STATISTICAL ANALYSIS PLAN (SAP)

Continuous Low-Pressure Pyriform Sinus Suction Drainage to Prevent Silent Aspiration in ICU-Acquired Dysphagia: A Single-Center Randomized Controlled Trial

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1. Purpose and scope

This Statistical Analysis Plan (SAP) prespecifies the statistical methods for the randomized controlled trial evaluating continuous low-pressure pyriform sinus suction drainage plus standard care versus standard care alone for prevention of silent aspiration and improvement of outcomes in ICU-acquired dysphagia (ICU-AD). The SAP is aligned with CONSORT and SPIRIT recommendations and is intended to reduce analysis-related bias.

2. Trial overview

Item	Description
Design	Single-center, prospective, parallel-group, superiority RCT (1:1).
Population	Adult ICU patients with ICU-acquired dysphagia after ≥48h invasive mechanical ventilation and extubation/decannulation; dysphagia confirmed by GUSS.
Arms	Control: standard dysphagia care bundle; Intervention: standard bundle + continuous low-pressure unilateral pyriform sinus suction drainage.
Sample size	112 participants (56 per group).
Follow-up	ICU outcomes through discharge/day 28; mortality follow-up to day 90.

3. Analysis populations

3.1 Intention-to-treat (ITT) population

All randomised participants analysed according to assigned group, regardless of protocol adherence. This is the primary analysis set.

3.2 Per-protocol (PP) population

Participants who received the allocated intervention as intended with no major protocol deviations. Major deviations include: incorrect allocation, withdrawal prior to any post-randomisation assessment, or substantial non-delivery of suction drainage in the intervention arm.

3.3 Safety population

All participants who received any study-related procedure (standard bundle and/or catheter placement). Analysed according to treatment received.

4. Endpoints

4.1 Primary endpoints

• Time to recovery of safe swallowing (days) from randomisation, defined by GUSS score reaching 20 and/or ability to tolerate oral intake as per protocol.

• Incidence of silent aspiration during ICU stay, measured using the prespecified aspiration test/biomarker and schedule.

4.2 Secondary endpoints

• Incidence of aspiration pneumonia during ICU stay.

• ICU length of stay (days) from randomisation to ICU discharge.

• 28-day all-cause mortality.

• 90-day all-cause mortality.

• Inflammatory markers at ICU day 5 (±1): serum CRP (mg/L) and WBC ($\times 10^9$/L) via routine lab methods.

• Safety outcomes: catheter-related adverse events and serious adverse events.

4.3 Global prioritized endpoint (GPC)

A generalized pairwise comparison (GPC) will be conducted on a prioritized hierarchy of outcomes: (1) 90-day survival (highest priority), (2) ICU length of stay, and (3) time to swallowing recovery. The net benefit (δ) and global Δ will be estimated with 95% confidence intervals using resampling.

5. General statistical principles

All tests will be two-sided with $\alpha=0.05$. Estimates will be reported with 95% confidence intervals. Primary endpoints are confirmatory; secondary endpoints are supportive/exploratory and

interpreted cautiously without multiplicity adjustment unless otherwise stated. Continuous variables will be summarized using mean±SD or median (IQR) depending on distribution; categorical variables as n (%).

Statistical analyses will be performed in R (version 4.2.1 or later), using packages including survival, gtsummary, and BuyseTest for GPC.

6. Handling of missing data

We anticipate minimal missingness for ICU outcomes. Mortality follow-up is expected to be complete. For missing covariates required in adjusted models, multiple imputation by chained equations may be used if >5% missingness is present; otherwise complete-case analysis will be performed. For time-to-event endpoints, participants will be censored at last known assessment; deaths prior to swallowing recovery will be handled as competing events or as non-recovery in sensitivity analyses.

7. Baseline comparability

Baseline characteristics will be summarized by group. Formal hypothesis testing of baseline differences will not be used for eligibility of models; clinically important imbalances will be considered for adjustment.

8. Primary endpoint analyses

8.1 Time to recovery of safe swallowing

Time-to-recovery will be analysed using Kaplan–Meier curves and compared using Cox proportional hazards regression, reporting hazard ratios (HR) with 95% CI. The primary Cox model will include group as the main predictor and may adjust for prespecified covariates (e.g., age, sex, APACHE II, SOFA, baseline GUSS severity, primary neurologic diagnosis). Proportional hazards assumptions will be assessed using Schoenfeld residuals and log(-log) plots.

Sensitivity analyses: (a) competing-risk analysis treating death before recovery as a competing event (Fine–Gray model); (b) per-protocol analysis; (c) alternative definitions of recovery if applicable.

8.2 Incidence of silent aspiration

Silent aspiration incidence will be analysed as a binary endpoint (any silent aspiration detected during ICU stay) using logistic regression, reporting odds ratios (OR) with 95% CI. If repeated measurements are available (e.g., daily tests), a mixed-effects logistic model or GEE may be used to account for within-subject correlation; the analysis approach will follow the prespecified data structure in the final dataset.

Adjusted models will include the same covariates as above where clinically appropriate.

9. Secondary endpoint analyses

9.1 Aspiration pneumonia

Aspiration pneumonia will be analysed using logistic regression (OR, 95% CI). A composite endpoint 'alive without aspiration pneumonia at day 28' may be analysed similarly.

9.2 ICU length of stay

ICU length of stay (days) will be compared between groups using (a) generalized linear models (e.g., negative binomial or gamma with log link) if skewed, or (b) Mann–Whitney U test as a nonparametric alternative. If death precludes discharge, sensitivity analyses will consider competing-risk frameworks or rank-based methods.

9.3 Mortality (28-day and 90-day)

Mortality will be analysed using Kaplan–Meier survival curves and Cox regression (HR, 95% CI). If proportional hazards is violated, alternative models (e.g., restricted mean survival time) may be reported.

9.4 Inflammatory markers (CRP and WBC at ICU day 5 ±1)

CRP (mg/L) and WBC ($\times 10^9$/L) will be summarized and compared between groups at ICU day 5 (±1 day). Analyses will use t-tests for approximately normally distributed values or Wilcoxon rank-sum tests if distributions are skewed. If baseline values are available, ANCOVA/linear regression adjusting for baseline marker levels may be applied.

9.5 Safety outcomes

Adverse events will be tabulated by type and severity. Rates will be compared descriptively, and Fisher’s exact test may be used for selected comparisons.

10. Generalized Pairwise Comparison (GPC) analysis

A GPC will be performed using the BuyseTest framework to estimate the net treatment benefit δ for each prioritized component and a global Δ. The hierarchy is: 90-day survival (higher is better), ICU length of stay (shorter is better), and swallowing recovery time (shorter is better). Pairs will be compared with clinically meaningful thresholds if prespecified; otherwise, strict comparisons will be used. Confidence intervals will be generated using nonparametric bootstrap resampling (e.g., 5,000 resamples).

11. Subgroup and sensitivity analyses

Prespecified subgroup analyses (interaction tests) may include:

• Baseline dysphagia severity (GUSS category: mild/moderate/severe).

• Primary ICU admission diagnosis category (neurologic vs non-neurologic).

• Age group (e.g., <65 vs ≥65).

• Duration of mechanical ventilation (e.g., 48–96h vs >96h).

Sensitivity analyses include: per-protocol analyses, alternative handling of death before recovery, alternative model specifications, and missing-data approaches.

12. Interim analyses and stopping rules

No interim efficacy analyses are planned. The intervention may be stopped at the individual level for intolerance or clinical safety concerns (e.g., bleeding, mucosal injury), as documented in the protocol.

13. Data presentation

Primary results will be presented using Kaplan–Meier plots for time-to-event outcomes and forest plots for effect estimates. Binary outcomes will be shown with absolute risks, risk differences, and odds ratios. GPC results will be presented as net benefits with confidence intervals and p-values.

14. Deviations from SAP

Any deviations from this SAP will be documented, justified, and reported in the final manuscript.