Lynghøj Nielsen, senior consultant, PhD.

Department of Pulmonary Medicine, Hvidovre Hospital, Kettegård Allé 30, 2650 Hvidovre.

Primary investigator: Ejvind Frausing Hansen, senior consultant, PhD.

Department of Pulmonary Medicine, Aarhus Hospital, Nørrebrogade 44, 8000 Aarhus C.

Primary investigator: Anders Løkke, senior consultant, PhD.

Department of Pulmonary Medicine, Aalborg Hospital, Hobrovej 18 -22, 9000 Aalborg.

Primary investigator: Ulla M. Weinreich, senior consultant, associate professor, PhD.

Department of Pulmonary Medicine, Odense Hospital, Southern Blvd. 29, 5000 Odense C.

Primary investigator: Christian Laursen, senior consultant, PhD.

GCP monitoring:

The GCP-unit, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 København NV,

Contact person: aa bb, tel.: 38 63 56 24

COP:TRIN, steering committee (steering committee members are mentioned first, then investigators):

1st Department of Pulmonary Medicine, Medical Department, Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup:

- Jens-Ulrik Jensen, professor of respiratory medicine, research leading senior consultant, PhD.
- Niels Seersholm, D.M.Sc., PhD.
- Pradeesh Sivapalan, MD, PhD, Post doc.

2. Department of Pulmonary Medicine, Hvidovre Hospital, Kettegård Allé 30, 2650 Hvidovre:

- Charlotte Ulrik, professor, senior consultant, D.M.Sc.
- Mia Moberg, senior consultant, PhD (SC member)
- Julie Janner, senior consultant, PhD (SC member)
- Rasmus Rude Laub, consultant.

3. Department of Pulmonary Medicine, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV:

- Helle Frost Andreassen, Leading senior consultant, PhD.
- Lars Pedersen, senior consultant, PhD.

4. Department of Pulmonary Medicine, Antwerp University Hospital, Belgium:

- Therese Lapperre, senior consultant, PhD.

5. Department of Pulmonary Medicine, Odense Hospital, 5000 Odense C, Denmark:

- Christian Laursen, senior consultant, PhD.

6. Department of Pulmonary Medicine, Aalborg Hospital, Hobrovej 18 -22, 9000 Aalborg:

- Ulla M. Weinreich, senior consultant, PhD.

7. Department of Pulmonary Medicine, Aarhus Hospital, Nørrebrogade 44, 8000 Aarhus C:

- Anders Løkke, senior consultant, PhD.

8. Department of Pulmonary and Infectious Diseases, Nordsjaellands Hospital, Dyrehavevej 29, 3400 Hillerød:

- Thyge Lynghøj Nielsen, senior consultant, PhD.

9. University of Manchester, Oxford Rd., Manchester, United Kingdom:

- Jørgen Vestbo, professor, MD, D.M.Sc.

10. Center for Genomic Medicine, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø:

- Rasmus Lykke Marvig, evolutionary researcher, M.Sc., PhD.

11. Department of Cardiology B, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø:

- Jørn Carlsen, senior consultant, associate professor, D.M.Sc.

12. Nordic Bioscience A/S, Herlev Hovedgade 207, 2730 Herlev:

- Morten Karsdal, adm. Director, PhD

Background information about the study drug:

Tablet Sildenafil.

The drug is an approved and marketed drug in Denmark for use in pulmonary arterial hypertension. Please see the enclosed product summary for further information.

1. Hypothesis and purpose:

1.1 Hypothesis:

In a subgroup of patients with exacerbation of Chronic Obstructive Pulmonary Disease (Acute Exacerbation of COPD, AECOPD), blood pressure in the pulmonary circulation increases, this causes shunting of unoxygenated blood to the left side of the heart and worsens existing hypoxemia and hypercapnia, which in turn stimulates contraction in the pulmonary circulation. Together these changes lead to organ dysfunction, prolonged period of illness and increased risk of death.

By decreasing the resistance in the pulmonary circulation pharmacologically, the above-mentioned changes completely or partially reverse and organ function and respiratory physiology can be ameliorated. This can shorten the time alive and to discharge from hospital.

1.2 Purpose:

The mortality rate associated with AECOPD admission and within the first month is approximately 20-25%. In chronic pulmonary hypertension, the general prognosis is worsened in COPD patients. However, it is unclear: 1) What the prevalence is of “acute reversible pulmonary hypertension in AECOPD” (AECOPD-rPH) in connection with AECOPD admission. 2) In the patients with AECOPD-rPH whether the prognosis is negatively affected by this. 3) In patients with AECOPD-rPH, whether the prognosis can be improved by drug treatment of this form of pulmonary hypertension.

The individual sub-goals are:

<u>Cohort study with 250 consecutive patients admitted with AECOPD:</u>

To clarify the prevalence of AECOPD-rPH. In order to differentiate this from chronic secondary pulmonary hypertension in connection with COPD, echocardiography is performed as indicated:

a. On day 1 = Baseline (<24 hours after admission and action diagnosis AECOPD). (+/- 3 days)
b. On day 29 = Baseline + 28 days (+/- 5 days)

To these days following will be determined:

- The prevalence of Tricuspid Return Gradient (TR) ≥40 mmHg in patients admitted with AECOPD as primary diagnosis.
- Median TR gradient.

The main analysis regarding this sub-goal is:

a. Prevalence of “acute reversible pulmonary hypertension in AECOPD”, defined as: (Prevalence of TR ≥40 mmHg day 1) - (prevalence of TR ≥40 mmHg day 11) in patients with AECOPD as primary diagnosis.
b. "All-cause mortality " on day 90 is determined for patients with and without "acute reversible pulmonary hypertension in AECOPD."

Randomized controlled intervention trial:

In patients with “acute reversible pulmonary hypertension with AECOPD/AECOPD-rPH.”:
"Number of days to discharge from hospital alive within 365 days" is determined for patients who received active treatment to reduce resistance and blood pressure in the pulmonary circulation with the drug Sildenafil, and in control patients who did not receive treatment with Sildenafil (open-label).

For analyzes of secondary endpoints, see below.

2. Background and scientific perspective:

2.1 COPD:

COPD is the leading cause of serious health problems as well internationally as nationally. In
Denmark, approximately 14% of people over 35 years, are affected by the disease (1). COPD is complicated by repeated acute exacerbations (AECOPD) characterized by worsening of symptoms, usually cough, increased sputum, and shortness of breath. AECOPD often leads to hospital admission and causes an accelerated loss of lung function, increased morbidity and mortality and has large economic consequences (2). In the first 12 months after an AECOPD, the risk of death is 15-28% (3, 4).

2.2 Pulmonary hypertension and COPD:

Symptoms of pulmonary hypertension in COPD patients (COPD-PH) partially overlap with those that are associated with COPD without concomitant pulmonary hypertension. The clinical suspicion of AECOPD-PH is challenging, which probably causes underdiagnoses of AECOPD-PH. Echocardiography is widely available as a non-invasive screening method for COPD-PH (5).

Despite significant advances in diagnosis and treatment of AECOPD, the prognostic significance and treatment options of AECOPD-PH remain unclear. In general COPD-PH specific treatment of pulmonary vasodilators have not been convincing (6), and therefore routine treatment of COPD-PH is not recommended (7). Echocardiographic probability of PH is assessed based on the tricuspid gradient and other echocardiographic signs compatible with PH (7):

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

B

Figure 1. Echocardiographic probability of PH assessed from the tricuspid gradient and other signs of PH as shown in Figure 1B.

2.3 Scientific justification of this study

The cohort study will bring awareness of the extent to which changes occur in the pressure conditions in the lung circulation during AECOPD. Besides, it will provide insight into how common "AECOPD-rPH" is. The study

will also be able to indicate whether changes in pressure conditions in the pulmonary circulation are associated with increased mortality and thus help to form the basis for the randomized trial.

The randomized controlled trial will clarify whether drug treatment with the purpose of lowering resistance and blood pressure in the pulmonary circulation can increase time “alive and discharged” in patients with AECOPD and who have developed “AECOPD-rPH”. The study will also clarify whether this treatment can improve respiratory physiology at crucial points (PaO_2 and $PaCO_2$). This study is part of a larger strategic venture (Chronic Obstructive Pulmonary Disease: Trial Network - COP: TRIN) to increase understanding of the pathophysiological mechanisms and genetic factors, thus improving treatment-results for COPD patients.

3. Method:

3.1 Design:

Study A: Cohort study. Cox proportional hazards multivariable analysis is performed.

Study B: Randomized 'open-label' intervention trial:

Investigate whether Sildenafil, a phosphodiesterase 5 inhibitor, can improve the prognosis in patients with AECOPD and “AECOPD- rPH”. At 1:1 randomization, patients are divided into two groups; one group will receive Sildenafil in addition to standard treatment, and the other group will receive standard treatment alone.

3 .2. Recruitment and inclusion:

3.2.1 Cohort study (study A)

Patients are recruited by investigators, who are employed in the participating department of pulmonary medicine, to inform and interview. This happens in cooperation with the patient admitted with AECOPD as primary diagnosis. Thereafter, patients receive oral and written information about the study. The interview will take place in an undisturbed room on the ward, and patients have been informed in advance of their right to bring an assessor. For the interview, the patient will also be assessed in relation to the inclusion and exclusion criteria. After the interview, the patient has 14 days to decide. If the patient wishes to participate, the consent form is signed, and the patient can then be included in the study.

Inclusion criteria:

- COPD (verified by a lung specialist based on clinical assessment and spirometry)
- Acute hospitalization, primary diagnosis "AECOPD"
- Informed consent

Exclusion criteria:

- Known pulmonary hypertension
- Known heart disease that affects the pumping function of the heart (left or right)
- Male <40 years
- Women <55 years
- Non-menopausal women> 55 years *
- Severe mental illness which significantly complicates cooperation
- Severe language barrier which significantly complicates cooperation
- Known drug allergy to 1) Sildenafil
- Get Sildenafil on other indication, consumption ≥50 mg/week

*Definition: Had menstruation within the last 12 months.

3.2.2 Randomized intervention trial (Study B):

Patients are recruited, informed and inquired by investigators who are employed at the participating department of Pulmonary Medicine. The patient is a candidate for inclusion if he/she is admitted to one of the participating wards with AECOPD as primary diagnosis, with ascertained "acute pulmonary hypertension during AECOPD." The physician responsible for the trial then provides the patient with oral and written information about the trial. The patient must be informed of his/her right to bring an assessor to the interview, which will take place in a quiet room on the ward. During the interview, it will be assessed whether the patient meets the inclusion or exclusion criteria. After the interview, the patient has 14 days to decide, and if the patient in question wants to participate in the study, the consent form must be signed. The patient can then be included in the study.

Inclusion criteria:

- COPD (verified by a lung specialist based on clinical assessment and spirometry)
- Acute hospitalization, primary diagnosis "AECOPD"
- Change in TR gradient of ≥ 5 mmHG from baseline to day 30, assessed by echocardiography by a specialist in cardiology or a senior consultant with a special interest in echocardiography

- Informed consent

Exclusion criteria:

- Known pulmonary hypertension
- Known heart disease that affects the pumping function of the heart (left or right)
- Male <40 years
- Women <55 years
- Non-menopausal women> 55 years*
- Severe mental illness which significantly complicates cooperation
- Severe language problems which significantly complicate cooperation
- Known drug allergy to 1) Sildenafil
- Get Sildenafil on other indication with consumption ≥50 mg/week

*Definition: Had menstruation within the last 12 months.

3. 3 Allocation in the randomized intervention trial (Study B):

Sponsor (main supervisor) generates a randomization sequence. Randomization will be in blocks of unknown sizes, and the final allocation will take place via an encrypted website, where inclusion and exclusion criteria are also required to be filled out correctly to randomize a patient.

The drug will be distributed in separate, sealed packages with labels which follow common rules.

3.4 Data collection, surveys and follow-up:

The primary daily project management is handled by the project manager (PhD-Student). In addition, a project group (investigators), consisting of health personnel from the

departments involved is trained to assist the project manager with recruitment, sample detaining and follow-up of patients. Data are collected on Case Report Forms (CRF), specific to each patient, where demographic data is registered. The Case Report Forms are kept in the archives of the departments involved for 15 years. A separate database is created in REDCap (www.Projectredcap.org) for data management. Each CRF will include data from patient records including demographic data, health status, current and former illnesses, results from clinical and paraclinical examinations, past and future contacts to the healthcare system including hospitalizations and prescribed medication. All sensitive personal information will be treated confidentially and in accordance with the Personal Data Ordinance and the Data Protection Act. The purpose of data collection is to optimize the analyzes. Personal data regarding patients who are to be included in the trial will therefore be passed on from the patients' responsible physician to the person

responsible for the trial, once the patient has given consent to this. In connection with self-monitoring or quality control, the sponsor, sponsor's representatives or any control authorities also have access to the information.

3.4.1 Cohort study (study A)

Echocardiography will be performed on patients at baseline (<24 hours after admission and the diagnosis of AECOPD) and also on days 11 (10 days after baseline) and 29 (28 days after baseline). On the first 50 participating patients, a blood sample will be taken at baseline and on day 29. The blood sample is thrombelastography (TEG), and the purpose is to examine the coagulation capacity of the blood. The TEG sample is analyzed on the same day. The patients' course is followed up to and including day 90 after baseline.

3.4.2 Randomized intervention trial (study B)

Blood samples are taken at the beginning of the study and before administration of Sildenafil and monitored every 3 days via bio analysts or project nurse/PhD-students. Sputum samples for physiological studies, to be examined for inflammation and oxygen content will also be made at inclusion. Sildenafil is started up in accordance to guidelines for the treatment of pulmonary hypertension (http://nbv.cardio.dk/pah).

Outpatient follow-up is performed on days 29, 60, 90 and 365:

- Echocardiography
- Spirometry
- COPD Assessment Test (CAT)
- Body Mass Index (BMI)
- Final follow-up of both primary and secondary endpoints after 12 months

3.5 Statistical analyzes:

Primary endpoint:

- Time "alive and discharged from hospital within 365 days from baseline."

Secondary endpoints:

- Time to prednisolone and/or antibiotic-required COPD exacerbation or death in the primary or secondary sector within 365 days
- Death on day 90
- Death within 12 months

- Alive and without COPD exacerbation on day 365
- Clinical cure, day 14 **
- Number of readmissions with COPD exacerbation within 12 months
- Number of days with non-invasive ventilation (NIV) or respiratory treatment during admission
- Delta PaO_2 day 1 (baseline) to day 4 (72 hours)
- Delta $PaCO_2$ day 1 (baseline) to day 4 (72 hours)
- pH day 4 (72 hours)
- Change in FEV1 from baseline to 3 months
- Change in COPD Assessment Test (CAT) from baseline to Day 29
- Change in Body Mass Index (BMI) from baseline to 90 days
- Delta TR gradient day 1 (baseline) to day 4 (72 hours)

**Clinical cure = Cessation or improvement of clinical signs and symptoms.

Clinical failure = Persistent or worsening in clinical signs and symptoms.

Data is processed and analyzed in SAS v.9.4, and graphs are generated in Microsoft Excel and SigmaPlot.

3.6 Sample size:

Cohort study:

Prerequisite: Cox regression. Type 1 error limit= 5%. Power= 80%.

Variance Inflation Factor (Xi… Xn): 0.3

Px = 0 (Absolute risk among persons without TR gradient ≥40 mmHg)

Sample size: 250

This gives a detection limit for a HR of 1.7. This is considered to be clinically relevant. Upon detection of a HR <1.7, it is very doubtful whether this is a real difference and - in addition - very doubtful whether an intervention targeted at pulmonary hypertension could change the prognosis in a later RCT.

Randomized controlled trial

Prerequisite: Type 1 error limit=5%. Power=80%.

Analysis: T-test.

The sample size is calculated based on the following estimate and indicative figures:

1) "Pulmonary hypertension" is defined for study purposes as TR gradient ≥ 40 mmHg

2) Patients with “acute reversible pulmonary hypertension with AECOPD”/AECOPD-rPH without Sildenafil (control group) are 8 days “discharged and alive within 14 days” on average (expected hospitalization 6 days).

With Sildenafil treatment, the number of days "discharged and alive within 14 days" can be increased to 10 (expected hospitalization 4 days). Admission time is expected reduced by 2 days.
Estimated sample size: 116 (58 + 58) patients.

4. Storage of biological material:

The following samples will be stored in a biobank:

1. Whole blood from the time of inclusion (20 mL).
2. EDTA, serum, heparin and citrate plasma from the time of inclusion and after 30 days (100 mL).
3. Any excess material from other blood or sputum samples.

This will be stored in a freezer at -80°C and analyzed during the analysis phase of the experiment. The biobank ceases to exist at the end of the experiment. The samples are expected to be fully analyzed by September 2024 and thereafter any residues will be transferred to the biobank for future research.

The following samples will be analyzed on the same day as blood withdrawal:

1. Whole blood from baseline and again on day 29 (3.5mL each time). The blood samples will be withdrawn from 100 patients and used for TEG. The samples must be analyzed within 2 hours after withdrawal.

4.1 Biobank for future research

Based on the material from the experiment, a biobank will be set up for future research. The purpose is to strengthen future COPD research. The material will be stored pseudonymized for up to 15 years (until September 2034) under applicable law. The material in the biobank will only be available for other studies if they have obtained separate approval from the Science Ethics Committee. In addition, participating patients must sign a separately informed consent, thereby allowing their material to be stored.

5. Side effects, risks and disadvantages:

The attending physician may at any time discontinue Sildenafil therapy if, in clinical and/or paraclinical judgment, it is deemed contraindicated.

<u>Blood tests:</u>

Serious side effects of regular blood sampling (venipuncture) are rare. A frequent side effect (5-15%) is bypassing discoloration of the skin around the puncture site due to small hemostasis in the skin and subcutis.

Side effects:

When treated with Sildenafil. (From www.medicin.dk)

Very common (> 10%)	Headache.
Common (1-10%)	Dyspepsia, Nausea. Facial redness, Nasal obstruction. Hot flashes. Dizziness. Visual disturbances (including color distortion, blurred vision, blue vision).
Uncommon (0.1-1%)	Abdominal pain. Hypertension, Hypotension. Hypesthesia. Hypersensitivity. Hematuria. Conjunctivitis, Phenomena of Light, Ocular Hyperemia, Tinnitus, Eye Pain.
Rare (0.01-0.1%)	Angina pectoris, Atrial fibrillation, Cerebral hemorrhage, Cerebrovascular events, Myocardial infarction, Sudden cardiac death, Transient cerebral ischemia, Ventricular arrhythmias. Cramps, Syncope. Stevens-Johnson syndrome, Toxic epidermal necrolysis. Allergy-like reactions. Bleeding from the penis, Hematospermia, Priapism *. Double vision, Glaucoma, Hearing loss, Myopia, Non- arteritis anterior ischemic optic neuropathy - NAION, Periorbital edema, Retinal thrombosis, Retinal hemorrhage, Retinopathy.

An adverse reaction (AR) is defined as any harmful and unwanted reaction caused by a drug of any does. An adverse event (AE) is defined as any unwanted event of a patient or a subject in a clinical trial after treatment with a drug, even though there might be no connection between the drug and the unwanted event. A serious event or serious adverse reaction (severe adverse reaction/event: SAR/SAE) is defined as an event or adverse reaction that results in death regardless of dose, is life-threatening, results in hospitalization or extension of

hospital stays, results in significant or permanent disability or incapacity of work or leading to a congenital abnormality or malformation.

The investigator must immediately (=within 24 hours) report serious incidents and serious side effects to the sponsor. Other events do not require immediate reporting but should be reported to the sponsor within 7 days after the person has completed his treatment.

As the trial drug is well known and used for approved indication, and as we are only interested in the clinical long-term effects of the drug, we will only register side effects that are not mentioned in the respective drug summary of the trial drug.

Registration and reporting of all accidental side effects ends when the study drug is stopped. The subjects are followed continuously for approx. 12 months after the end of treatment.

All incidents and registered side effects are reported at the end of the trial in a closing report to SST. All serious incidents / adverse events must be registered annually, and a report on participant safety must be prepared. The serious side effects must also be stated in the final report to the SST.

The product summary attached to the application is used to evaluate whether a serious related adverse reaction is unexpected and therefore possibly a SUSAR (Suspected Unexpected Serious Adverse Reactions).

The sponsor will immediately notify the National Board of Health in the event of suspicion of an unexpected and serious side effects. In case of fatal or life-threatening side effect, this must be registered and reported to SST no later than 7 days after the sponsor has become aware of such a suspected adverse reaction. No later than 8 days after the report, the sponsor must notify SST of all relevant information about sponsor's and investigator's follow-up on the report. All other unexpected and serious suspected side effects are reported to the SST no later than 15 days after the sponsor has become aware of these.

The investigator must immediately report serious incidents and side effects to the sponsor.

The report must be followed up by a detailed written report, and in both the immediate

reporting as in the subsequent report, the investigator must identify the subjects with a personal code number. When reporting a death, the investigator must provide any additional information that the sponsor may request.

6. Finances:

The research project is supported by an independent research fond, the Novo Nordisk Fond. The grant finances payment for the persons responsible for the trial (researchers and supervisors), remuneration of auxiliary staff, payment of laboratory examinations and equipment, as well as specific antibiotic treatment.

6.1 Budget ratios

Project coordinator: PhD study Sat n.: 1.779.600 KR.

Monitoring Good Clinical Practice: Based on the average. Monitoring of 15% of all data: DKK 173,208.

Sildenafil (study medicine): Co-financing (Department of cardiology B): DKK 340,233.

PhD expense 180.000 kr.

Senior researcher (co-financing) DKK 547,344.

7. Remuneration / benefits:

Patients do not receive remuneration for participation.

8. Availability of information:

The Steering Committee is convinced that knowledge sharing creates more and better scientific results. Requests about sharing of knowledge from other groups will be presented to the steering committee, and as long as the hypothesizes to be investigated is not scheduled for investigation by investigators in our group, we will allow the use of our data. However, it must be emphasized that data is used for a specific purpose, not for future purposes in general. This is stipulated by the steering committee in order for the data to be used in a responsible manner in order to test hypotheses with a relevant scientific content.

9. Publication of experimental results:

All experimental results will be published in scientific contexts, including international journals. This will happen regardless of whether the results are positive, negative or inconclusive. If the results cannot be published in scheduled journals, they will be published online at **www.clinicaltrial.gov.**

10. Statement of scientific ethics:

The study will be performed by the Declaration of Helsinki and under the rules of The Health Act, the Personal Data Ordinance and the Data Protection Act. The study is reported to the Danish Data Protection Agency.

Recruitment and inclusion will take place as previously described (section 3.3.1). Participation requires a signed consent declaration. The participants can withdraw their participation consent at any time and exit the study trial without this affecting their right to future treatment. Patients also have the right to be accompanied by an assessor during the information - conversation and are entitled to time for reflection within the possibility of the trial. Declaration of consent is signed.

The aim of the trial is to investigate whether targeted treatment for pulmonary hypertension in patients with AECOPD can reduce the length of hospital stay and mortality in a group of patients with severe lung disease

- an area that has so far been sparsely elucidated, and where the need for evidence-based guidelines for management and treatment is great.

Potential disadvantages and side effects are described in a separate section (5). Here it appears, among other things, that the likelihood of serious side effects for both treatment and study are rare. The treating physician always has the option of discontinuing treatment if it is assessed contraindicated.

Experimental method and statistical analyzes are carefully considered in terms of being able to pass on and apply relevant and safe research results for clinical practice. Based on the above considerations, we believe that the experiment is scientifically sound and can be carried out without exposing the trial participant to unjustifiable risks.

11. Exclusion from and interruption of trials:

There will be regular monitoring and quality control of the study. If the physician responsible for the study, finds it necessary participants can be taken out of the study. The physician may also terminate the examination at any time if there is a medical justification (development of an allergy to the medicine), a safety risk, or a requirement from the authorities. As mentioned in the above paragraph, the subject can also at any time withdraw informed consent and come out of the study.

12. Information on compensation or reimbursement schemes:

Patients who participate in these studies and who believe they have suffered an injury can seek compensation via patient compensation (**http://patienterstatningen.dk/**). Cf. applicable Danish law.

13. References:

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