CLINICAL INVESTIGATION PLAN

Remote MONITORing of patients with chronic obstructive pulmonary disease using a tablet system. A randomized cross over pilot study of feasibility evaluation and quality of life measurements

Study Code:	Monitor
Version Number:	1.0
Date:	20180319
Sponsor	Sahlgrenska University Hospital
Principal investigator:	Anders Ullman, MD PhD Head of COPD center Sahlgrenska University Hospital Vita Stråket 12 413 45 Göteborg

Revision summary sheet				
Regarding	**Revision description**	**Revision date**	**Version no.**	**Signature**

SIGNATURE PAGE

I confirm that I have read and understood this protocol and that I will work according to the protocol. By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ISO 14155, and local regulations governing the conduct of clinical studies.

I will accept the monitors overseeing of the study.
I will promptly submit the protocol to applicable ethical committee.

Signature Principal Investigator	Date (yyyy-mm-dd)
Anders Ullman	
Signature Sponsor	Date (yyyy-mm-dd)
Anders Ullman	

Sponsor:
Sahlgrenska University Hospital

Investigational site:
COPD center
Sahlgrenska University Hospital
Vita Stråket 12
413 45 Göteborg

Principal investigator
Anders Ullman, MD, PhD
Head of COPD center
Sahlgrenska University Hospital
Vita Stråket 12
413 45 Göteborg

Coordinating investigator(s)

Claes-Göran Löfdahl, MD, PhD
COPD center
Sahlgrenska University Hospital
Vita Stråket 12
413 45 Göteborg

Malte Frerichs, authorized nurse
COPD center
Sahlgrenska University Hospital
Vita Stråket 12
413 45 Göteborg

Monitor
Gothia Forum
Gröna stråket 12
413 45 Göteborg
+46 31 342 96 70
Gothia.forum@vgregion.se

Synopsis

Title of Protocol	Remote MONITORing of patients with chronic obstructive pulmonary disease using a tablet system. A randomized cross over pilot study of feasibility evaluation and quality of life measurements
Study purpose	This clinical investigation will evaluate the patient-equipment interface and patient preference in the use of modern possibilities for remote monitoring of patients with COPD in a personalized care approach.
Study Design Summary	This clinical trial is an open, randomized, controlled cross-over study. Eligible subjects to include will be given the possibility to participate in the study. They will at their first visit be randomized to start either telemonitoring, using the tablet system arm or to normal standard of care period for 26 weeks. After 26 weeks the subject will have a second visit and after that, four weeks (wash out) of standard of care or telemonitoring treatment. After that there will be a third visit and the subject will start the second treatment period with the alternative management. At the end of this period (56 weeks) there will be a fourth (last) visit at the center for the subject.
Study duration	56 weeks
Study site	1 investigative site
Subject population	The target population are patient diagnosed with COPD according to international guidelines.
Inclusion criteria	For inclusion in the study, subjects must fulfil the following criteria: • Willingness to participate and provision of informed consent • Diagnosis of COPD • FEV_1/FVC (post bronchodilator) <0.7 • GOLD severity grade D • FEV, < 80% predicted • Cognitive ability relevant for the studies as judged by the investigator • Living in their own home and able to manage their activities of daily living

Exclusion criteria	• Rapidly progressing severe disease other than COPD and COPD-related diseases, influencing the Health-Related Quality of Life (HRQOL) during the study time as judged by the investigator • Long-term stay (>2 weeks) away from home during the study period, where there are no possibility to get internet connection • COPD exacerbation during 1 month before start of study
Primary Investigation Objectives	The primary objective is to evaluate the impact and feasibility of tele monitoring and video contact in personalized care of moderate and severe COPD patients. This should be compared to normal standards of care. The cross-over design evaluates the influence on general HRQOL of this tablet and monitoring system.
Secondary Investigation Objectives	The secondary objective(s) is to observationally evaluate various measurements used in this tablet system to give knowledge and background for an extensive, future cohort study of patients with moderate and severe COPD managed in this investigation center. The following measurements will then be used: 1. CAT (COPD assessment test): well established symptom related questionnaire for COPD to evaluate change in COPD-related Health status. 2. EQ5D: Generalised health related quality of life, to compare with SF-12 and to use in preliminary cost-utility analysis and to evaluate in comparison to other measurements of HRQoL 3. HADS Anxiety, depression: Established measurement of depression and anxiety, to evaluate any change in the patient's mental status. 4. mMRC: Established earlier dyspnea measurement scale for COPD, to compare this measurement with other newly developed measurements of symptoms in patients with COPD. 5. Observational cost-utility evaluation 6. Incidence of device related and procedure related serious adverse events will be performed
Primary Outcome Measure	Change of SF-12 over each treatment period
Secondary Outcome Measure	Cost-utility evaluation- the difference in costs between the two treatments divided by the difference in quality adjusted life years (QALYs) For other secondary measures: Descriptive statistics will be used.

Table of Contents

LIST OF APPENDICES

NA

LIST OF ABBREVIATIONS

Abbreviation	Explanation
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
EQ-5D	EuroQol 5-dimensions
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-Related Quality of Life
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Disease
MRC	Medical Research Council Dyspnea
PRO	Patient Reported Outcome
SF	Site File
SF-12	Short Form-12
SpO2	Peripheral capillary oxygen saturation
TMF	Trial Master File
QALYs	Quality adjusted life years

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a group of progressive lung diseases including emphysema, chronic bronchitis, refractory (non-reversible) asthma, and some forms of bronchiectasis. The disease is characterized by increasing breathlessness. COPD is one of the most important chronic diseases with regard to disability and mortality. In the western world it is the third most common cause of mortality **(1).** In Sweden it is estimated about 700 000 patients suffer from COPD of various degrees. Current treatment recommendations focus on smoking cessation, improvement of physical activity, physiotherapy, preventive measures to decrease the risk for exacerbations, mainly due to infections. Symptomatic pharmacological treatment to decrease symptoms and also decrease the risk for exacerbations is recommended **(2, 3)**. In addition it is well established that a majority of COPD patients also suffer from other chronic diseases, as e g cardiovascular diseases, osteoporosis and metabolic diseases.
A careful and close contact with the health care system, often with a specialized nurse in the open care department, has been shown to be beneficiary in several studies showing subsequent decreasing exacerbation rates **(4).** To further improve the contact with open care departments and the patients various approaches using telemedicine and remote monitoring have been evaluated **(5)**. In a Cochrane review from 2012 it was concluded that “tele healthcare interventions can significantly reduce the risk of emergency department attendance and hospitalization, but has little effect on the risk of death”**(6).** Later studies and reviews have given varying results, with a positive effect also on Health-Related Quality of Life (HRQOL) measurements in one systematic review **(7)**, but with a questionable effect in another review **(8)**. The most recent single studies show different results. One big Danish study, however not well randomized and with a high withdrawal rate, could not find any effect on HRQOL **(9)**, whereas a recent randomized study of patients with COPD and concomitant cardiac failure showed improvement of walking distance, decreasing hospitalization and death rate **(10)**. Also specific HRQOL measurements, physical activity profile and evaluation of dyspnea was better in the telemedicine group.

A probable reason for the varying results is due to variations in design, varying choices of outcomes and variations in patient adherence to the equipment **(11, 12)**. E g the above mentioned Danish study made an intention to treat evaluation without any relation to patient preference for the handling and they also had a withdrawal rate of about 50% **(9)**.

Thus, there is still a need to evaluate the patient-equipment interface and patient preference in the use of modern possibilities for remote monitoring of patients with COPD in a personalized care approach.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1. Summary description of the investigational device and its intended purpose

The device for this trial is the application cVitals provided by FocusCura. The device has obtained CE marking to monitor patients with chronic conditions. Health care professionals and patients monitor the course of their disease by tracking vital signs and outcomes of questionnaires for transferring and evaluation of data from external devices or patient reported outcomes (PRO) in questionnaire forms used for healthcare monitoring. The study device will be used according to this CE marking intentions.

FocusCura is certified for information security under ISO 27001 and quality management under ISO 9001. The servers that FocusCura uses to store personal information are located in EU data centers, they have ISO 27001 certification. Transmitting of data always use HTTPS (SSL) connections.

The subjects monitor the measurements at home and healthcare professionals are given the permission by the patient to be able to see all the values. Within the application there are 2 questionnaires integrated where the subject describes symptoms, COPD Assessment Test (CAT) and Medical Research Council Dyspnea Scale “MRC”. Furthermore measurements of objective health related parameters will be monitored according to specification 6.2.1.

2.2. The manufacturer of the investigational device

The device is manufactured by:

FocusCura
Odijkerweg 1
3972 NE Driebergen-Rijsenburg
The Netherland

2.3. Device specifications

The device used for this trial is the application cVitals with medical CE marking CE-TMA-20140401 class 1.

2.4. Traceability

Version number of the Investigational Medical Devices (cVitals application) will be documented for each patient in the eCRF.

2.5. Necessary training in device use

Prior to study initiation, Investigator and staff will receive demonstration and training in device operating procedures and study protocol. Training will be documented in Site File (SF) and Trial Master File (TMF).
Study participants will receive appropriate training to enable them to use the study device accurately according to the study protocol. The training will be recorded in the eCRF.

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

There is a need to improve the open care of patients with COPD, to improve quality of life, in this great contingent of the total current health care need in the society. A possible way to improve this would be to establish a home monitoring of important measurements of these COPD patients with the aim to improve symptom control, prevent and detect as well as treat exacerbations at an early stage. This study will evaluate that possibility by using a tablet system, and in a personalized care manner take possible advantages of this system. The current knowledge in this area is ambiguous and further studies are needed, to evaluate the equipment as well as the patient handling of it.

4. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1. Anticipated clinical benefits

Compared to usual care the subjects will get an increased level of control of their disease under the phase of extended monitoring. For the patient the use of the tablet system will incur a better overview of the health status, and possibly an earlier detection of any deterioration. The earlier contact with the health care center, will also give better and more detailed information to the center staff.

4.2. Anticipated Adverse Device Effects (ADE)

The tablet system and external measurement devices do not *per se* incur any risk for the patients.

4.3. Risks associated with participation in the clinical investigation

A special concern is the questions of patient integrity when using an internet-based handling of data. These concerns are carefully handled with personal login to the equipment, and data handling in a secure database. In case of technical problems with the equipment, the patients will always have the possibility to contact the study center.

4.4. Risk/benefit assessment

According to the above described risks versus benefits we judge the risk for the patient to be minimal and the potential benefit for the individual patient as well as for future healthcare organization to be of greater importance.

5. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

The primary objective is to evaluate the impact and feasibility of tele monitoring and video contact in personalized care of moderate and severe COPD patients. This should be compared to normal standards of care. The cross-over design evaluates the influence on general HRQOL of this tablet and monitoring system.
The hypothesis is that telemonitoring gives a better general HRQOL in moderate and severe COPD patients during the use of this telemonitoring system.

The secondary objective(s) is to observationally evaluate various measurements used in this tablet system to give knowledge and background for an extensive, future cohort study of patients with moderate and severe COPD managed in this investigation center. The following measurements will then be used:

1. CAT (COPD assessment test): well established symptom related questionnaire for COPD to evaluate change in COPD-related Health status.
2. EQ-5D: Generalised health related quality of life, to compare with SF-12 and to use in preliminary cost-utility analysis and to evaluate in comparison to other measurements of HRQoL
3. HADS (Hospital Anxiety and Depression Scale): Established measurement of depression and anxiety, to evaluate any change in the patient's mental status.
4. mMRC: Established earlier dyspnea measurement scale for COPD, to compare this measurement with other newly developed measurements of symptoms in patients with COPD.
5. Observational cost-utility evaluation
6. Incidence of device related and procedure related serious adverse events will be performed

6. DESIGN OF THE CLINICAL INVESTIGATION

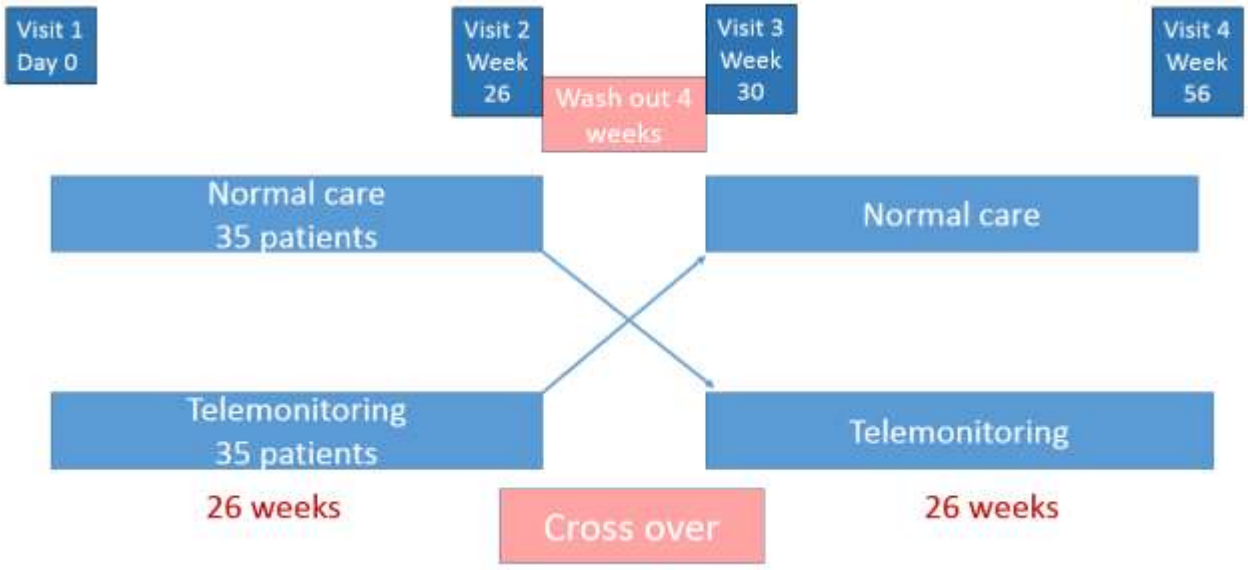
6.1. General

This clinical trial is an open, randomized, controlled cross-over study.
This study will evaluate the possibility to use a tablet system with measurements of disease related parameters in patients with COPD, and to compare any influence of this system on general health related quality of life as to ordinary care without this system.

The feasibility character of the study have been the reason why a cross-over design in relatively few patients has been chosen. It also gives a possibility to get information directly from the patients on positive and negative issues with the tablet system. For the length of the study, the rational

have been to give patients the possibility to well adapt to the use of the assigned management. Furthermore this study will give possibilities for future more extensive studies of healthcare systems used in COPD health care to be evaluated. The inborn error of a cross over design will be dealt with a wash out of 4 weeks between treatments and also initial measurement of the primary outcome at start of both treatment periods.

Eligible subjects to include will be given the possibility to participate in the study. They will at their first visit be randomized to start either telemonitoring, using the tablet system arm, or to normal standard of care period for 26 weeks. After 26 weeks the subject will have a second visit and after that, four weeks (wash out) of standard of care. After that there will be a third visit (week 30) and the subject will start the second treatment period with the alternative management. At the end of this period (56 weeks) there will be a fourth (last) visit at the center for the subject.



The study will in total include 4 on clinic visits during the total study period of 56 weeks.

Visit 1 Following informed consent process, screening evaluation will determine subject eligibility for the study. Visit includes inclusion/exclusion criteria, medical- and COPD history, demography, questionnaires, vital functions, training in the technical equipment,
Visit 2 (Week 26 ± 2 weeks). Questionnaires, vital functions, Patient Reported Outcome, Adverse Events (AE)
Visit 3 (Week 30 ± 2 weeks). Questionnaires, vital functions, Patient Reported Outcome, AE
Visit 4 (Week 56 ± 2 weeks). Questionnaires, vital functions, Patient Reported Outcome, AE

During the telemonitoring treatment period the subjects will register; vital functions (blood pressure, heart rate, weight, SpO2) twice a week, physical movement daily by using a fitness device, have videocalls with a nurse weekly the first 4 weeks and thereafter every fourth week the last 5 months. Twice a week (± 2 days) questionnaires (CAT and MRC) should be filled out at home.

6.2. Investigational device(s) and comparator(s)

During the telemonitoring period of 26 weeks the subjects will utilize the cVitals application daily by log in and follow the instructions given.

6.2.1. Auxiliary devices

The following devices will be part of the equipment that every subject gets during the treatment arm with telemonitoring:

- cContact – an application to obtain a secure video connection between subject an health care professionals. cContacts is provided by FocusCura.

- The following study related equipment will be provided by ATEA, a Swedish company, leasing the devices to the centre:
    - IOS based iPad from apple for using the applications cVitals and cContact.
    - Electronic Sphygmomanometers “Track” from iHealth labs Europe: Medical class 2a CE0197, to measure blood pressure and pulse frequency. Will be used in accordance with intended use.
    - Pulse Oximeter “Air” from iHealth labs Europe: Medical class 2a CE0197, to measure oxygen saturation of the blood. Will be used in accordance with intended use.
    - Scale “lite” from iHealth labs Europe to weigh the subject.
    - Fitness device “Wave” from iHealth labs Europe to measure physical movement every day when the subject is awake.

6.3. Subjects

6.3.1. Inclusion criteria

For inclusion in the study, subjects must fulfil the following criteria:

- Willingness to participate and provision of informed consent
- Diagnosis of COPD
- FEV_1/FVC (post bronchodilator) <0.7
- GOLD severity grade D
- FEV, < 80% predicted
- Cognitive ability relevant for the studies as judged by the investigator
- Living in their own home and able to manage their activities of daily living

6.3.2. Exclusion criteria

For exclusion in the study, subject must not fulfil the following criteria:

- Rapidly progressing severe disease other than COPD and COPD-related diseases, influencing the HRQOL during the study time as judged by the investigator
- Long-term stay (>2 weeks) away from home during the study period, where there are no possibility to get internet connection
- COPD exacerbation during 1 month before start of study

6.3.3. Restrictions

Journeys for longer than 2 weeks should not be performed during the study period, where there are no possibility to get internet connection.

6.3.4. Subject withdrawal or discontinuation

Subjects are free to discontinue their participation in the study at any time without prejudice to further treatment. The subjects may be withdrawn from the study at the discretion of the investigator due to safety concerns or if judged non-compliant with study procedures. Other reasons for discontinuing a subject are incorrect enrolment and subjects lost to follow-up.

6.3.5. Subject enrolment and randomization

The study will include 70 subjects starting the study, and for each participant the total study participation of the study including 4 weeks wash out will be approximately 56 weeks. It is estimated that the total study duration, from start of the enrollment period until last subjects last visit will be approximately 24 months. Subject eligibility will be established before randomization. Subjects will be randomized strictly sequentially, as subjects are eligible for randomization. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study. As stated in the statistical considerations below, there will be no need to replace withdrawn patients as the planned number of patients gives room for a drop-out rate of 17 %. The estimated drop-out rate is 10 %.

Identified potential study subjects, listed at the COPD center at Sahlgrenska University Hospital, will be given thorough information regarding the study, both orally and in writing, by qualified staff at the COPD center. After the subject has been given the opportunity to ask any question regarding the study they will be asked to consent to study participation. If they do, they will sign the informed consent form.

At randomization, all eligible subjects will be given a randomization number that assigns them to one of the treatment groups. The randomization numbers are sequentially allocated to the subjects in the order of randomization.

The eCRF software creates the randomization numbers at randomization visit.

A randomization list will be produced with random assignment of treatment groups in the specified ratio of 1:1.

The sponsor may decide to stop the trial or part of the trial at any time. If a trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, the investigator should promptly inform the Ethics Committee and provide a detailed written explanation. The regulatory authority should be informed according to national regulations.

6.4. Procedures

Subjects fully evaluated at the COPD-center at Sahlgrenska university hospital and who according to the investigator are eligible to the study with regard to inclusion and exclusion criteria, including

their willingness to take part in the cross over designed study with comparison of a tablet based system and ordinary care, will be randomized to start with either normal care or telemonitored care.

Each visit is described in detail in this section.

Study activities performed at on clinic visits is specified in Table 1.

Table 1 Study activities

Visit Number	1	2	3	4
Study Week:	Day 0	Week 26	Week 30	Week 56
Visit window (weeks)		±2	±2	±2
Informed consent	X			
Randomization	X			
Demography	X			
Medical history	X			
COPD history	X			
Patient Reported Outcome (CAT, MRC, HADS, EQ-5D, SF-12)	X	X	X	X
Vital functions (blood pressure, heart rate, weight, height[1], SpO2)	X	X	X	X
Inclusion/exclusion criteria	X			
Instructing in the technical equipment	(X)[2]		(X)[2]	
Adverse Events		X	X	X

[1] Height is only measured on the visit 1

[2] At Visit 1 or 3 depending on when starting the telemonitoring treatment period.

On clinic - Visit description

Visit 1 Screening/Randomization visit (Day 0)

Following informed consent, screening evaluation will determine subject eligibility for the study. No study-specific procedures may be performed prior to informed consent signature. Visit 1 is anticipated to last approximately 2,5 hours.

The Screening/Randomization visit includes performing/collecting the following information:

- Demographic – including age and gender.
- Patient Reported Outcome – CAT, MRC, HADS, SF-12, EQ-5D
- Training in technical equipment – subjects will be informed and given instructions how to use technical equipment (when assigned to telemonitoring arm)
- COPD History – including grade/severity of COPD, date of diagnosis or length of COPD

- Current and Past Medical History – including concomitant medications.
- Vital functions – including blood pressure, heart rate, weight, height, SpO2

The subject will then be randomized to either normal care or telemonitoring treatment period to start with for the first 26 weeks.

Visit 2 (Week 26 ± 2 weeks), approximately 2 hours
Patient Reported Outcome – CAT, MRC, HADS, SF-12, EQ-5D
Vital functions – including blood pressure, heart rate, weight, SpO2
Adverse Events

Wash out period of 4 weeks. Will apply for both normal care and telemonitoring treatment assignments.

Visit 3 (Week 30 ±2 weeks), approximately 2 hours
Patient Reported Outcome – CAT, MRC, HADS, SF-12, EQ-5D
Vital functions – including blood pressure, heart rate, weight, SpO2
- Training in technical equipment – subjects will be informed and given instructions how to use technical equipment (when assigned to telemonitoring arm)
Adverse Events

Normal care or telemonitoring for 26 weeks depending on which arm the subject has been randomized to first.

Visit 4 (Week 56 ±2 weeks), approximately 2 hours
Patient Reported Outcome – CAT, MRC, HADS, SF-12, EQ-5D
Vital functions – including blood pressure, heart rate, weight, SpO2
Adverse Event

Telemonitoring - visit description
Study activities performed in the telemonitoring treatment period is specified in Table 2.

Table 2 Study activities during telemonitoring at home

Study month with telemonitoring	1	2	3	4	5	6
Visit Window (days)	±2	±2	±2	±2	±2	±2
Questionnaires (CAT, MRC)	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
Vital functions (blood pressure, heart rate, weight, SpO2)	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
Vital functions (activity measurement)	daily	daily	daily	daily	daily	daily

Video Call with nurse (conversation about health condition and vital parameters)	Weekly 4 weeks	monthly	monthly	monthly	monthly	NA[1]

[1] On clinic Visit week 26 or 56 depending on treatment randomization

For subjects starting the use of the tablet system they will get a thorough introduction in the use of the equipment.

On a daily basis the subject will perform vital functions using the cVitals application and follow the instructions given.
Measure physical movement by wearing the Fitness device “Wave” during the whole day when subject is awake. Data will automatically be transferred and no further action is needed by the subject.

Twice a week subject will perform additional vital functions:
Blood pressure and heart rate will be measured using the Electronic Sphygmomanometers “Track”.
Weight will be taken using the Scale “lite”
Oxygen saturation will be measured using Pulse Oximeter “Air”
And
Complete two PRO´s (integrated in the application):
CAT
MRC
All this is estimated to take approximately 20-30 min each time.

For the first 4 weeks there will be weekly videocalls with a COPD-center nurse discussing health condition and vital parameters.
Thereafter there will be monthly videocalls with a COPD-center nurse for the remaining 5 months, i.e. 4 further calls. The videocalls will take approximately 15 min.

Normal care
During normal care the subjects will get the possibility to call the COPD-center via telephone on their own initiative e g with worsening symptoms as usual.

6.4.1. Concomitant medication

Medications that are considered necessary for the subject´s safety and well-being may be given at the discretion of the investigators unless not specified in the exclusion criteria. Concomitant medication will be recorded in the Case Report Form.

6.5. Monitoring plan

A study monitor will be appointed by the sponsor. The monitor will be appropriately trained and informed about the nature of the study, subject written information, GCP and applicable regulatory requirements. The monitor’s qualifications will be documented.

The monitor will have regular contacts with the clinic to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, to verify inclusion/exclusion criteria, study main endpoints, check safety reporting and that therapy accountability is being carried out. The investigator should ensure that all persons assisting with the trial are adequately informed and trained about the protocol, the investigational products(s) and their trial related duties and factions. The monitor will check that training has been performed and that this is documented. The monitor will also ensure source data verification (comparison of the data in the CRF with the medical records and other source data). The monitor must have direct access to source data. The extent of monitoring will be defined in a monitoring plan.

7. STATISTICAL CONSIDERATIONS

The study has a cross-over design with each a 6 month treatment period. There is a 4 weeks wash out between treatments. The number of included subjects is calculated to be 70. The change of SF-12 over each treatment period, from start to end, will be statistically evaluated. The comparison will primarily be done with Wilcoxson signed rank test.

The power calculation with alpha 0.05 gives a power of 0.8 to detect a difference of 4,5 units on the physical SF-12 scale if 58 subjects are evaluable (based on a SD of 12 units). We calculate the maximal drop out is around 10%. Thus, starting from 70 patients there is no need to replace patients who withdraw, from the study. The design allows a drop-out of 17 %. There will be no interim analysis. The analysis of data will be done on all subjects that have followed the protocol. Subjects who withdraw from the protocol will be followed for the full study period for any unexpected adverse event.

The exploratory cost-utility analysis will be a within trial analysis and it will aim at estimating the incremental cost-effectiveness ratio (ICER), i.e. the difference in costs between the two treatments divided by the difference in quality adjusted life years (QALYs). The costs will include COPD medication and visits, phone contacts and hospitalization related to COPD as well as loss of productivity (sick-leave) caused by COPD. The number of QALYs will be based on EQ5D.

For other secondary measurements, descriptive statistics will be used.

8. DATA MANAGEMENT

The investigator will ensure that all data collected in the study are recorded in a timely manner according to any instructions provided.

An electronic Case Report Form (CRF) will be used for data collection. The investigator will ensure that the data are recorded and that any corrections in the CRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness and timeliness of the data recorded. The investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All source data including informed consent, a copy of the completed

CRF, original protocol with amendments and the final report will be stored for a minimum period of ten years after termination of the trial, in accordance with Swedish regulation/law.

Staff designated by Gothia Forum and working on behalf of the Sponsor will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are issued electronically. Designated investigator site staff is required to respond to the query and confirm or correct the data.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and available for data analysis.

The investigator must maintain source documents for each subject in the study. A source data verification log will be included in the Investigator Study File (ISF).

9. AMENDMENTS TO THE CIP

Modifications to the signed protocol are only possible through approved protocol amendments and with the agreement of all responsible persons. Details of non-substantial amendments are to be clearly noted in the amended protocol.
A change that concerns; a new trial site, new principal investigator and or a new informed consent form should only be submitted to the concerned Ethics Committee.
In case of a substantial protocol amendment (e.g. change of; main purpose of the trial, primary/secondary variable, measurement of primary variable, investigational product, or dosing), the concerned Ethics Committee and Competent Authority must be informed and should be asked for its opinion/approval prior implementation of amended protocol, as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by the Sponsor and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee and competent authority, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone numbers).

10. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Periodic monitoring of protocol compliance will be performed. The sponsor has the right to suspend enrollment at site deemed to have excessive protocol compliance issues. The investigator agrees to conduct the investigation in accordance with this protocol. An investigator

must not deviate from the protocol without first receiving approval in writing from the IRB/EC. Under emergency circumstances, deviations from the CIP to protect the rights, safety and wellbeing of the subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and explained on CRFs and reported to the sponsor and the EC as soon as possible. Investigators will also adhere to procedures for reporting investigation deviations to the IRB/EC in accordance with the specific IRB/EC reporting policies and procedures.

11. DEVICE ACCOUNTABILITY

The monitoring equipment will be stored at the COPD center and will be distributed to the subjects when they start the telemonitoring period of the study. At the end of this period the device will be returned to the center and the tablet system will be cleared from all subject data.

The version number of the applications used will be documented in the eCRF for each subject.

12. STATEMENTS OF COMPLIANCE

Audits and inspections
Authorized representatives of the sponsor, a Competent Authority or an Ethics Committee may perform audits or inspection at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, ISO 14155 and any applicable regulatory requirements.

Ethics
The study will be performed in compliance with the protocol, with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ISO 14155 and applicable regulatory requirements.

Ethics Committee
The final study protocol, including the final version of the Informed Consent Form and other information given to subjects e.g. advertisements, must be approved or given a favorable opinion in writing by an Ethics Committee (EC) as appropriate. The Principal Investigator is responsible for informing the EC of any amendment to the protocol, in accordance with local requirements. Progress reports and notifications of any serious and unexpected adverse drug reactions will be provided to the EC according to local regulations and guidelines.

Insurances
The study subjects are covered by the Patient Insurance according to the Swedish Patient Injury Act.

13. INFORMED CONSENT PROCESS

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The monitor(s), the auditor(s), and the CA(s) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject' or the subject's legally acceptable representative is authorizing such access.

The original, signed Informed Consent Form (ICF) must be stored in the Investigator's Study File. A copy of the signed ICF must be given to the subject.

If a protocol amendment requires a change to the ICF, the EC must approve modifications that lead to a revised ICF before the revised form is used.

Subject data protection
The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.
The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the sponsor will be identified by Subject ID.
The Informed Consent Form will also explain that for data verification purposes, authorized representatives of the sponsor, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

14. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
NOTE 1: This definition includes events related to the investigational device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)
Adverse event that:
a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or

- a permanent impairment of a body structure or a body function, or

- in-patient hospitalization or prolongation of existing hospitalization, or

- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.
NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

14.1. Recording of AE and DD

All AE's and DD´s occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the protocol. All ADE's will be recorded in the CRF.
The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.
The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.
All ADE that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

14.2. Adverse events and incidents with medical devices

All adverse events and incidents with medical devices in the study will follow national regulations and routines available for regular hospital reporting of medical devices.

15. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

Sponsor may choose to suspend or prematurely terminate the investigation for the following reasons:

- Device deficiency or malfunction
- Subject safety issue
- Production limitation
- Administrative decision

In the case of a recurring system malfunction or subject safety issue observed across multiple subjects, the overall study may be suspended while the problem is diagnosed. The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. In the case of device-related serious adverse events, the Medical Monitor will consult with the sponsor and principal investigator to ensure that the necessary steps are taken to protect the safety and well- being of the subjects.
In the event that that study is stopped, the investigator will promptly inform the subjects and ensure appropriate therapy and follow-up. Additionally the investigator will promptly inform the IRB/EC and provide a detailed written explanation. The pertinent regulatory authorities will be informed according to local regulations.

16. PUBLICATION POLICY

After completion of the study, the results will be analyzed and a clinical study report will be prepared. Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee. In addition, upon study completion and finalization of the study report the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

17. BIBLIOGRAPHY

1. WHO. Ten top causes of deathe http://www.who.int/mediacentre/en/2017 [
2. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 http://goldcopd.org [
3. Läkemedelsverket. COPD - treatment recommendations(in Swedish) https://lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/Kroniskt_obstruktiv_lungsjukdom_KOL_behandlingsrekommendation.pdf [
4. Lofdahl CG, Tilling B, Ekstrom T, Jorgensen L, Johansson G, Larsson K. COPD health care in Sweden - A study in primary and secondary care. Respir Med. 2010;104(3):404-11.
5. Cruz J, Brooks D, Marques A. Home telemonitoring in COPD: a systematic review of methodologies and patients' adherence. Int J Med Inform. 2014;83(4):249-63.
6. McLean S, Nurmatov U, Liu JL, Pagliari C, Car J, Sheikh A. Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis. Br J Gen Pract. 2012;62(604):e739-49.
7. Cruz J, Brooks D, Marques A. Home telemonitoring effectiveness in COPD: a systematic review. Int J Clin Pract. 2014;68(3):369-78.
8. Gregersen TL, Green A, Frausing E, Ringbaek T, Brondum E, Suppli Ulrik C. Do telemedical interventions improve quality of life in patients with COPD? A systematic review. Int J Chron Obstruct Pulmon Dis. 2016;11:809-22.
9. Lilholt PH, Witt Udsen F, Ehlers L, Hejlesen OK. Telehealthcare for patients suffering from chronic obstructive pulmonary disease: effects on health-related quality of life: results from the Danish 'TeleCare North' cluster-randomised trial. BMJ Open. 2017;7(5):e014587.
10. Bernocchi P, Vitacca M, La Rovere MT, Volterrani M, Galli T, Baratti D, et al. Home-based telerehabilitation in older patients with chronic obstructive pulmonary disease and heart failure: a randomised controlled trial. Age Ageing. 2017:1-7.
11. Broendum E, Ulrik CS, Gregersen T, Hansen EF, Green A, Ringbaek T. Barriers for recruitment of patients with chronic obstructive pulmonary disease to a controlled telemedicine trial. Health Informatics J. 2016.
12. Stausholm MN, Egmose A, Dahl SC, Lilholt PH, Cichosz SL, Hejlesen OK. Stratification of telehealthcare for patients with chronic obstructive pulmonary disease using a predictive algorithm as decision support: A pilot study. J Telemed Telecare. 2017;23(3):410-5.