

STATISTICAL ANALYSIS PLAN

Official Title: Evaluating a Customised Antibiotic Duration Strategy in Acute Exacerbations of COPD: a Single-Centre, Open-Label, Randomised Non-Inferiority Trial of 7-Day Versus 14-Day Antibiotic Therapy

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Sponsor and trial site: Capital Development Authority (CDA) Hospital Islamabad, Pakistan

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Version history

Version	Date	Summary of changes
1.0	June 2026	Draft SAP for the multicentre design: randomisation and analyses stratified by site; target enrolment 558; primary time point stated as Day 30 or Day 7/14.
1.1	30th September 2026	Aligned with protocol version 2.0: single site, so no stratification or site adjustment; single primary outcome, clinical success at Day 30 (± 3 days); clinical success at Day 14 (± 2 days) as a secondary outcome; sample size 560 (252 evaluable per arm plus 10% attrition); covariates for adjusted analyses prespecified; per-protocol population defined at Day 30; Hodges–Lehmann estimate for antibiotic consumption. All changes were made before any participant was enrolled.

1. Purpose

This statistical analysis plan (SAP) specifies the analyses for the trial described in protocol version 2.0. It will be finalised and signed before database lock and before any unblinded aggregate outcome data are examined. Any later change will be documented as a dated SAP amendment with its justification and reported in the trial publications.

2. Trial design

This is a single-centre, prospective, parallel-group, open-label, randomised controlled non-inferiority trial in which adults with AECOPD are allocated 1:1 to a 7-day antibiotic course (experimental arm) or a 14-day course (active comparator arm). Outcome assessors and the trial statistician are blinded to allocation, following a prospective, randomised, open-label, blinded-endpoint (PROBE) design.

Participants are randomised 1:1 using a computer-generated sequence of randomly permuted blocks of variable size, without stratification, because there is a single trial site.

3. Objectives and hypotheses

The primary objective is to determine whether a 7-day antibiotic regimen is non-inferior to the conventional 14-day regimen in achieving clinical success at Day 30 after randomisation in adults hospitalised with AECOPD with suspected or confirmed bacterial infection.

The secondary objectives are to compare the two regimens with respect to clinical success at Day 14 after randomisation, time to symptom resolution, antibiotic-related adverse events, treatment failure, relapse, rehospitalisation and all-cause mortality within 30 days, and total antibiotic consumption in adults hospitalised with AECOPD at a tertiary care hospital in Pakistan.

Let π_7 and π_{14} be the proportions of participants achieving clinical success at Day 30 in the 7-day and 14-day arms. The null hypothesis is that the 7-day regimen is inferior by at least the non-inferiority margin ($H_0: \pi_7 - \pi_{14} \leq -10$ percentage points). The alternative hypothesis is that the 7-day regimen is non-inferior ($H_1: \pi_7 - \pi_{14} > -10$ percentage points).

METHODS AND ANALYSIS

4. Outcomes

4.1 Primary outcome

The primary outcome is clinical success at Day 30 (± 3 days) after randomisation. It is a binary outcome. A participant is classified as a clinical success only if all of the following criteria are met at the Day 30 assessment: (a) the exacerbation-related signs and symptoms present at baseline (dyspnoea, sputum volume and sputum purulence) have resolved or substantially improved, as judged by the blinded outcome assessor using predefined criteria, together with a reduction of at least 2 points from baseline in the COPD Assessment Test (CAT)²⁴ score, the minimal clinically important difference;²⁵ (b) no additional or alternative systemic antibiotic has been given for a respiratory indication after the allocated course, and the course has not been extended because of lack of improvement; (c) there has been no hospital readmission or emergency department visit for AECOPD; and (d) the participant is alive. Participants who do not meet all four criteria are classified as clinical failures. The outcome is reported as the number and proportion of participants with clinical success in each arm and compared between arms as the risk

difference (7-day minus 14-day). Day 30 is the same assessment point in both arms and falls after both allocated courses have been completed, so the comparison reflects the full consequence of stopping treatment earlier, including any relapse after the shorter course.

4.2 Secondary outcomes

1. clinical success at Day 14 (± 2 days) after randomisation, defined as for the primary outcome;
2. time to resolution of exacerbation symptoms (days);
3. incidence of antibiotic-related adverse events and serious adverse events;
4. treatment failure by Day 30, defined as the need for additional or alternative systemic antibiotics because of clinical deterioration or lack of improvement, escalation to non-invasive or invasive ventilation or intensive care after Day 3, or death;
5. relapse by Day 30, defined as a new or worsening exacerbation requiring systemic antibiotics or corticosteroids after initial clinical improvement;
6. rehospitalisation for any cause and for AECOPD within 30 days;
7. all-cause mortality within 30 days;
8. total antibiotic consumption per participant, in defined daily doses (DDD).²⁶

Each secondary outcome is analysed and reported separately; secondary outcomes are not combined into a composite and are not used to support a claim of non-inferiority. Assessments at Day 3–5 and Day 7 are used for monitoring, adherence and safety and are not outcome comparisons.

5. Sample size

The sample size was calculated for the primary non-inferiority comparison of clinical success at Day 30. We assumed a clinical success proportion of 80% in both arms, a non-inferiority margin (δ) of 10 percentage points, a one-sided type I error rate of 0.025 and 80% power, and used the normal approximation for the difference between two independent proportions:²⁷

$$n = (Z_{1-\alpha} + Z_{1-\beta})^2 \times [p_C(1 - p_C) + p_T(1 - p_T)] / [\delta - (p_T - p_C)]^2$$

where p_C and p_T are the expected success proportions in the 14-day and 7-day arms. With $p_C = p_T = 0.80$ and $\delta = 0.10$, $n = (1.960 + 0.842)^2 \times 0.32 / 0.10^2 = 251.2$, rounded up to 252 participants per arm (504 in total). Allowing for 10% attrition ($252/0.90$), the target enrolment is 560 participants (280 per arm). Assuming no true difference between the arms is conservative. The calculation relates only to the single primary comparison at Day 30; no other outcome or time point contributed to it, and no adjustment for multiplicity is required. The same target applies to the intention-to-treat and per-protocol populations; the per-protocol result carries particular weight in a non-inferiority trial.

6. Analysis populations

The intention-to-treat (ITT) population includes all randomised participants, analysed in the arm to which they were allocated regardless of treatment received, protocol deviations or early withdrawal. The per-protocol (PP) population includes randomised participants who received an antibiotic course consistent with their allocated duration (± 2 days), had no major protocol deviation affecting assessment of the primary outcome, and have primary outcome data at Day 30. The safety population includes all randomised

participants who received at least one dose of study antibiotic, analysed according to the treatment actually received.

7. General principles

The primary hypothesis is tested at a one-sided significance level of 0.025, implemented as a two-sided 95% CI. All other estimates are reported with two-sided 95% CIs; p-values, where reported, are two-sided. Treatment effects are expressed as 7-day minus 14-day (risk differences, median differences) or 7-day relative to 14-day (relative risks, hazard ratios).

The trial statistician remains blinded to allocation, working with coded arm labels, until the SAP is signed and the database is locked. Analyses will be performed in R version 4.6.0 (R Core Team, 2026) and other related software, and the analysis code will be version-controlled and retained with the trial master file.

8. Participant flow and baseline characteristics

The flow of participants will be presented in a CONSORT diagram showing the numbers screened, eligible, randomised, receiving the allocated duration, lost to follow-up, withdrawn and analysed in each population, with reasons.

Baseline characteristics will be summarised by arm as frequencies and percentages or as means with standard deviations or medians with interquartile ranges, without formal testing of baseline balance.

9. Primary analysis

The difference between arms in the proportion achieving clinical success at Day 30 (7-day minus 14-day) will be estimated with its two-sided 95% CI calculated by the Miettinen–Nurminen method.²⁸ Non-inferiority of the 7-day regimen will be concluded only if the lower limit of the 95% CI lies above –10 percentage points in both the ITT and PP populations; if the two populations disagree, non-inferiority will not be claimed and the discrepancy will be reported and explored. This is the single confirmatory hypothesis of the trial: it concerns one outcome at one time point, is tested at a one-sided α of 0.025 and requires no adjustment for multiplicity. A binomial generalised linear model with an identity link, adjusted for age, sex, baseline CAT score and number of exacerbations in the previous year, will be fitted as a supportive analysis.

10. Sensitivity and supportive analyses of the primary outcome

The following analyses are prespecified to assess the robustness of the primary result: (a) the same analysis in the per-protocol population, which is required for the non-inferiority conclusion; (b) a complete-case analysis restricted to participants with an observed Day 30 assessment; (c) if more than 5% of primary outcome data are missing, multiple imputation by chained equations under a missing-at-random assumption, with an imputation model including allocated arm, age, sex, baseline CAT score and number of exacerbations in the previous year, and estimates combined by Rubin's rules; and (d) a binomial generalised linear model with an identity link adjusted for age, sex, baseline CAT score and number of exacerbations in the previous year. If the identity-link model fails to converge, a linear probability model with robust standard errors will be used.

11. Secondary analyses

Clinical success at Day 14, treatment failure, relapse and rehospitalisation will be compared using risk differences with 95% CIs; relative risks will also be reported. Time to resolution of exacerbation symptoms will be described with Kaplan–Meier curves and compared with the log-rank test, and a hazard ratio with 95% CI will be obtained from a Cox proportional hazards model. Antibiotic-related adverse events and serious adverse events will be summarised in the safety population and compared using risk differences with 95% CIs. Because deaths are expected to be few, all-cause mortality will be reported descriptively. Total antibiotic consumption will be summarised as median (IQR) and compared with the Mann–Whitney U test, with the Hodges–Lehmann median difference and its 95% CI. A prespecified adjusted analysis of secondary binary outcomes using modified Poisson regression²⁹ will account for the baseline covariates listed above. Secondary outcomes are exploratory, will be reported with 95% CIs without adjustment for multiplicity, and will not be used to support a claim of non-inferiority.

Secondary outcome	Type	Method	Effect measure
Clinical success at Day 14	Binary	Miettinen–Nurminen CI; modified Poisson regression for relative risk	Risk difference; relative risk
Time to resolution of exacerbation symptoms	Time to event	Kaplan–Meier, log-rank test, Cox proportional hazards model (proportional hazards checked with Schoenfeld residuals)	Hazard ratio
Antibiotic-related AEs and SAEs	Binary	Safety population; risk difference with 95% CI	Risk difference
Treatment failure by Day 30	Binary	As for Day 14 clinical success	Risk difference; relative risk
Relapse by Day 30	Binary	As for Day 14 clinical success	Risk difference; relative risk
Rehospitalisation (any cause; AECOPD) within 30 days	Binary	As for Day 14 clinical success	Risk difference; relative risk
All-cause mortality within 30 days	Binary	Descriptive	Counts and percentages
Total antibiotic consumption (DDD)	Continuous	Median (IQR); Mann–Whitney U test	Hodges–Lehmann median difference

12. Missing data

Active follow-up will be used to keep missing data to a minimum. In the primary ITT analysis, participants without a Day 30 clinical success assessment will be classified as treatment failures. A complete-case analysis will be performed as a sensitivity analysis, and if more than 5% of primary outcome data are missing, multiple imputation by chained equations under a missing-at-random assumption will also be undertaken. Participants without an observed event in time-to-event analyses will be censored at their last known status. Protocol deviations, extensions of treatment, early discontinuation, crossover and non-protocol antibiotic use will be recorded and summarised by arm, and the flow of participants will be reported in a CONSORT diagram.

13. Multiplicity

The trial has a single confirmatory hypothesis, concerning one outcome at one time point, and no adjustment for multiplicity is required. Requiring non-inferiority in both the ITT and PP populations does not inflate the type I error. Secondary outcomes are exploratory and are reported with 95% CIs without adjustment.

14. Subgroup analyses

No subgroup analyses are prespecified.

15. Interim analyses and data monitoring

No formal interim analysis of efficacy is planned. Accumulating safety data will be reviewed periodically by the data monitoring committee. There are no formal stopping rules for efficacy.

16. Protocol deviations and adherence

Protocol deviations, extensions of treatment, early discontinuation, crossover and non-protocol antibiotic use will be recorded and summarised by arm. The actual duration of antibiotic therapy and the agents used will be summarised by arm. Major deviations leading to exclusion from the per-protocol population will be classified, blinded to allocation, before database lock.

17. Safety analyses

Adverse events and serious adverse events will be analysed in the safety population according to the duration actually received, summarised by arm as the number and percentage of participants with at least one event and by type, severity and relationship to antibiotic treatment.

18. Approval

Role	Name	Signature	Date
Trial statistician	Hamid Khan	Hamid	30/9/2026
Principal investigator	Dr Fazal Rabbi	Fazal	30/9/2026