STATISTICAL ANALYSIS PLAN

Sponsor project number:	REDOX 2016
EudraCT number:	2016-000441-32
Title:	REgistry-based randomized controlled trial of treatment Duration and mortality in long-term OXygen therapy (REDOX) A Multicenter, Phase IV, Registry-Based, Randomized Controlled Trial (R-RCT)

Based on protocol version 1.8, date 2020-01-22

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SAP version: FINAL

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1 Introduction

The purpose of this plan is to give a complete and detailed description of the statistical analyses and the descriptive statistics that will be included in the report for the study REDOX. This SAP is based on protocol version "200122 REDOX Final Study Protocol v1.8_FINAL" The study biostatistician at Uppsala Clinical Research Center (UCR) is responsible for the writing of the plan and the execution of the statistical analyses. The results will be presented according to the output specification (see Appendix 2 Output Shells). This plan is completed prior to un-blinding/closing of the study database. The study report will include the analyses of the primary endpoint and secondary objectives concerning the primary endpoint. Following secondary objectives will not be analyzed and reported at UCR:

Compared to patients with LTOT prescribed for 15 h/day, does continuous oxygen therapy 24 h/day:

- Fail to reduce the rate of an incident diagnosis of cardiovascular disease?
- Fail to reduce the level of breathlessness?
- Fail to reduce fatigue?
- Fail to improve level of self-reported physical activity?
- Fail to improve health-related quality of life (HRQOL)?
- Fail to improve cognition?
- Fail to increase the patient's preference in continuing LTOT?

The statistical methods for the above are described in this plan, in order to be outlined before the analysis database is un-blinded and locked. However, these will be analyzed subsequently by the Sponsor Region Blekinge.

2 SAP version history

Version	Date	Reason for change
1.1	2023-04-05	
1.2	2023-04-06	See previous version
1.3	2023-04-24	See previous version

3 Abbreviations and definitions

Different patient groups will be used in the tabulations. The group *All randomized patients* consists of all patients who have fulfilled all the inclusion criteria but not any of the exclusion criteria, submitted signed informed consent to participate in the study and thereby received a patient number (=randomization number). Incorrectly registered patients are not included.

Screened subject	Patients who has signed the Informed Consent Form (ICF)
Randomized subjects	Patients who have fulfilled eligibility criteria and have been randomized
Screening failure	Patients that have been screened but have not been randomized, will be considered as screen failures
Withdrawals	Patients that were randomized but did not complete the study
Discontinued	Patients who discontinued LTOT

Summary table of abbreviations and definitions used in this plan

AE	Adverse event
COPD	Chronic obstructive pulmonary disease
DV	Derived variables
EVF	Erythrocyte volume fraction
FEV_1	Forced expired volume in one second
VC	Vital capacity
ITT	Intention-to-treat – all randomized patients who has started LTOT, regardless of adherence (see section 6.1 in this SAP)
IQR	The InterQuartile Range (the second and third quartiles, or the middle half of the data set)
kPa	Kilopascal
LPO	Last patient out
LTOT	Long-term oxygen therapy
OS	Output shells
PaO_2	Partial pressure of arterial oxygen
PP	Per protocol – patients who fulfill certain criteria (see section 6.2 in this SAP)

R-RCT	Registry-based, randomized, controlled trial
SAE	Serious adverse event
Safety population	All randomized patients who have started LTOT. This includes incorrectly randomized patients.
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
Swedevox	Swedish register for respiratory failure
UCR	Uppsala Clinical Research centre

4 Study objectives and outcome variables

4.1 Objectives

Long-term oxygen therapy (LTOT) prescribed 24 h/day vs. 15 h/day. Centers prescribing LTOT in the Swedish quality register for respiratory failure (Swedevox). Study end is defined as Last Patient Out (LPO), which is the date when last patient has been followed for 12 months.

4.1.1 Primary objective

Compared to patients with LTOT prescribed for 15 h/day, does continuous oxygen therapy 24 h/day fail to reduce the rate of all-cause death or first hospitalization at one year?

4.1.2 Secondary objectives

Compared to patients with LTOT prescribed for 15 h/day, does continuous oxygen therapy 24 h/day:
(underlined objectives will be analyzed and reported by UCR)

- Fail to reduce the mortality rate from all causes?
- Fail to reduce hospitalization rate from all causes?
- Fail to reduce mortality rate from respiratory disease?
- Fail to reduce mortality rate from cardiovascular disease?
- Fail to reduce hospitalization rate from respiratory disease?
- Fail to reduce hospitalization rate from cardiovascular disease?
- Fail to reduce the rate of an incident diagnosis of cardiovascular disease?
- Fail to reduce the level of breathlessness?
- Fail to reduce fatigue?
- Fail to improve level of self-reported physical activity?
- Fail to improve health-related quality of life (HRQOL)?
- Fail to improve cognition?
- Fail to increase the self-reported oxygen utilization?
- Fail to decrease the rate of LTOT withdrawal?
- Fail to increase the patient's preference in continuing LTOT?

4.2 Outcome variables

The outcome variables that will be analyzed and reported at UCR are underlined. This will be performed in the subgroups stated in Section 6.4. The secondary outcome variables that are not underlined will be analyzed later by the sponsor Region Blekinge with methods outlined in this SAP.

4.2.1 Primary outcome variable

All-cause mortality or 1st hospitalization 1 year after randomization.

4.2.2 Secondary outcome variables

- Mortality rate from all causes at 3 and 12 months
- Mortality rate from respiratory disease at 3 and 12 months
- Mortality rate from cardiovascular disease at 3 and 12 months
- Hospitalization rate from all causes at 3 and 12 months
- Hospitalization rate with a primary diagnosis of respiratory disease or respiratory infection at 3 and 12 months
- Hospitalization rate with a primary diagnosis of cardiovascular disease at 3 and 12 months
- Rate of an incident diagnosis of cardiovascular disease at 3 and 12 months

Self-reported questionnaire data collected at 3 and 12 months:

- Self-rated oxygen utilization
- Breathlessness (Multidimensional Dyspnea Profile; MDP)
- Fatigue (FACIT-Fatigue)
- Informant-rated cognition (IQCODE and FAQ)
- Self-rated cognition (BAS)
- Health-related quality of life (CAT and EQ5D-5L)
- Global impression of change from baseline (GIC)
- Self-reported physical activity
- Preference of continuing treatment

5 Study design

5.1 Design

This is a multicenter, single-blinded (analyst), effectiveness, phase IV, register-based, randomized controlled trial (R-RCT).

5.2 Population

Inclusion Criteria

- Age 18 years or older
- Standard eligibility criteria for non-palliative LTOT at rest (see protocol for references):

- PaO_2 < 7.4 kPa or oxygen saturation < 88 % breathing air, *or*
- PaO_2 < 8.0 kPa on air and either signs of heart failure or polycythemia (EVF > 0.54)

Exclusion Criteria

- Standard contraindications for LTOT
  - Smoking or contact with open fire
  - Other inability to safely comply with LTOT
- Already on LTOT for more than 4 weeks

- Inability to comply with any of the study interventions (LTOT 15h /day or 24 h/ day) as judged by the responsible oxygen staff
- Opt out from being registered in Swedevox
- Inability to give informed written consent to participate in the study as judged by the responsible oxygen staff
- Lack of Swedish identification number
- Previous participation in the study

5.3 Interventions

Intervention: LTOT prescribed for 24 h/day.

Control: LTOT prescribed for 15 h/day. The patient is instructed to use LTOT during sleep and to not use LTOT for a total 9 hours during daytime.

Treatment duration: From the date of randomization to 12 months after randomization (end of trial).

5.4 Follow-up

5.4.1 Clinical follow-up

The patient's medical record will be marked with the allocated LTOT duration at each center, to facilitate follow-up of the prescribed LTOT duration at subsequent clinical contacts. Clinical contacts, other treatments, and follow-up are undertaken according to routine clinical care at each center and are unaffected by study participation. Adverse events are reported within the framework of the routine clinical care.

5.4.2 Registry-based follow-up

All 48 units prescribing and managing LTOT in Sweden report to the National Registry for Respiratory Failure (Swedevox). Data on patient characteristics and the prescribed oxygen therapy are obtained from Swedevox. The completeness of the baseline data will be checked using Swedevox and optimized through contacts with participating centers by the national Swedevox coordinator and by the Study Coordinator.

The main endpoints of mortality and hospitalizations are assessed using national Swedish governmental registries: date and causes of death (Causes of Death Register), and the date and diagnoses/procedural codes of hospitalizations (National Patient Register of in- and outpatient care). Data are cross-linked

between registers using each participant's unique Swedish identity number. In addition, data will be obtained on dispensed outpatient medications (Prescribed Drug Register). Endpoints are assessed at 3 and 12 months after randomization (study end).

5.4.3 Questionnaire and reminder at 3 and 12 months

At 3 months (range 2 to 5 months) and 12 months (range 10 to 14 months) after randomization, all non-deceased participants (according to the Population Register) are sent a letter marked by the patients randomization number by the UCR Registry Unit (separated from the Clinical Research Unit responsible for managing of the study) which includes: 1) a standardized reminder about the allocated treatment to the patient and caregiver(s) (see study protocol, Appendix 2); 2) a questionnaire including data on smoking and on secondary endpoints (see study protocol, Appendix 3) and instructions about how to fill out and return it within 2 weeks in a stamped return envelope. If the questionnaire has not been returned to the UCR data management unit within 3 weeks, a reminder letter is sent home to the patient. The questionnaire data are entered into a database as reported (missing and incomplete data accepted) and quality checked by the UCR data management unit.

5.5 Blinding

This is a single-blinded (analyst) trial. The coordinating investigator, UCR study staff and statistician responsible for analyzing the study data will be blinded to the allocated treatment group. The patient, principal investigators and co-investigators, responsible study nurses, study monitor, caregiver, and the clinical oxygen staff will be aware of the allocated daily treatment duration.

5.6 Study outline

- Patient starting LTOT
- Inclusion/exclusion criteria
- Written consent
- Randomization in Swedevox at or within four weeks of starting LTOT
- Questionnaire three months after randomization, including self-reported adherence
- Study end at 1 year after randomization:
  Primary endpoint of all-cause mortality or hospitalization
  Secondary endpoints (registries and 12-month questionnaire, including self-reported adherence)

5.7 Study assessments

Item	Baseline	3 months	1 year (study end)
Swedevox Register			
Demographics	X		
Height and weight	X		
Spirometry	X		
Blood gases on air and oxygen	X		
Primary and secondary causes of starting LTOT	X		
Oxygen dose, equipment and duration	X		
Use of long-term mechanical ventilator	X		X
Date and reason of LTOT withdrawal		X	X
Causes of Death Register			
Date, place, and causes of death		X	X
Patient Register			
Diagnoses / comorbidity and procedures	X	X	X
Hospitalizations	X	X	X
Prescribed Drug Register			
Dispensed drug prescriptions	X	X	X
Clinical visits			
Adverse events		(X)[a]	(X)[a]
Patient questionnaire			
Self-reported oxygen utilization		X	X
Breathlessness (MDP; NRS of worst; refractory; mMRC)		X	X
Fatigue (FACIT-Fatigue)		X	X
Self-reported physical activity (modified Grimby questionnaire)		X	X
Cognitive questionnaires (BAS, IQCODE and FAQ)		X	X
HRQOL (EQ5D-5L and CAT)		X	X
Global impression of change (GIC)		X	X
Treatment preference		X	X

[a] Adverse events will be collected at the patient's ordinary clinical visits.

6 Definition of analysis populations

As non-adherence to the allocated treatment might cause a potential bias towards equivalence between treatments, in which analysis according to the intention to treat (ITT) principle would not be conservative, all endpoints will be analyzed according to both the ITT and the Per Protocol (PP) principle in the subpopulations stated in section 6.3.

The classification of study patients into different analysis populations will be performed after the unblinding of treatment allocation to the analyst.

6.1 Intention to treat (ITT) population

A randomized patient will only be excluded from the analysis ITT set if LTOT was never started.

6.2 Per protocol (PP) population

A randomized patient will be excluded from the PP set if LTOT has been discontinued or the mean LTOT utilization during follow-up to the primary endpoint is below 20 h/day for the 24 h/day group, and below 13 h/day or above 17 h/day in the LTOT 15 h/day group. Self-reported oxygen utilization at 12 months, or if that is unavailable, at 3 months will be used for PP classification.

6.3 Safety population

All randomized patients who have started treatment with long-term oxygen therapy (LTOT) belong to the *Safety population* and will be studied with regard to adverse events. If there are no incorrectly randomized patients or patients who started the wrong treatment, the safety population will be the same as the ITT population.

6.4 Subpopulations

Primary analysis:

I. All randomized participants

Secondary analyses:

II. Participants with more severe resting hypoxemia (PaO2 < 7.4 kPa on air) at LTOT start

III. Participants with more moderate hypoxemia (PaO2 7.4–8.0 kPa on air) at LTOT start

IV. Participants with verified COPD (COPD as primary diagnosis and FEV1/FVC < 0.7 after bronchodilation) [defined using primary diagnosis + spirometry in Swedevox]

V. Participants with primary diagnosis other than COPD

7 Statistical analysis

7.1 Study conduct and Subject/Patient disposition

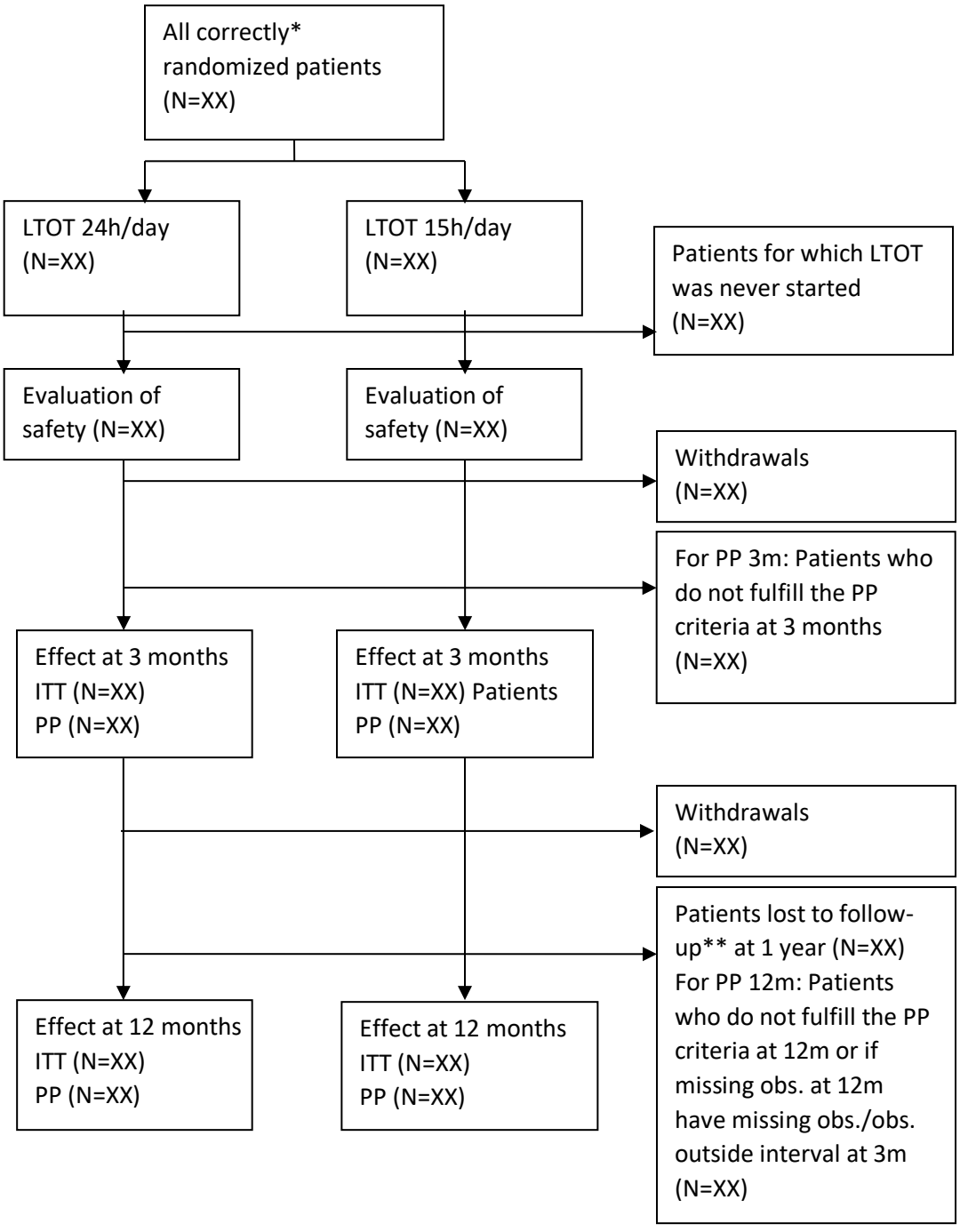
Recruitment between sites and over time will be presented. A figure with number of patients included over time will be constructed. Inclusion will also be described as Kaplan-Meier plots of patients randomized per calendar month, first and last inclusion date, descriptive statistics of time from randomization to death or censoring, and number of patients by randomizing centre, for the ITT, PP and subgroup populations. *(Table 4 and 5) (Figure 1 and 2)*

The number of patients screened and randomized in the study will be presented together with the number of patients completed the study. The numbers withdrawn in total and for each pre-defined withdrawal reason will be presented. The number of LTOT discontinued patients will be presented separately. The allocation of patients to each analysis population group will also be presented together with the reasons for exclusions from Analysis sets. If applicable, a table with number of protocol deviations by category will be created. Number of patients will be presented by treatment and in total. Screening failures (and reasons) will be presented in a listing.
(Table 1,2 and 3)

CONSORT flow chart (will be presented as table)

* A patient is correctly randomized if he or she fulfills the inclusion criteria but not the exclusion criteria, has signed informed consent and has been randomized in Swedevox within four weeks of starting LTOT.

**All registry data available except for withdrawals



7.2 Baseline characteristics

Baseline characteristics will be described by randomized treatment and in total for the ITT, PP and subgroup populations. Categorical data will be described as total number and percentage, with missing data as a separate category. Numerical data will be described using number of patients with data, and median, IQR, arithmetic mean and standard deviation for patients with data.

The randomized treatment groups will be compared using the chi-square test statistic for categorical variables and the Wilcoxon's test statistic for numerical data, using observed cases. The results will be presented as p-values, but are not to be considered as statistical tests. They will only be used if needed to satisfy a non-CONSORT journal house style that requires Table 1 p-values. All perceived differences will be due to chance since the groups are randomized.
(Table 6)

7.3 External validity

De-identified and aggregated data for the complete Swedevox LTOT cohort for same time period (date of first to last patient randomized), in total and per participating unit will be compared regarding:

1. Proportion of randomized patients
2. Baseline characteristics

A table with baseline characteristics such as age, gender, smoking, BMI etc. will be constructed and proportion randomized patients among these will be presented.

7.4 Adherence

Completed randomized treatment or reason for not completing randomized treatment will be presented as total number and percentage, by randomized treatment, for the ITT and subgroup populations. Any loss to follow-up for the composite endpoint of death or 1st hospitalization will be presented as patient listings. For statistical analyses of outcomes, the total number of patients with data for the analysis will be tabulated in the descriptive statistics for the outcome in question. The report will contain sufficient information to construct a CONSORT diagram. *(Table 1 and Table 9)*

Duration of treatment (number of days during the study) will be presented descriptively by randomized group using mean, SD, median, IQR, min and max value for observed cases, in the ITT and subgroup population. *(Table 8)*

Self-rated hours of oxygen utilization can be given as a point estimate or an interval estimate by the patient in the 3- and 12-month questionnaires. The midpoint will be used in the analyses when interval estimates are given. For the PP analysis of the primary endpoint, the 3-month observation of self-reported oxygen utilization will be used if the 12-month observation is missing.

7.5 Analysis of primary variable

The primary endpoint of the composite event of death or 1st hospitalization at 1 year (day 365; day 0 being the day of randomization) is analyzed with Cox´s proportional hazards model. Proportional hazard assumption will be investigated using graphical diagnostics based on the Schoenfeld residuals. The results will be presented as the hazard ratio (HR) for LTOT 24h/day vs. 15h/day with 90% two-sided

confidence interval and the one-sided p-value for the hypothesis test if the lower limit exceeds 0.67 (see section 9.1) A two-sided p-value for the difference between treatments will also be presented. (OS table 10 and table 11). The ITT population will be used for primary analysis but all endpoints will be analyzed according to both the ITT and the Per Protocol (PP) principle.

Statistical significance is defined as a p-value < 0.05. As a sensitivity analysis, the primary analysis is repeated adjusting for sex and age at randomization in years. A frailty model will be performed with "center" as a random effect to account for the clustering by hospital.

Cases withdrawing from LTOT treatment are for the primary analysis handled as

1) Per protocol, if it is due to improved oxygenation.
2) Having reached endpoint, if it is due to adverse event (such as excessive nose bleeding etc.).
3) Censored, if it is due to cancellation of treatment for reasons other than treatment allocation or adverse events (such as starting to smoke etc.).

7.6 Analysis of secondary variables

Hospitalizations are analyzed using Fine Gray regression [ref 1,2,3] accounting for death as competing event. All-cause mortality will be analyzed as the secondary outcome. Number of competing events will be presented for each analysis. Other secondary endpoints are analyzed using two-sided Student's t-tests for continuous variables (including HRQOL, breathlessness, cognition, fatigue, activity, and health care usage) and chi-2 test for categorical variables (causes of death, cognition, treatment preference). Correlational analyses, including of factors predictive of the primary and secondary outcomes will be conducted using linear regression (continuous outcomes), logistic regression (categorical outcomes), and Cox and Fine-Gray regression models (time to event outcomes).

All analyses are subject to underlying conditions – if not fulfilled due to e.g. a too small sample, it will not be attempted. Analyses of secondary variables other than the ones underlined in section 4.2.2 will be performed at Region Blekinge.

7.7 Handling of missing data and data outside range

No imputation of missing data for variables used in the primary or secondary analyses will be performed. Only observed data will be used in the analyses.

If the date on a 3-month or 12-month form is either missing or unreadable we assume that the form was filled out at exactly 3 months or 12 months, respectively. For the PP analysis of the primary endpoint, the 3-month observation of self-reported oxygen utilization will be used if the 12-month observation is missing.

Data from forms submitted after hospitalization will not be used in the analysis of the primary outcome.

7.8 Evaluation of safety

Adverse events will be presented as plain text in a listing. If applicable, the number of adverse events will be compiled per treatment group in a frequency table. No statistical test between the treatment groups will be performed.

8 Analysis data base definitions

8.1 Data sources and terminology

Swedevox include individual participant data including the date and main reason of starting LTOT; arterial blood gases (PaO2 and PaCO2) on air and on oxygen; in some cases the oxygen saturation (SaO2); equipment, prescribed oxygen flow rate (liters/min); prescribed treatment duration (h/day); age; gender; height and weight (for calculation of the body mass index); performance status; and spirometry that should be representative of the patient's stable status before starting LTOT: the forced expired volume in one second (FEV1) and forced vital capacity (FVC). These data will be used for characterizing the participants at study start and for categorization into analysis groups according to severity of hypoxemia and underlying cause of starting LTOT (COPD vs. ILD).

More detailed information regarding data sources will be described in DMP (Data Management Plan)

9 Determination of sample size

9.1 Limit of non-superiority and Hypotheses

A time-to-composite event survival analysis, with composite event equal to death or 1st hospitalization as endpoint, is used. The hypothesis of non-superiority of continuous oxygen is tested. The null hypothesis is rejected if the hazard ratio (HR) of continuous oxygen vs. 15h/day exceeds the limit 0.67. The use of oxygen is burdensome and with hospitalization, being less serious than death, incorporated into the primary endpoint, the HR of 0.67 was judged to be the appropriate limit for the composite primary outcome. This was the difference in mortality or hospitalization that the investigators judged to be clinically worthwhile. (See also section 10 Changes to the planned analysis.)

H_0: $HR_{24h/day\ vs.\ 15h/day} \leq 0.67$

H_A: $HR_{24h/day\ vs.\ 15h/day} > 0.67$ Continuous oxygen is <u>not</u> better than 15h/day;

If significance is obtained, the conclusion is that LTOT prescribed for 24 h/day does not reduce the rate of the composite event of all-cause death or 1st hospitalization at 1 year compared to LTOT prescribed for 15 h/day in patients starting LTOT for chronic respiratory failure.

9.2 Sample size calculation

Calculation of the final required sample was based on a time-to-composite event survival model with the use of the Cox proportional hazards (PH) model and checked against the results of the log-rank test statistic. Assuming 80% power to verify a hazard ratio for death or 1st hospitalization of more than 0.67 in the 24h group vs. the 15h group, a one-sided type I error rate of 0.05, and an event rate of 80% based on Swedevox registry data, we calculated a total sample size of 189 patients with Cox PH and 181 using the log-rank statistic. Making allowances for a loss of patients in the PP analysis, <u>the final planned total trial size is 230</u>, with 1:1 allocation. No patient is expected to be lost to follow-up for the primary composite endpoint of death or 1st hospitalization in the ITT population, due to the use of national registries. The following R code for a Cox PH non-inferiority calculation, inverting the hypothesized hazard ratio from the non-superiority hypothesis for this study, was used for the sample size calculation:

#Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 177.
#Hazard Ratio, hr
#Null-Hypothesis Hazard Ratio, hr0
#Overall Probability of Event, pE
#Proportion of Sample in Group 'A', pA

```
> hr=1
> hr0=1.5
> pE=0.8
> pA=0.5
> alpha=0.05    # 1-sided test
> beta=0.20
> (n=((qnorm(1-alpha)+qnorm(1-beta))/(log(hr)-log(hr0)))^2/(pA*(1-pA)*pE))
[1] 188.0317
> ceiling(n)
[1] 189
```

10 Changes to the planned analysis (2020-01-22)

The original design of this trial was based on a time-to-event survival analysis with death as endpoint and the hypothesis of non-superiority of continuous oxygen with a hazard ratio (HR) of 0.83 (larger than this would indicate non-superiority). This was the difference in mortality that the investigators judged to be clinically worthwhile. With the current design, which was specified in amendment 3 (2020-01-22), time-to-composite event survival analysis is used, with composite event equal to death or 1st hospitalization. Since the use of oxygen is burdensome and hospitalization less serious than death, an HR of 0.67 was judged to be appropriate for the composite primary outcome. The recently published large study of LTOT (LOTT) (see protocol reference 13) had an HR of 0.60 in their amendment for the composite endpoint of death or 1st hospitalization and an expansion of the primary analysis population, but that study is for supplemental oxygen vs. none (which should reduce the HR) and patients that were less ill with milder hypoxemia (which should increase the HR) and thus not directly comparable.

Summary of differences as compared to the original protocol

1. A composite event of death or 1st hospitalization, instead of death as the event.
2. A lower limit of non-superiority; 0.67 instead of 0.83.
3. The primary analysis is based on all randomized patients, instead of only the COPD patients.
4. A simplification of the secondary analyses due to the reduction of the sample size.

11 Description of derived variables

The description of derived variables is attached in appendix Draft_SAP_v1.0 (DV).docx.

12 Description of output

The output specification (output shells, OS), describing tables, graphs and lists that will be included in the study report, is attached in appendix Draft_SAP_v1.0 (OS).docx.

13 Statistical software

Statistical analyses will primarily be performed using SAS v. 9.4 or later and/or R (Version 4.2.3).

14 References

[1] Zhou, B., Fine, J., Latouche, A., and Labopin, M. (2012). "Competing Risks Regression for Cluster Data." *Biostatistics* 13:371–383.

[2] Zhou, B., Latouche, A., Rocha, V., and Fine, J. (2011). "Competing Risks Regression for Stratified Data." *Biometrics* 67:661–670.

[3] Fine, J. P., and Gray, R. J. (1999). "A Proportional Hazards Model for the Subdistribution of a Competing Risk." *Journal of the American Statistical Association* 94:496–509.

DERIVED VARIABLES

*Socialstyrelsen will provide us with the date of event. Time to event (in days) will be calculated by UCR

*Time to composite event (All-cause mortality/ All-cause Hospitalization)	Included in the order from Socialstyrelsen
*Time to all-cause mortality	Included in the order from Socialstyrelsen
*Time to 1st hospitalization	Included in the order from Socialstyrelsen
Mortality from respiratory disease	respiratory disease or infection (A40; J00-J99)
Mortality from cardiovascular disease	Underlying cause of death (UCD) heart disease (I00-I99)
Hospitalization from respiratory disease	UCD respiratory disease or infection (A40; J00-J99)
Hospitalization from cardiovascular disease	UCD heart disease (I00-I99)
Time to Mortality from respiratory disease	Death (from respiratory disease) date – Study start date
Time to Mortality from cardiovascular disease	Death (from cardiovascular disease) date – Study start date
Time to Hospitalization from respiratory disease	Date of hospitalization from respiratory disease – Study start date
Time to Hospitalization from cardiovascular disease	Date of hospitalization from cardiovascular disease – Study start date
Time from start until the patient stops being treated	End of treatment – Date for start of treatment
Discontinued LTOT	From Swedevox Registry
Withdrawals	DATE_OF_LTOT_WITHDRAWAL REASON_W
ITT	All randomized patients that start LTOT
PP	A randomized patient will be excluded from the PP set if LTOT has been discontinued before the primary outcome assessment or the mean LTOT utilization during follow-up to the primary endpoint is below 20 h/day for the 24 h/day group, and below 13 h/day or above 17 h/day in the LTOT 15 h/day group
COPD	J44; exacerbation: J44.0 and J44.1
Heart disease	I00-I99
Respiratory disease or infection	A40; J00-J99
fev1/fvc	FEV1/FVC
BMI	WEIGHT(kg)/(HEIGHT (m)*HEIGHT (m))
Age	Round down (RANDOMIZATION_DATE - DATE_OF_BIRTH)/365.25
Duration of treatment	Number of days with treatment during the study
Self-rated hours of oxygen	Self-reported oxygen use (mean hours/24h) is categorized using 1) average use since starting LTOT, or (if missing) mean h/day last week; using the

	questionnaire at 12 months, or (if missing) 3 months (and the described algorithm used for each time point).
Subgroup 1 Participants with more severe resting hypoxemia at LTOT start	PaO_2 < 7.4 kPa breathing air
Subgroup 2 Participants with more moderate hypoxemia at LTOT start	PaO_2 7.4–8.0 kPa breathing air
Subgroup 3 Participants with spirometry verified COPD	Primary diagnosis COPD or emphysema, and FEV_1/FVC < 0.7 after bronchodilation) [defined using primary diagnosis + spirometry data in Swedevox]
Subgroup 4 Participants with other conditions than COPD	Other primary diagnosis than COPD in Swedevox

OUTPUT SHELLS

Appendix 2 for SAP for study REDOX 2016

Version: FINAL

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1 Tables

The most of the tables will be presented by ITT, PP, subgroups and at 3 and 12 months, where applicable.

The subgroups mentioned in this plan are corresponding to following definitions:

Subgroup 1= **Patients with more severe resting hypoxemia (PaO2 < 7.4 kPa on air) at LTOT start**

Subgroup 2= **Patients with more moderate hypoxemia (PaO2 7.4–8.0 kPa on air) at LTOT start**

Subgroup 3= **Patients with verified COPD (FEV1/FVC < 0.7 after bronchodilation)**

Subgroup 4= **Patients with primary diagnosis other than COPD**

Table 1 Subject disposition

	Treatment group		
	LTOT 24h/day n	LTOT 15h/day n	Total n
Patients screened /enrolled			x
Patients randomized in the study	x	x	x
Patients completed the study, n(%)*	x(x)	x (x)	x (x)
Patients discontinued LTOT, n (%)*	x(x)	x (x)	x (x)
- due to x**	x(x)	x (x)	x (x)
- due to xx**	x(x)	x (x)	x (x)
- due to xxx**	x(x)	x (x)	x (x)
Patients withdrawn from the study, n(%)*	x (x)	x (x)	x (x)
- due to x**	x(x)	x (x)	x (x)
- due to xx**	x(x)	x (x)	x (x)
- due to xxx**	x(x)	x (x)	x (x)
Patients included in Safety population***	x(x)	x (x)	x (x)
Patients included in Intention to Treat (ITT) population*	x(x)	x (x)	x (x)
Patients included in Per Protocol (PP) population*	x(x)	x (x)	x (x)
Patients with more severe resting hypoxemia at LTOT start *	x(x)	x(x)	x(x)
Patients with more moderate hypoxemia at LTOT start *	x(x)	x(x)	x(x)
Patients with verified COPD*	x(x)	x(x)	x(x)
Patients with other conditions than COPD*	x(x)	x(x)	x(x)

*the denominator is the number of randomized patients

** the denominator is the number of withdrawn patients

***I f there are no incorrectly randomized patients or patients who started the wrong treatment, the safety population will be the same as the ITT population.

Table 2 Reason for exclusion from analysis sets

Based on the number of randomized subjects

	LTOT 24h/day n	LTOT 15h/day n	Total n
Number of excluded from Intention to Treat (ITT)	x	x	x
Reason for Exclusion from Intention to Treat (ITT)			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)
- due to xxx etc..	x(x)	x(x)	x(x)
Number of excluded from Per Protocol Analysis Set (PP)	x	x	x
Reason for Exclusion from Per Protocol Analysis Set (PP)			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)
- due to xxx etc..	x(x)	x(x)	x(x)
Number of excluded from Subgroup 1	x	x	x
Reason for Exclusion from Subgroup 1			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)
- due to xxx etc..	x(x)	x(x)	x(x)
Number of excluded from Subgroup 2	x	x	x
Reason for Exclusion from Subgroup 2			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)
- due to xxx etc..	x(x)	x(x)	x(x)
Number of excluded from Subgroup 3	x	x	x
Reason for Exclusion from Subgroup 3			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)

- due to xxx etc..	x(x)	x(x)	x(x)
Number of excluded from Subgroup 4	x	x	x
Reason for Exclusion from Subgroup 4			
- due to x*	x(x)	x(x)	x(x)
- due to xx*	x(x)	x(x)	x(x)
- due to xxx etc..	x(x)	x(x)	x(x)

Table 3 Protocol deviations

NOTE: This table will be created if there is enough data. Otherwise, protocol deviations will be presented in a listing

Protocol deviations	LTOT 24h/day n	LTOT 15h/day n	Total n
Number of protocol deviations	x	x	x
Protocol deviations Categories			
xxx	x(%)	x(%)	x(%)
xxx	x(%)	x(%)	x(%)
xxx	x(%)	x(%)	x(%)
xxx	x(%)	x(%)	x(%)
Etc.	x(%)	x(%)	x(%)

*Denominator is number of major protocol deviation

Table 4 Number of patients by randomizing center

Center	Number of screened patients n	Number of included patients n	Number of included patients n(%)*	Number of patients included in ITT population n	Number of patients included in PP population n	Number of patients included in subgroup= **Patients with more severe resting hypoxemia at LTOT start**	Number of patients included in subgroup= **Patients with more moderate hypoxemia at LTOT start**	Number of patients included in subgroup= **Patients with verified COPD**	Number of patients included in subgroup= **Patients with other conditions than COPD**
Falun									
Göteborg									
Malmö									
Etc…									
All sites									

*Denominator in the number of screened patients

Table 4.1 Number of patients by randomizing center: treatment group: LTOT 24h/day

Similar table as table above

Table 4.2 Number of patients by randomizing center: treatment group: LTOT 15h/day

Similar table as table above

Table 5 Time from randomization to death/hospitalization or censoring

Time to event = time from randomization to (death / hospitalization) / time from randomization to censoring

First and last inclusion date will be presented

Table 5.1 ITT

	Variable	N	Mean	Median	IQR	Minimum	Maximum
LTOT 24h/day	Time to death	xx	xx.x	xx.x	xx.x	xx	xx
	Time to first hospitalization	xx	xx.x	xx.x	xx.x	xx	xx
	Time to Composite	xx	xx.x	xx.x	xx.x	xx	xx
LTOT 15h/day	Time to death	xx	xx.x	xx.x	xx.x	xx	xx
	Time to Hospitalization	xx	xx.x	xx.x	xx.x	xx	xx
	Time to Composite	xx	xx.x	xx.x	xx.x	xx	xx
Total	Time to death	xx	xx.x	xx.x	xx.x	xx	xx
	Time to Hospitalization	xx	xx.x	xx.x	xx.x	xx	xx
	Time to Composite	xx	xx.x	xx.x	xx.x	xx	xx

Table 5.2 At 3 months (PP)
Table 5.3 At 3 months (Subgroup 1)
Table 5.4 At 3 months (Subgroup 2)
Table 5.5 At 3 months (Subgroup 3)
Table 5.6 At 3 months (Subgroup 4)

Table 5.7 At 12 months (ITT)
Table 5.8 At 12 months (PP)
Table 5.9 At 12 months (Subgroup 1)
Table 5.10 At 12 months (Subgroup 2)
Table 5.11 At 12 months (Subgroup 3)
Table 5.12 At 12 months (Subgroup 4)

Table 5.13 Event rate at 3 months (ITT)

	Statistics	LTOT 24h/day	LTOT 15h/day	Total
Composite (All-cause mortality/ All-cause Hospitalization)	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
All-cause Hospitalization	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Number of competing events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
All-cause mortality	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
Mortality from respiratory disease	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
Mortality from cardiovascular disease	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Person-years	xxx	xxx	xxx

	Statistics	LTOT 24h/day	LTOT 15h/day	Total
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
Hospitalization from respiratory disease	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Number of competing events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		
Hospitalization from cardiovascular disease	Number of patients	xx	xx	xx
	Number of events	xx	xx	xx
	Number of competing events	xx	xx	xx
	Person-years	xxx	xxx	xxx
	Events/Participants	xx.x	xx.x	xx.x
	Event rate per 100 patient-years (95% CI)	xx.x	xx.x	xx.x
	HR (95% CI) - p-value	xx.x (x.xx-x.xx) – 0.xxxx		

Table 6 Demographics and characteristics at baseline

Table 6.1 ITT

Variable	Statistics	LTOT 24h/day n	LTOT 15h/day n	Total n	*P-value
Age (years)	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Sex	Male, n (%)	x (x)	x (x)	x (x)	0.xxx
	Female, n (%)	x (x)	x (x)	x (x)	
	Missing	x (x)	x (x)	x (x)	
Height	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Weight	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Body Mass Index (BMI)	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Smoking status	Never smoked	x (x)	x (x)	x (x)	0.xxx
	Former smoker	x (x)	x (x)	x (x)	
	Current smoker	x (x)	x (x)	x (x)	
	Unknown	x (x)	x (x)	x (x)	
Performance status	Can handle normal activity (WHO 0)	x (x)	x (x)	x (x)	0.xxx
	Symptoms but almost completely recovered (WHO 1)	x (x)	x (x)	x (x)	
	Confined to bed (<50% of daytime) (WHO 2)	x (x)	x (x)	x (x)	
	Staying in bed (>50% of daytime) (WHO 3)	x (x)	x (x)	x (x)	
	Unable to get out of bed (WHO 4)	x (x)	x (x)	x (x)	
	Missing	x (x)	x (x)	x (x)	
Primary diagnosis	COPD	x (x)	x (x)	x (x)	0.xxx
	Emphysema	x (x)	x (x)	x (x)	

Variable	Statistics	LTOT 24h/day n	LTOT 15h/day n	Total n	*P-value
	Other respiratory disease	x (x)	x (x)	x (x)	
	Pulmonary fibrosis	x (x)	x (x)	x (x)	
	Sarcoidosis	x (x)	x (x)	x (x)	
	Other parenchymal disease	x (x)	x (x)	x (x)	
	Hypertension	x (x)	x (x)	x (x)	
	Chronic pulmonary embolism	x (x)	x (x)	x (x)	
	Other pulmonary vascular disease	x (x)	x (x)	x (x)	
	Heart disease	x (x)	x (x)	x (x)	
	Thoracic deformity	x (x)	x (x)	x (x)	
	Hypoventilation	x (x)	x (x)	x (x)	
	Tumor in lung or pleura	x (x)	x (x)	x (x)	
	Other	x (x)	x (x)	x (x)	
Secondary diagnosis	COPD	x (x)	x (x)	x (x)	0.xxx
	Emphysema	x (x)	x (x)	x (x)	
	Other respiratory disease	x (x)	x (x)	x (x)	
	Pulmonary fibrosis	x (x)	x (x)	x (x)	
	Sarcoidosis	x (x)	x (x)	x (x)	
	Other parenchymal disease	x (x)	x (x)	x (x)	
	Hypertension	x (x)	x (x)	x (x)	
	Chronic pulmonary embolism	x (x)	x (x)	x (x)	
	Other pulmonary vascular disease	x (x)	x (x)	x (x)	
	Heart disease	x (x)	x (x)	x (x)	
	Thoracic deformity	x (x)	x (x)	x (x)	
	Hypoventilation	x (x)	x (x)	x (x)	
	Tumor in lung or pleura	x (x)	x (x)	x (x)	
	Other	x (x)	x (x)	x (x)	
Liquid oxygen	Yes	x (x)	x (x)	x (x)	0.xxx
	No	x (x)	x (x)	x (x)	
	Unknown	x (x)	x (x)	x (x)	
Oxygen concentrator	Yes	x (x)	x (x)	x (x)	0.xxx
	No	x (x)	x (x)	x (x)	
	Unknown	x (x)	x (x)	x (x)	
Portable oxygen	Yes	x (x)	x (x)	x (x)	0.xxx
	No	x (x)	x (x)	x (x)	

Variable	Statistics	LTOT 24h/day n	LTOT 15h/day n	Total n	*P-value
	Unknown	x (x)	x (x)	x (x)	
Type of portable oxygen	Liquid oxygen	x (x)	x (x)	x (x)	0.xxx
	Oxygen tubes	x (x)	x (x)	x (x)	
	Portable concentrator	x (x)	x (x)	x (x)	
	Unknown	x (x)	x (x)	x (x)	
Prescribed oxygen flow rate (l/min)	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Prescribed treatment duration (hours/day)	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
PO2 air	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
PCO2 air	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
SPO2 air	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
PO2 oxygen	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
PCO2 oxygen	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
SPO2 oxygen	n	x	x	x	0.xxx

Variable	Statistics	LTOT 24h/day n	LTOT 15h/day n	Total n	*P-value
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
FEV1	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
FVC	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	
Concurrent treatment with home bilevel PAP (bilevel positive airway pressure)	n	x	x	x	0.xxx
	Mean (SD)	x (x)	x (x)	x (x)	
	Median (IQR)	x (x)	x (x)	x (x)	
	Missing	x	x	x	

* The treatment groups chi-square test statistic for categorical variables and the Wilcoxon's test statistic for numerical data using observed cases

Table 7 External validity

Aggregated data for the complete Swedevox LTOT cohort for same time period (first to last patient randomized) will be compared to study data. A table with baseline characteristics (as in table 6) such as age, gender, smoking, BMI etc. will be constructed. Proportion randomized patients among these will be presented.

Table 8 Number of days of treatment

*This table shows the total LTOT duration (number of days)

	LTOT Duration of treatment		
Population	Statistics	LTOT 24h/day n	LTOT 15h/day n
ITT	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		
PP	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		
Subgroup 1	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		
Subgroup 2	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		
Subgroup 3	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		
Subgroup 4	n		
	Mean (SD)		
	Median (IQR)		
	Min-Max		

Table 9 Description of outcomes

The table below shows the descriptive data by treatment group for each outcome.

Table 9.1 ITT

	Outcome	Statistics	LTOT 24h/day n	LTOT 15h/day n	Total n
At 3 months	All-cause mortality	n(%)			
	All-cause Hospitalization	n(%)			
	Composite (All-cause mortality/ All-cause Hospitalization)	n(%)			
	Mortality from respiratory disease	n(%)			
	Mortality from cardiovascular disease	n(%)			
	Hospitalization from respiratory disease	n(%)			
	Hospitalization from cardiovascular disease	n(%)			
	Self-reported hours of oxygen* (within 24 hours)	n			
		Mean (SD)			
		Median (IQR)			
		Min-Max			
At 12 months	All-cause mortality	n(%)			
	All-cause Hospitalization	n(%)			
	Composite (All-cause mortality/ All-cause Hospitalization)	n(%)			
	Mortality from respiratory disease	n(%)			
	Mortality from cardiovascular disease	n(%)			
	Hospitalization from respiratory disease	n(%)			
	Hospitalization from cardiovascular disease	n(%)			
	Self-reported hours of oxygen* (within 24 hours)	n			
		Mean (SD)			
		Median (IQR)			
		Min-Max			

* Self-reported oxygen use is defined as mean hours/day. If missing, we will use mean h/day last week, using the questionnaire at 12 months, or (if missing) 3 months.

Table 9.2 PP

Table 9.3 Subgroup 1

Table 9.4 Subgroup 2

Table 9.5 Subgroup 3

Table 9.6 Subgroup 4

Table 10 Analysis of the primary variable

Table 10.1 Primary outcome

Population	Outcome	Reference group	HR (90% CI)	p-value*	p-value**
ITT	Composite event of death or 1st hospitalization at 1 year	LTOT 15h/day	x.xx (x.xx-x.xx)	x.xx	x.xxx
PP	Composite event of death or 1st hospitalization at 1 year	LTOT 15h/day	x.xx (x.xx-x.xx)	x.xx	x.xxx

*The p-value for the difference between treatments H0: HR=1

** The p-value corresponds to the one-sided test, at 5% significance level, that the lower limit exceeds the hypothesized value 0.67

Table 10.2 Primary outcome adjusted for sex and age

Similar table as in 10.1 repeated adjusting for sex and age (in years) at randomization. A frailty model will be performed with "center" as a random effect to account for the clustering by hospital.

Table 11 Analyses of secondary variables

Table 11.1 Secondary outcome (ITT)

Population	Outcome	Reference group	n events/competing events	HR (90% CI)	p-value*	p-value**
At 3 months	Composite event of death or 1st hospitalization	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	All-cause mortality	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	All-cause Hospitalization***	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Mortality from respiratory disease	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Mortality from cardiovascular disease	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Hospitalization from respiratory disease***	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Hospitalization from cardiovascular disease***	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
At 1 year	All-cause mortality	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	All-cause Hospitalization ***	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Mortality from respiratory disease	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx

	Mortality from cardiovascular disease	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Hospitalization from respiratory disease***	LTOT 15h/day	xx/xx	x.xx (x.xx-x.xx)	x.xx	x.xxx
	Hospitalization from cardiovascular disease***	LTOT 15h/day	xx	x.xx (x.xx-x.xx)	x.xx	x.xxx

*** Hospitalizations are analyzed using Fine Gray regression accounting for death as competing event

Table 11.2 Secondary outcome (PP)

Table 11.3 Secondary outcome (Subgroup 1)

Table 11.4 Secondary outcome (Subgroup 2)

Table 11.5 Secondary outcome (Subgroup 3)

Table 11.6 Secondary outcome (Subgroup 4)

Table 11.7 Analysis of Self-reported hours of oxygen

Similar table as in 10.1

	Population	Outcome	Mean difference (95% CI)	p-value**
At 3 months	ITT	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	PP	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 1	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 2	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 3	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 4	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
At 1 year	ITT	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	PP	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 1	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 2	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 3	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx
	Subgroup 4	Self-reported hours of oxygen* (within 24 hours)	x.xx (x.xx-x.xx)	x.xx

* Self-reported oxygen use is defined as mean hours/day. If missing, we will use mean h/day last week, using the questionnaire at 12 months, or (if missing) 3 months. (Duration=number of hours per day)

**t-test for mean difference

Table 12 Adverse events (PP and ITT)

Table 12.1 Adverse events

This table will be constructed if there is enough data.

	LTOT 15h/day n=	LTOT 24h/day n=	Total n=
Number of patients with AE (Total number of AE)	n[n]	n[n]	n[n]
Number of patients with SAE (Total number of SAE)	n[n]	n[n]	n[n]
Number of patients with possibly related AE (Number of possibly related AE)	n[n]	n[n]	n[n]
Number of patients with probably related AE (Number of probably related AE)	n[n]	n[n]	n[n]
Number of patients with unrelated AE (Number of unrelated AE)	n[n]	n[n]	n[n]
Number of AE with maximum intensity=MILD	n	n	n
Number of AE with maximum intensity=MODERATE	n	n	n
Number of AE with maximum intensity=SEVERE	n	n	n
Number of patients with maximum AE intensity=MILD	n	n	n
Number of patients with maximum AE intensity=MODERATE	n	n	n
Number of patients with maximum AE intensity=SEVERE	n	n	n

Table 12.2 Time to adverse events

		LTOT 15h/day n=	LTOT 24h/day n=	Total n=
Time to adverse events (all adverse events)	n			
	Mean (SD)			
	Median (IQR)			
	Min-Max			

2Figures

NOTE: All figures below are based on dummy data

Figure 1 Figures for inclusion over time

Figure 1.1 Cumulative enrollment over time in the study (all randomized patients)

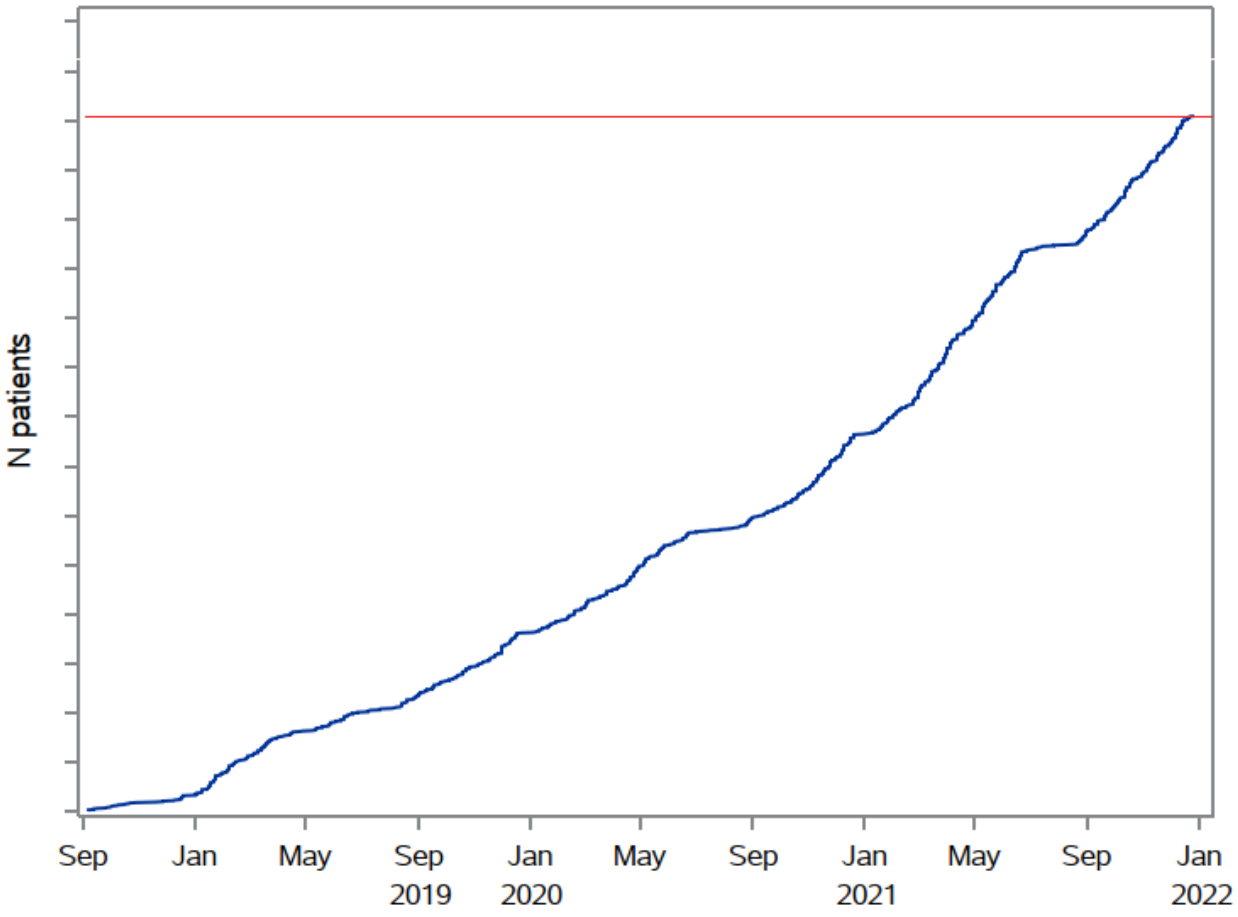


Figure 1.2 Cumulative enrollment over time in the study (by treatment)

If applicable

Figure 1.3 Cumulative enrollment over time in the study (by site)

If applicable

Figure 1.4 Cumulative enrollment over time in the study (by subgroup)

If applicable

Figure 1.5 Histogram with number of included patients by site and by treatment group

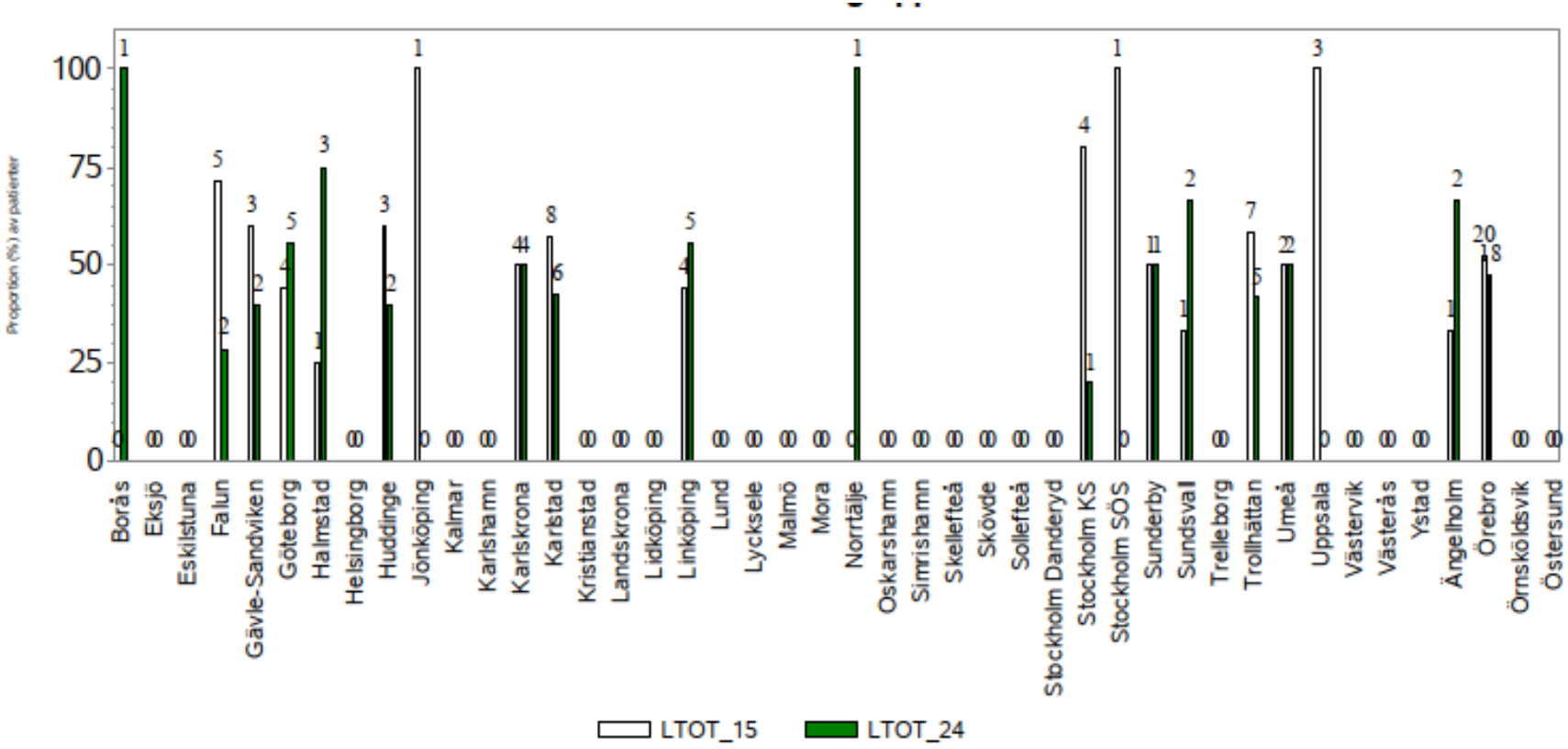


Figure 1.6 Reasons why the screened patients were not included in the study

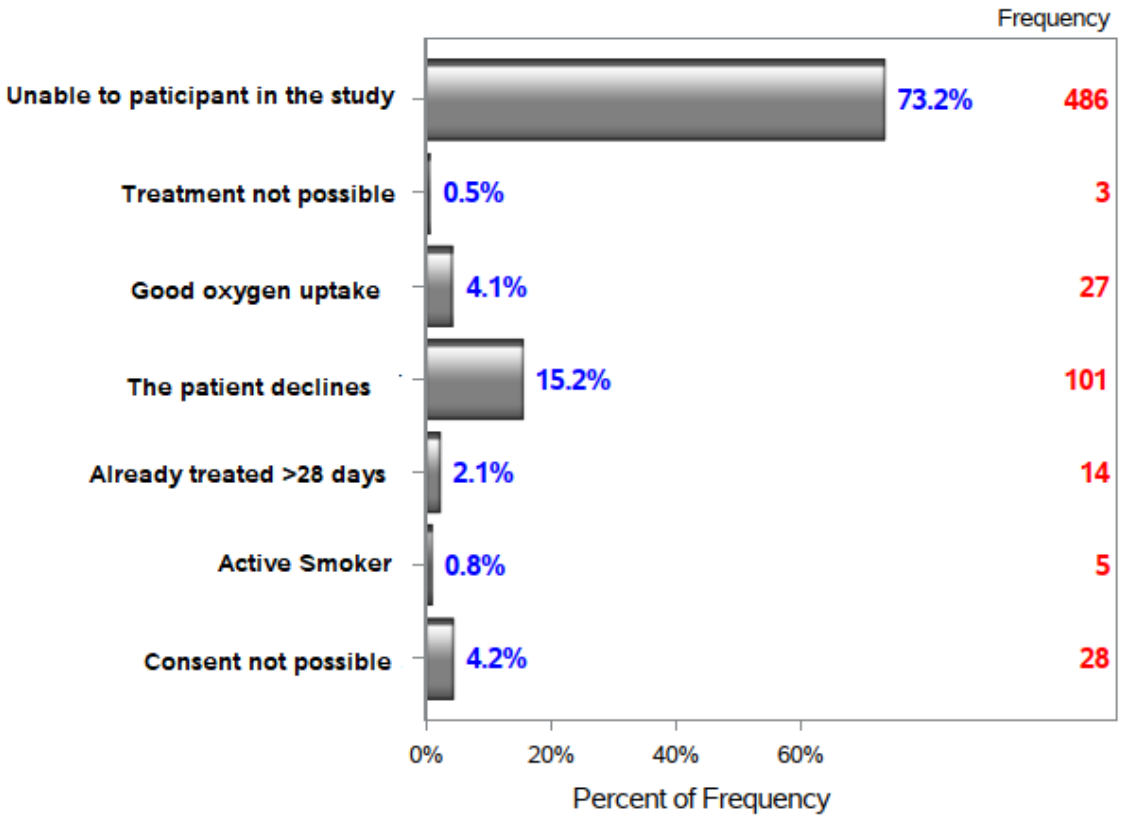


Figure 1.7 Kaplan-Meier figure: Time from start until the patient stops being treated

A figure will be constructed and presented by treatment arm. Patients who stop being treated with oxygen before one year will be censored at this time.

Figure 2 CONSORT flow chart

* A patient is correctly randomized if he or she fulfills the inclusion criteria but not the exclusion criteria, has signed informed consent and has been randomized in Swedevox within four weeks of starting LTOT.

**All registry data available except for withdrawals

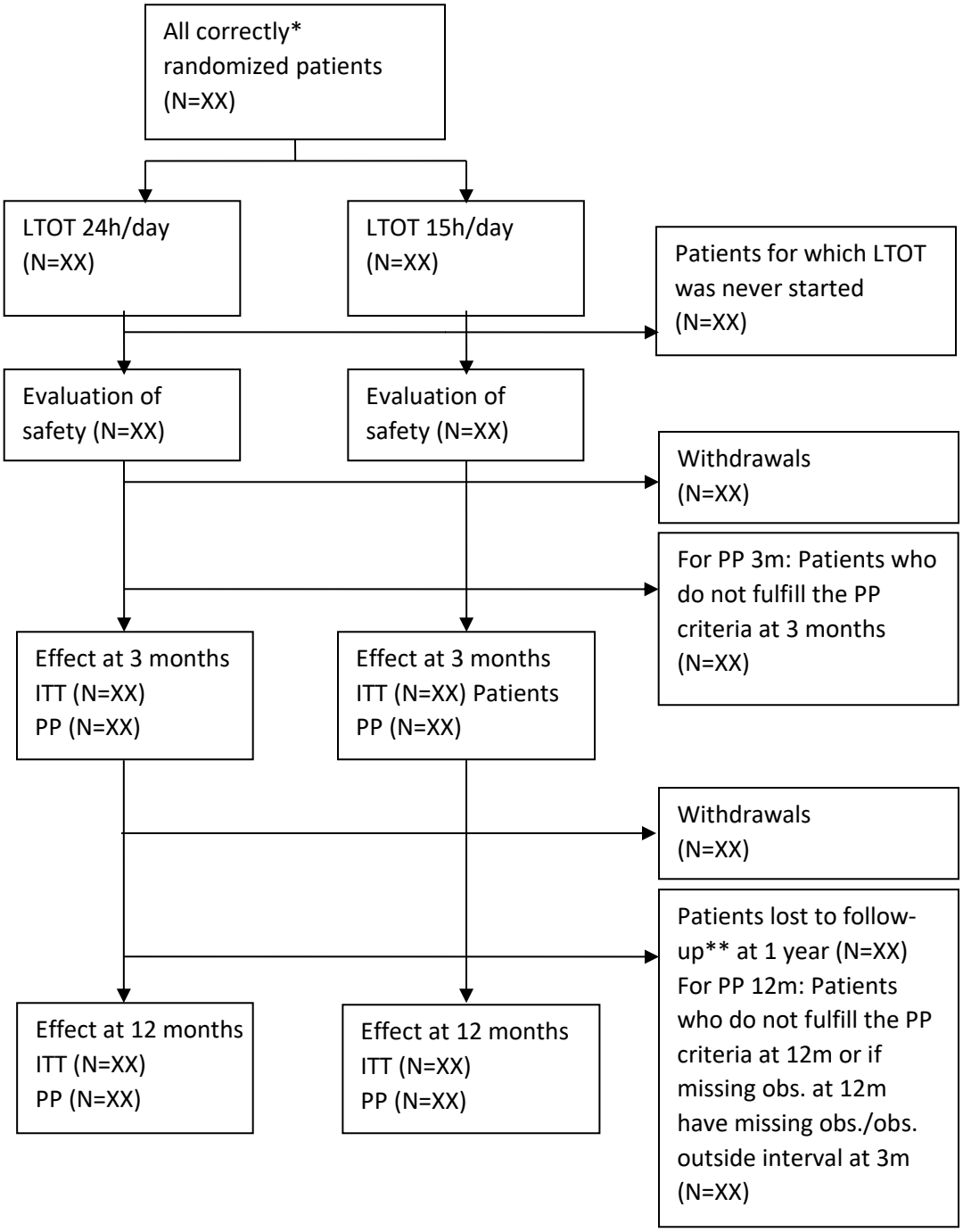
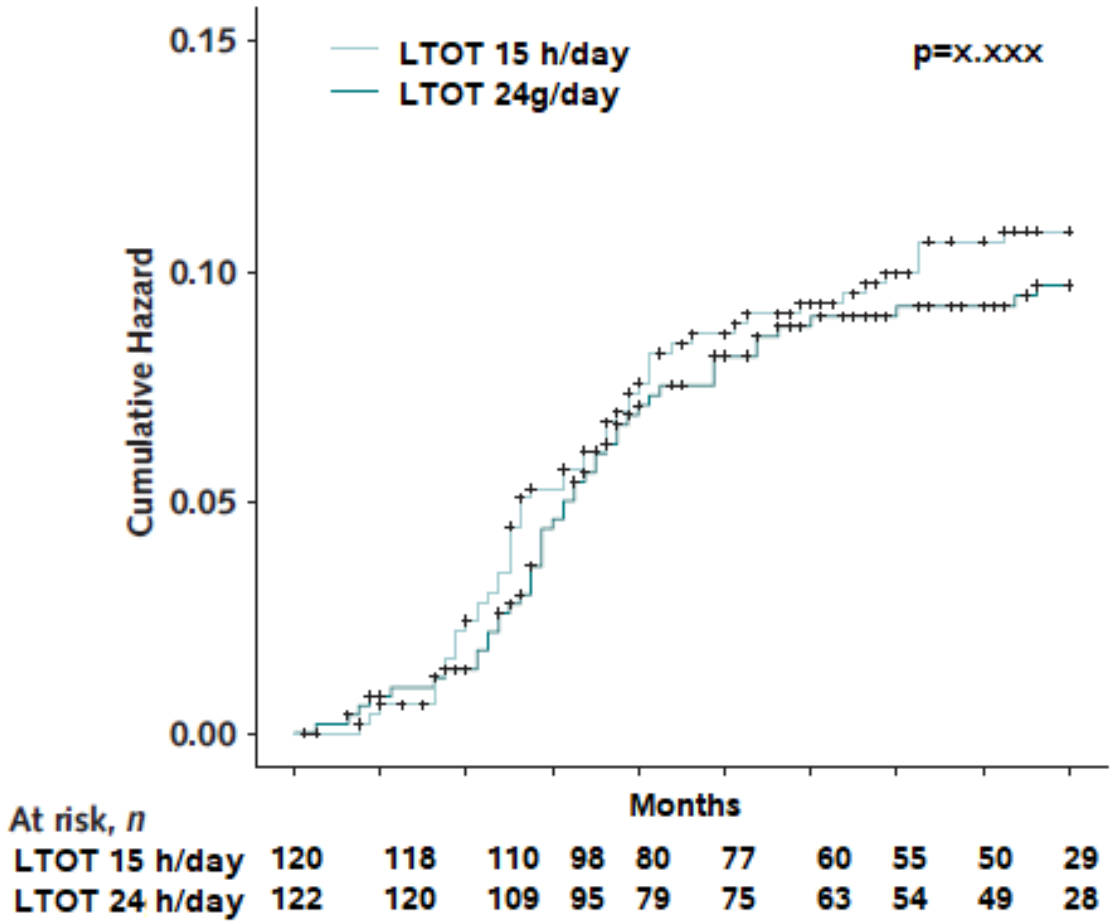


Figure 3 Cumulative hazard by treatment

Figure 3.1 Primary outcome (ITT)



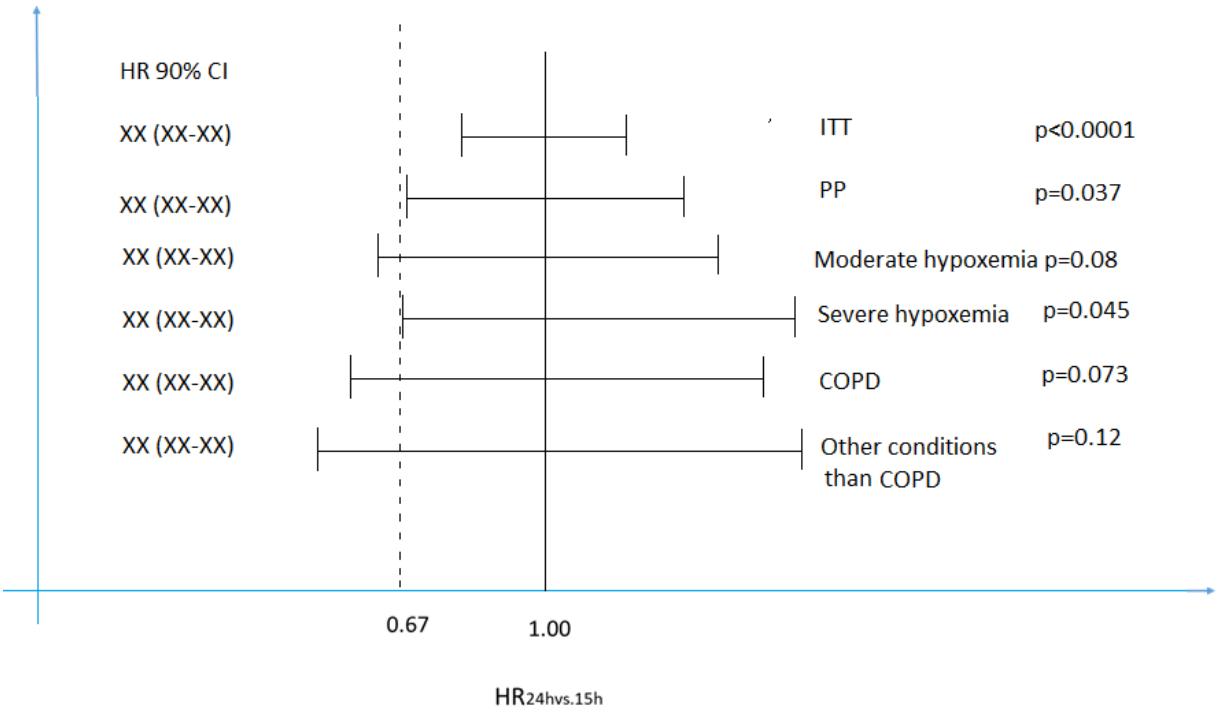
Similar figures will be constructed for all primary and secondary outcomes (at 3 months and 1 year) presented by ITT, PP, Subgroups 1-4.

Figure 4 Kaplan-Meier figures

Kaplan-Meier figures will also be presented for all primary and secondary outcomes

Figure 5 HR with non-superiority limit for the primary endpoint

90% confidence intervals for HR24hvs.15h, for the ITT, PP and subgroup populations. The p-value corresponds to the one-sided test, at 5% significance level, that the lower limit exceeds the hypothesized value 0.67.



Similar figures will be created for all secondary endpoints

3 Listings

Participant characteristics should also include center, population and randomized treatment group.