Statistical Analysis Plan (SAP)

Study Title: Shortened Antibiotic Treatment of Community-Acquired Pneumonia: A Nationwide Danish Randomized Controlled Trial

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Introduction

For background and rationale of the study: See "Introduction" in the study protocol, p. 8.

The aim of the study is to assess the efficacy and safety of shortened antibiotic treatment duration of community-acquired pneumonia (CAP) in hospitalized immunocompetent adult patients based on clinical stability criteria in a beta-lactam antibiotic setting.

Study Methods

Trial design and intervention

Multicentre noninferiority randomized controlled trial with two parallel treatment arms. Randomization are performed individually 1:1 at day 5 of antibiotic treatment for CAP. Participants are stratified by centre.

The intervention group receives antibiotic treatment for 5 days, while the control group receives antibiotic treatment for 7 days or longer determined by their treating physician.

Sample size

The sample size estimation of the study is calculated from the primary composite outcome: 90-day readmission-free survival.

Based on similar previous studies, short-term mortality is expected to be between 2-4% in both treatment arms, while the readmission rate within 30 days is expected to be between 5-7%. This corresponds to an estimated event rate for the primary outcome of approximately 9%, equivalent to a 90-day readmission-free survival of 91% in both treatment arms.

The non-inferiority margin represents the largest clinically acceptable difference and is set to 6%. At a power of 80% and a two-sided 90% confidence interval, a total of 564 patients are required.

A sample size re-estimation (SSR) will be considered at the first planned interim analysis, when 100 patients have been randomized and completed the 90 days follow-up. If the overall event rate falls outside the expected range of 7-11%, a SSR based upon blinded review of overall data (i.e. without knowledge of the group-specific event rates) will be performed. If the overall event rate is below 7%, then the final sample size will be reduced, using the original sample size formula and replacing the initial estimate of 9% with the observed rate. If the overall event rate exceeds 11%, the sample size will be increased correspondingly. Any sample size adjustment will be reported to the regulatory authorities as a protocol amendment.

Framework

The hypothesis for the primary outcome is noninferiority, while the hypotheses for all secondary outcomes are superiority.

Interim analysis

Interim analyses will be performed on the primary endpoint when 100, 300 and 500 patients have been randomized and completed the 90 days of follow up. The Peto approach will be applied to reveal substantial

differences between the intervention and control group that would require premature termination of the trial.

Timing of final analysis and outcome assessments

Final analysis of the study outcomes will be performed collectively after the study has ended, i.e. the last patient has completed the 90 days of follow up. Time points for collecting outcome measures are described in detail in the study protocol: See "Outcome measures" and "Measurements and investigations" pp. 12 and 16-17, respectively.

Statistical Principles

Confidence intervals and P values

For the primary outcome, non-inferiority is assessed in a one-sided test at a significance level of 0.05 with the use of 90% confidence interval. Non-inferiority is established, if the lower limit of the 90% confidence interval for the absolute risk difference between the two treatment groups does not exceed -6%. If the 90% confidence interval for the primary outcome lies entirely above zero, then a test of superiority will be performed subsequently.

For all other statistical analyses, a two-tailed p-value < 0.05 is considered statistically significant.

Adherence and protocol violations

See "Dropout" in the study protocol, p. 22.

Analysis populations

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be performed. Intention-to-treat analysis will comprise all participants including dropouts.

Trial Population

Screening data

Screening data will be presented in a CONSORT flow diagram.

Eligibility

See "Patient selection" in the study protocol, p. 10.

Recruitment

See the CONSORT flow diagram.

Withdrawal/follow-up

See "Withdrawal from the study" and "Dropout" in the study protocol, pp. 21-22.

Baseline patient characteristics

Baseline characteristics will include age, gender, tobacco use, alcohol consumption, immunization against pneumococcal disease and influenza, comorbidities, nursing home residency, activities of daily living, and disease severity.

Descriptive data will be reported as counts and frequencies, means and standard deviations or medians and interquartile ranges, depending on distribution.

Analysis

Outcome definitions

Primary Outcome Measure

- 90-day readmission-free survival [within 90 days]

Secondary Outcome Measures

- Duration of antibiotic treatment [within 90 days]
  - *Days that the participant receives antibiotic treatment for pneumonia, adding intravenous and oral therapy*
- Length of hospital stay [within 90 days]
  - *Days from the date of hospital admission for pneumonia to the date of discharge*
- Antibiotic adverse events [within 90 days]
  - *Number of participants with adverse events with possible relation to the antibiotic treatment of pneumonia*
- Serious adverse events [within 90 days]
  - *Number of participants with serious adverse events according to International Council of Harmonisation-Good Clinical Practice (ICH-GCP) guidelines*
- Major complications [within 90 days]
  - *Number of participants with major complications, including pleural effusion, pleural empyema, lung abscess, respiratory failure, severe sepsis, renal failure, use of non-invasive or invasive ventilation, need for vasopressors, and intensive care unit (ICU) admission*
- Use of antimicrobials after discharge [within 90 days]
  - *Days of antibiotic treatment given for any reason after hospital discharge*
- Post-discharge follow-up visits [within 90 days]
  - *Number of participants with medical visits after hospital discharge, including visits at the outpatient clinic and at the general practitioner*
- Readmissions [days 30 and 90]
  - *Number of participants with readmissions for reasons related to or unrelated to pneumonia*
- Mortality [in-hospital, days 30 and 90]
  - *Number of deaths by any cause*

Analysis methods

Comparisons between the two groups will be performed with chi-square test or Fisher's exact test for categorical data, depending on sample size. Continuous data will be subject to Student's *t* test for parametric distributions or Wilcoxon rank sum test for non-parametric distributions. Subgroup analyses on the primary outcome will be performed for disease severity (CURB-65 score), antibiotic group (empiric antibiotic therapy), and investigation centres by logistic regression. Non-inferiority plots will be performed on the primary outcome for both ITT and PP analyses.

Missing data

Only observed data will be used for analysing study outcomes. Efforts taken to limit missing data on dropouts are described in "Dropout" in the study protocol, p. 22.

Harms

See "Adverse events and side effects" in the study protocol, pp. 23-24.

Statistical software

Statistical analyses will be performed using R software.

References

See "References" in study protocol, pp. 31-33.