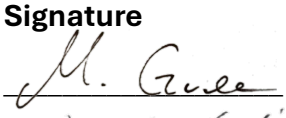
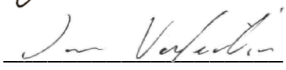
STOP-COPD: Statistical Analysis Plan (SAP)

Signatures

I confirm that the statistical analysis plan outlined below has been agreed upon prior to any data analysis and reflects the planned analytical methods for the STOP-COPD trial.

Name	Title	Signature	Date
Martin Faurholdt Gude	Principal Investigator		22-Apr-2025
Jan Brink Valentin	Trial Statistician		22-Apr-2025

Introduction

This Statistical Analysis Plan (SAP) outlines the predefined statistical methods and considerations for the STOP-COPD trial. The aim of the study is to investigate whether titrated oxygen therapy administered prehospitally reduces mortality and other adverse outcomes in patients with suspected acute exacerbation of chronic obstructive pulmonary disease (AECOPD), compared with standard high-flow oxygen treatment.

This SAP is version 1.0 and was finalized prior to any data analysis. It is fully aligned with the trial protocol, version 4.3 (dated 08.12.2023).

Objectives

Primary objective:

To determine whether a prehospital titrated oxygen strategy in patients with suspected acute exacerbation of chronic obstructive pulmonary disease (AECOPD) reduces 30-day all-cause mortality compared to standard high-flow oxygen therapy.

Secondary objectives:

- To assess whether titrated oxygen therapy improves patient-reported dyspnoea (rated on a 0–10 verbal rating scale) compared to standard care.

- To evaluate whether titrated oxygen therapy reduces the in-hospital need for non-invasive ventilation (NIV) or invasive ventilation.
- To assess the impact of titrated oxygen therapy on 24-hour and 7-day mortality.
- To determine whether titrated oxygen therapy reduces the proportion and severity of respiratory acidosis ($PaCO_2$ > 6.3 kPa and pH < 7.35) on hospital arrival.
- To evaluate subgroup effects of titrated oxygen on mortality, acidosis, ICU admission, and assisted ventilation by prehospital transport time.
- To assess differences in time to ICU admission, NIV, and invasive ventilation between treatment arms.
- To compare 30-day hospital readmission rates.
- To compare total hospital length of stay and ICU length of stay

Method

Study design, population

STOP-COPD is a single-centre, prospective, randomized (1:1), patient-blinded, acute, controlled superiority trial conducted in the Central Denmark Region. A total of 1,888 patients aged >40 years with suspected AECOPD and need of inhaled bronchodilators will be included. The study will assess the impact of targeted vs. standard oxygen delivery during prehospital treatment.

Endpoints

Primary endpoint

- 30-day all-cause mortality.

Secondary endpoints

- 24-hour and 7-day mortality
- Respiratory acidosis on hospital arrival.
- Severity of acidosis (pH value).
- Requirement for in-hospital invasive or non-invasive ventilation.
- ICU admission and ICU length of stay.

- Total hospital length of stay.
- Hospital discharge diagnosis.
- Readmission within 30 days from discharge.

Safety endpoints:

- Untreated hypoxia (SpO_2 under 88% after allocation).
- Prehospital termination of treatment.

Covariates

Descriptive and adjustment covariates include:

- Age, sex
- Known COPD
- Home oxygen therapy, home non-invasive ventilation (NIV)
- Prior acute exacerbation(s) of COPD (AECOPD)
- Smoking status
- Treatment limitations (e.g., do-not-resuscitate (DNR), no intensive care unit (ICU) admission)
- Comorbidities (assessed by the Charlson Comorbidity Index (CCI))
- Forced expiratory volume in one second (FEV_1) % predicted (within last 12 months), Global Initiative for Chronic Obstructive Lung Disease (GOLD) category
- Use of opioids or benzodiazepines
- Emergency medical services (EMS) response details (emergency medical technician (EMT) or paramedic; initial contact via general practitioner (GP) vs. emergency medical dispatch center (EMDC) through 1-1-2)
- Physiological parameters at EMS arrival:
    - Peripheral oxygen saturation (SpO_2)
    - End-tidal carbon dioxide ($EtCO_2$)
    - Respiratory rate, heart rate, systolic and diastolic blood pressure
    - Glasgow Coma Scale (GCS) score
    - Temperature
    - Patient-experienced dyspnoea (rated 0–10)

- Feasibility metrics:
    - Number of patients included
    - Number of patients withdrawing consent after inclusion
    - Number of eligible patients unwilling to participate
    - Number of included patients deviating from protocol
    - Number of included patients not received treatment according to protocol
    - Number of included patients switched to other treatment group

Note: Baseline characteristics will be reported as medians with interquartile ranges (IQR) or as frequencies and percentages, as appropriate.

Statistical analysis

Differences in mortality endpoint, including the primary outcome, are estimated as risk difference (RD) and relative risk (RR) and is performed using linear and Poisson regression, respectively, with cluster robust variance estimation in which the randomization blocks constitute the clusters. In addition, the mortality outcome analyses will be presented with number-needed-to-treat/number-needed-to-harm and corresponding concordance index using probit regression analysis.

Binary outcomes, including admission to ICU, 24 hours, 7 days and 30 days in-hospital NIV, acidosis on hospital arrival, readmission, untreated hypoxia, SpO2 under 88% after allocation, and prehospital termination of treatment will be analyzed similar to mortality. Only non-ICU patients will be included when analyzing NIV.

Length of hospital stay, and length of ICU stay will be analyzed using Aalen-Johansen and Cox regression analysis. Additionally, differences in mean length of stay will be estimated using tobit regression analysis. Patients will be followed from inclusion until event, death, or 30 days follow-up whatever comes first.

To ensure completeness of outcome capture, especially for events such as death occurring outside of hospital or delayed registrations, a 90-day safety follow-up will be implemented. This extended follow-up is solely for the purpose of verifying and supplementing the 30-day data and will not alter the primary time frame used for main analyses.

Cluster robust variance estimation will be applied for Cox and tobit regression analyses.

Moreover, time to NIV, invasive ventilator treatment, and readmission will be analyzed using Aalen-Johansen and Cox regression analysis. Patients will be followed from discharge when analyzing readmission and otherwise from inclusion until event, death, or 30 days follow-up whatever comes first. Cluster robust variance estimation will be applied for Cox regression analyses. Only non-ICU patients will be included when analyzing NIV.

Finally, degree of acidosis based on pH, and patient experienced dyspnea on verbal rating scale will be analyzed using linear and quantile regression to estimate difference in mean and median. Cluster robust variance estimation will be applied for both analyses.

All outcomes will be analyzed unadjusted on an intention-to-treat (ITT) basis, and the results will be presented with 95% confidence intervals (CI).

Subgroup analysis

Subgroup analyses will be conducted for both primary and secondary outcomes, stratified as follows:

- Oxygen saturation prior to bronchodilator administration: <88%, 88–92%, >92%
- Prehospital transport time: Continuous variable; interaction terms will be evaluated.
- Final diagnosis of AECOPD (Yes/No): Based on ICD coding or discharge diagnosis.
- Ventilation requirement: NIV and/or invasive ventilation (Yes/No)

Where relevant, subgroup analyses will include interaction terms in regression models to evaluate effect modification. Results will be presented with appropriate subgroup effect estimates and 95% confidence intervals.

Missing data and sensitivity analyses

In addition to ITT analyses, we will perform per protocol (PP) analyses with adjustment for significant differences in patient characteristics between treatment groups. We will apply conventional adjustment for regression analyses and inverse probability of treatment weights (IPTW) for Aalen-Johansen curves. Balanced diagnostics are conducted using the threshold criteria given by Zhang et al.(1) Same thresholds criteria will be taken into account when assessing which parameters to adjust for.

Patients with missing data on the outcome will be excluded in the ITT and PP analyses. However, sensitivity analysis will be made using multiple imputations chained equations with 100 imputation sets and including relevant variables with first and second order terms in the imputation model.(2) Possible differences in patient characteristics and exposure between complete cases and dropouts are addressed by an additional sensitivity analysis adjusted by appropriate patient characteristics using inverse probability of treatment weights (IPTW).

Interim analyses

Interim analyses will be conducted at enrollment milestones of 200, 500, 1000, and 1500 patients. The analyses will include:

- Comparison of primary, secondary, and safety outcomes across treatment arms.
- Summary of baseline characteristics and feasibility metrics.
- Swimmer plots visualizing individual outcomes and safety events.

The Data Monitoring and Safety Committee (DMSC) may request additional interim analyses or escalation of monitoring intensity. Formal stopping criteria are defined in the DMSC charter.

Analysis Populations

- Intention-to-Treat (ITT): All randomized patients, analyzed according to assigned treatment group.
- Per-Protocol (PP): Patients receiving treatment according to protocol without major deviations.
- Safety Population: All patients who initiated any treatment, analyzed according to treatment received.

All results will be reported with 95% confidence intervals.

Implementation of analysis plan and data Handling

Study data will be collected and managed using research electronic data capture (REDCap). The trial statistician will have direct access to the data, and can unblind the data if required. Both interim and final analyses will be conducted by two statisticians independently and mutually assessed and revised until identical results are reached. Results of the interim analyses will be summarized in a short report including swimmers plot and made available for the DMSC. At each interim analysis the trial statistician downloads the unblinded trial data to a secure location, which can only be accessed by

the two statisticians conducting the analysis. Unblinded data will only be available for the two statisticians until the follow-up period have been concluded.

References

1. Zhang Z, Kim HJ, Lonjon G, Zhu Y. Balance diagnostics after propensity score matching. Ann Transl Med. 2019 Jan;7(1):16.

2. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377–99.