Statistical analysis plan (SAP)

Statistical analysis plan version	Cause of changes
Statistical analysis plan (included in original protocol)	First release.
Statistical analysis plan V1	Review of SAP before data base lock.

1 ANALYSIS PLAN

1.1 Generalities

SAP
Statistical analysis will be performed by a statistician from URCEST.

Statistical analysis plan presented below has been written before data base lock.
All modifications made to the analysis plan for the initial strategy will be documented in the analysis report.

Software
Analyses will be performed using SAS software (version 9.4 or updated version) and R software (version 4.2.2 or updated version).

Planned analyses:
No interim analysis is planned. Analyses will be performed at the end of the study after data base lock.

1.2 Hypotheses for calculating the required number of subjects

Previous reports suggested the following assumptions: - The in hospital mortality is 3% (range 0 – 7%) (Isbister et al. Fosberg et al. and Weiss et al) with no reported difference between patients that were intubated and those who were not - The median length of ICU stay is 2 days for intubated patients vs. 0 for non-intubated patients (Donald et al.) - The median length of hospital stay for intubated patients is 6 days vs 2 days for non-intubated patients. (Donald et al. and EPITOX)
Sample size calculations were performed by simulating 1000 samples on SAS software.

A) The samples were assigned basic distribution features as following assumptions:
- In hospital mortality of 3% in both groups,
- With 30% intubated patients in the control group that will be intubated, we estimate that the mean length of ICU stay will be 1 days in the control group vs 0 days in the intervention group (standard deviation 2 days in both groups),
- Mean length of hospital stay of 4 days vs 2 days in the intervention group (standard deviation 8 days in both groups).

Within each sample the score for each patient was computed based on comparison of each patient in one group to all patients in the second group. These values were further compared by Mann-Whitney procedure within each of 1000 samples and their p-values recorded. The proportion of tests with p-value < 0.05 was 98% with a sample size of 100 patients in each study group. Therefore, we may expect that sample size of minimum 100 patients in each study group will provide the study with 98% power to detect a difference in primary outcome at 5% of significance (Finkelstein et al., Statistics in medicine, 1999; Beitler et al, Supplementary 1, JAMA, 2019). Accounting for 10% of lost to follow up patients and 10 % of patient refusing to consent to the continuation of the trial, we need to include 240 patients.

1.3 Selection of populations

The primary analysis will be for a modified Intent to treat population set (mITT), which included all randomized patient with the exclusion of patients that did not provided consent and opposed to the use of their data. Following the intention-to-treat principle, patients will be analyzed according to the procedure assigned.

- Per protocol (PP) population set :

All patients randomized, treated without major protocol violations/deviations.
Pre-defined major protocol violations/deviations are:

- ✓ Non-respect of at least one selection criteria (except “Patients affiliated to French social security (“AME” excepted)” and “Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom)”.
- ✓ Non-respect of the randomized procedure allocation and/or duration (wrong procedure followed, premature discontinuation of procedure – except for death)
- ✓ Missing data for the primary efficacy endpoint
- ✓ Inclusion in another interventional study

Not pre-defined major protocol deviations identified during a blinded data review before final data base lock will be classified.

- Safety population (SP) set :

All randomized patients. Patients will be analyzed according to procedure received.

1.4 Description of planned statistical methods

Baseline characteristics of patients will be described overall and per group.
Qualitative data will be described with frequencies and percentages; quantitative data will be described with mean and standard error or with median and interquartile interval, minimum and maximum.

Principal criterion analysis

Analysis will be conducted based on the modified intent to treat (mITT) population.
This endpoint will be analyzed by:

A) Using first the Finkelstein-Schoenfeld method (Finkelstein et al., Statistics in medicine, 1999) that compares patients along a hierarchy of endpoints, with each patient will be compared to every other patient in the trial. For each pairwise (patient-to-patient comparison), a win, loss, or tie is defined in a hierarchical manner based on which fared better. The comparisons are first performed on the basis of the most important outcome (death), and only if neither patient has experienced that outcome will the win-lose-tie comparison be based on the second outcome of less important. A score will be attributed to each comparison performed (equality (tie): 0, winner: 1, loser: -1):

1. If both patients die at any time during the hospital stay period a score of 0 will be assigned to each.
2. If a patient survives and the other does not (in-hospital death), scores 1 and -1 will be assigned respectively.
3. If both patients are alive, then the score awarded will depend on the ICU length of stay: the patient with the shortest length of stay will win and receive a score of 1 while the one with the longest time will lose and will be given a score of -1.
4. In case of a novel equality, the score awarded will depend on the length of hospital stay: the patient with the shortest delay will win and receive a score of 1 while the one with the longest time will lose and will be given a score of -1.
5. If both patients survive during the hospital stay period and have equal ICU length of stay and equal hospital length of stay, a score of 0 will be assigned to each.
6. The scores of all pairwise comparisons will be summed to obtain a cumulative score for each patient. These cumulative scores will be ranked and compared between intervention and control groups using the Mann-Whitney / Wilcoxon rank sum test.

Table 1: Calculation method of the hierarchical endpoint (Finkelstein-Schoenfeld method)

Index patient died during the hospital stay period	Comparison patient died during the hospital stay period	ICU length of stay for index patient vs. comparison patient	Hospital length of stay for index patient vs. comparison patient	Points for index patient	Points for comparison patient
Yes	Yes	Not used	Not used	0 (tie)	0 (tie)
No	Yes	Not used	Not used	+1 (win)	-1 (lose)
Yes	No	Not used	Not used	-1 (lose)	+1 (win)
No	No	Shorter	Not used	+1 (win)	-1 (lose)
No	No	Longer	Not used	-1 (lose)	+1 (win)
No	No	Same	Shorter	+1 (win)	-1 (lose)
No	No	Same	Longer	-1 (lose)	+1 (win)
No	No	Same	Same	0 (tie)	0 (tie)

B) Complementary analyses will be performed:

- **a)** Using the win ratio (Pocok Eur H J 2016)**.** The win ratio was motivated by the Finkelstein–Schoenfeld test, with the aim of providing an estimate of the treatment effect (the win ratio) and confidence interval, in addition to a P-value. Each patient will be compared to every other patient in the trial as described above (unpaired method). The win ratio will be calculated as NW / NL with NW = number of winners and NL = number of losers in the treatment group. 95%CI will also be estimated.
- **b)** Using the win odds (Dong et al., Pharmaceutical Statistics, 2023): in addition, win odds (odds of win proportions) and its 95%CI will be estimated.
- **c)** Using stratified win ratio and win odds (and 95%CI) to take into account site as stratification variable. (Dong et al. Pharmaceutical Statistics, 2023).

For these analyses, R package WINS will be used and Dong et al.'s method to calculate variance will be used (Dong et al., Pharmaceutical statistics, 2016).

Sensitivity analyses will also be performed on PP populations using the same methods.

Secondary criteria analyses

Proportion of in-hospital death (truncated at 28 days) will be described in each group. Proportion difference between groups and its 95% confidence interval will be calculated using a generalized linear regression mixed models with binomial distribution (logit link) considering each site as random effect and strategy as fixed effects.

ICU length of stay (truncated at 28 days), length of mechanical ventilation until hospital discharge or at day 28 and hospital length of stay (truncated at 28 days) will be described in each groups using mean and standard deviation (SD) or median and interquartile range (IQR), according to the distribution. Difference between groups and its 2-sided 95%CI will be calculated using generalized linear regression mixed models with Poisson distribution (log link) (or other distribution appropriate to the data) considering each site as random effect and strategy as fixed effects.

Proportion of: patients with mechanical ventilation at day 28, ICU admission and rapid onset pneumonia (as defined by the US CDC definition of pneumonia, Abbott et al. BJA 2018) will be described in each group. Proportion difference between groups and its 95% confidence interval will be calculated using a generalized linear regression mixed models with binomial distribution (logit link) considering each site as random effect and strategy as fixed effects.

Proportion of adverse events from intubation (hypoxemia, dental trauma, regurgitation, cardiac arrest, intubation difficulty score (IDS) ≥ 5, hypotension or oesophageal intubation) will be described in each group using frequencies and percentages 1) in the entire population and 2) among intubated patients. In the entire population, proportion difference between groups and its 95% confidence interval will be

calculated using a generalized linear regression mixed models with binomial distribution (logit link) considering each site as random effect and strategy as fixed effects.

Sensitivity analyses will be performed on PP populations using the same methods.

Additional analyses

Additional analyses will be performed 1) to compare primary endpoint between intubated patients vs. not intubated, 2) to compare primary endpoint between randomization groups in patients with a Glasgow Coma Scale (GCS) < 7, 3) to compare primary endpoint between randomization groups after excluding patients intoxicated with tricyclic antidepressant or neuroleptic or crack / cocaine or amphetamine / MDMA / ecstasy or other substance (except GHB). Analysis methods for primary endpoint analysis described previously will be performed.

Proportion of first pass failure will be described in each group with frequencies and percentages 1) in the entire population and 2) among intubated patients. In the entire population, proportion difference between groups and its 95% confidence interval will be calculated using a generalized linear regression mixed models with binomial distribution (logit link) considering each site as random effect and strategy as fixed effects.

1.5 Anticipated level of statistical significance

All tests will be two-sided, statistical significance will be considered when P value of the primary endpoint will be <0.05 and when the 95%CI of the secondary end points did not include the null value. No adjustment will be planned for multiplicity.

1.6 Method for taking into account missing, unused or invalid data

In case of missing data on principal criteria, missing=failure (death) method will be applied as replacement measure for hospital survival, and the median of all included patients' length of ICU or hospital stay will be used to replace any missing data. No replacement of other missing data is planned.

1.7 Economic evaluation

Choice of the type of economic evaluation
A cost-consequence analysis (CCA) was chosen in this analysis because it provides information for spending decisions when implementation strategies are expected to have outcomes that are too disparate to be combined meaningfully. The CCA will include health outcomes and hospital costs. Health outcomes will be included length of 28-day mortality, and severe adverse events including mechanical ventilation, ICU admission, and rapid onset pneumonia. Hospital costs will encompass the costs of intensive care and hospital stay.

Study Perspective
The analysis will consider only the production costs of the hospital since all relevant resources are hospital-based.

Time Horizon
The follow-up period is 28 days.

Discount rate
In view of the short duration of this study, no discount rate is applied.

Estimating resources and costs
Resource was collected using the electronic Case Record Form (eCRF) developed for the NICO trial, completed by hospital information system. During the initial hospital admission, the total length of stay and ICU length of stay, combined with the specific DRG costs, will be reported.

Cost for the index admission: The cost will be calculated based on the cost of the DRG from the national cost study, adjusted for the actual use of life support systems and the actual length of stay. This cost will be obtained by using the full DRG cost, subtracting ICU costs (which are added later) and estimating a per diem cost. The per diem cost is multiplied by the actual (non-ICU) length of stay. ICU days are added for an amount of 967.28€[1] per day in 2023 but the active tariff at the time of the analysis will be used since this tariff changes annually.

Cost for the re-admission: This includes any repeat hospital admissions during the 28-day follow up period the cost is calculated as described above

		Calculation method	**Sources of data**	**Valorisation**
Index admission	**ICU (Intensive Care Unit)**	Cost of intensive care = (cost of an intensive care unit x number of supplements)	e-CRF and/or refund databases (e.g. local PMSI for APHP centres and EDS for non-APHP centres). ICU data are collected from the e-CRF.	The cost of an ICU will be valued by the tariff set by the French national Health Insurance scheme.
	Hospital stay	Cost of hospital stay = (cost of the stay for the DRG/average length of stay observed in ENC) x duration of stay	e-CRF and/or refund databases (e.g. local PMSI for APHP centres and EDS for non-APHP centres).	The cost of the stay is valued using DRGs from the most recent national production cost study (ENCC) at the time of analysis.
Re-admission at 28 days		Cost of hospital stay = (cost of the stay for the DRG / average length of stay observed in DRG) x duration of stay	e-CRF and/or refund databases (e.g. local PMSI for APHP centres and EDS for non-APHP centres).	The cost of the stay is valued using DRGs from the most recent national production cost study (ENCC) at the time of analysis.

Costs will be presented by group as means and standard deviations. The difference in costs and its bootstrapped 95% confidence interval will be calculated.

All costs are presented in euros, and valued using the latest cost/charge schedule available (2023).

Outcomes and measure
The health outcomes of interest for the cost-consequence analysis is the 28-day mortality, and severe adverse events (binary, present or not present), including mechanical ventilation, ICU admission, adverse events from intubation, and rapid onset pneumonia.

Cost-consequences analysis

The Cost-consequence analysis will adopt a scorecard approach to compare the costs and benefits associated with conservative and standard management. An economic summary measure will not be calculated.

Statistical analysis
The economic evaluation will be conducted according to the intention to treat.

The mean difference in costs will be estimated using a generalized linear mixed (GLM) model with the log link function and a gamma distribution, and the mean difference in effects (severe adverse events

[1] ATIH, “Tarifs MCO et HAD.” [Online]. Available: https://www.atih.sante.fr.

at 28 days) will be estimated using a generalized linear mixed models with a logit-link function. These models will be adjusted on treatment arm, and clustering at the hospital-level.

We will use the nonparametric bootstrapping with a minimum of 1000 replications to compute 95% confidence intervals (Cis) for incremental costs, incremental consequences.

Handling missing cost and effect data

The study has been designed to minimize missing data. Since patients are in hospital, any adverse events (deaths, adverse events) that occur in the hospital or ICU will be recorded in the hospital's claims database. However, the possibility of missing cost and outcome data required to perform the economic evaluation cannot be ruled out. The multiple imputation chained equation (MICE) with predictive mean matching will be utilised for imputing missing values of effects and costs. The imputation model will be adjusted for appropriate covariates based on good practice guide by Faria et al. 2014[2].

Sensitivity analyses

- Sensitivity analyses will be conducted on Per Protocol population to assess whether protocol deviations influenced the results.
- A seemingly unrelated regression (SUR) model will be fitted for estimating differential mean total costs and consequences.
- Deterministic (one-way) sensitivity analysis will be conducted by varying the key parameters (such as DRG cost, quantity of resource use).

Statistical analysis will be performed R Studio® software (version 4.1.2 or updated version).

Presentation of results (Dummy Tables and Figures)

Table 1 shows the proportions of missing data for the key parameters used in the analysis

Table 2: Data completeness for key parameters used in the economic analysis (missing data)

	Interventional group N (%)	Control group N (%)	Difference in % missing
Index admission			
ICU days			
Duration stay (days)			
Re-admission at 28 days			
Duration stay (days)			
Consequences			
Cumulative mortality in hospital at 28 days			
Adverse events at 28 days			

[2] Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials

Table 3: Descriptive statistics for resource utilization, consequences by treatment group

	Interventional group (95%) CI	Control group (95%) CI	Difference in Mean (95%) CI
Index admission			
ICU days, N (%)			
Duration stay (days)			
Re-admission at 28 days			
Duration stay(days)			
Consequences			
Cumulative mortality in hospital at 28 days, N (%)			
Adverse events at 28 days, N (%)			

Table 4: Costs associated with resource used

	Interventional group (95%) CI	Control group (95%) CI	Mean cost difference (95% CI)
Index admission			
Hospital stay, N (%)			
ICU, N (%)			
Re-admission at 28 days			
Hospital stay, N (%)			

Values are mean (standard deviation) in € 2023. CI = confidence interval

	Coordinator	Biostatisticien / Coordinator data management and statistic	Health economist
First name Name	Yonathan FREUND		
Date	4 juil. 2023		
Signature			

Table 3: Descriptive statistics for resource utilization, consequences by treatment group

	Interventional group (95%) CI	Control group (95%) CI	Difference in Mean (95%) CI
Index admission			
ICU days, N (%)			
Duration stay (days)			
Re-admission at 28 days			
Duration stay(days)			
Consequences			
Cumulative mortality in hospital at 28 days, N (%)			
Adverse events at 28 days, N (%)			

Table 4: Costs associated with resource used

	Interventional group (95%) CI	Control group (95%) CI	Mean cost difference (95% CI)
Index admission			
Hospital stay, N (%)			
ICU, N (%)			
Re-admission at 28 days			
Hospital stay, N (%)			

Values are mean (standard deviation) in € 2023. CI = confidence interval

	Coordinator	Biostatisticien / Coordinator data management and statistic	Health economist
First name Name		Janine CACHANADO	
Date		04/07/2023	
Signature			

Table 3: Descriptive statistics for resource utilization, consequences by treatment group

	Interventional group (95%) CI	Control group (95%) CI	Difference in Mean (95%) CI
Index admission			
ICU days, N (%)			
Duration stay (days)			
Re-admission at 28 days			
Duration stay(days)			
Consequences			
Cumulative mortality in hospital at 28 days, N (%)			
Adverse events at 28 days, N (%)			

Table 4: Costs associated with resource used

	Interventional group (95%) CI	Control group (95%) CI	Mean cost difference (95% CI)
Index admission			
Hospital stay, N (%)			
ICU, N (%)			
Re-admission at 28 days			
Hospital stay, N (%)			

Values are mean (standard deviation) in € 2023. CI = confidence interval.

	Coordinator	Biostatisticien / Coordinator data management and statistic	Health economist
First name Name			DURAND-ZBEEDA
Date			06/07/2023
Signature			