“Non-invasive airway management of comatose poisoned emergency patients”

NICO

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS NOT CONCERNING A HEALTH PRODUCT

Version no. 5.0 dated 28/12/2022
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SIGNATURE page for a research PROTOCOL

Research code number: APHP200013

Title: Non-invasive airway management of comatose poisoned emergency patients - NICO

Version no. 5.0 dated 28/12/2022

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	Non-Invasive Airway Management in comatose poisoned emergency patients
Acronym/reference	NICO
Coordinating investigator	Yonathan FREUND, Emergency Department, Hôpital Pitié Salpêtrière, APHP.SU
Scientific Director	Frédéric ADNET, Emergency Department and EMS, Hôpital Avicenne, APHP.HUSSD
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	A decreased level of consciousness is a common reason for presentation to the emergency department (ED) and is often the result of intoxication (up to 1% of all ED visits and 3% of ICU admission). In France, approximately 165 000 poisoned patients are managed each year. Originally developed in head injured patients, the Glasgow Coma Scale (GCS) is a validated reproducible score evaluating the level of consciousness: a GCS ≤ 8 is strongly associated with reduced gag reflex and increased incidence of aspiration pneumonia. Although recommended for patients with traumatic brain injury and coma, it remains unknown whether the benefit of an invasive management of airways with sedation, intubation and mechanical ventilation should be applied to other causes of coma in particular for acute poisoned patients. We hypothesize that a conservative management with close monitoring without immediate endotracheal intubation of these patients is effective and associated with less in-hospital complications (truncated at 28 days) compared to routine practice management (in which the decision of immediate intubation is left to the discretion of the emergency physician).
Main objective and primary endpoint	To compare, between conservative management and routine practice, a composite hierarchical outcome of in-hospital mortality and morbidity truncated at 28 days, in comatose poisoned patients. The primary criterion is a hierarchical composite endpoint of : 1. In-hospital death (truncated at 28 days) 2. Length of ICU stay (truncated at 28 days) 3. Length of hospital stay (truncated at 28 days)
Secondary objectives and endpoints	Secondary objectives include the comparison between groups of each component of the composite endpoints and, in-hospital adverse events and the total hospital costs. Secondary endpoints include : - in-hospital death (truncated at 28 days) - ICU length of stay (truncated at 28 days) - Hospital length of stay (truncated at 28 days) - Proportion of patient with Mechanical ventilation at day 28 - Length of mechanical ventilation until hospital discharge or at day 28 - Proportion of ICU admission - Proportion of Rapid onset pneumonia - Adverse events from intubation (hypoxemia, dental trauma, regurgitation, cardiac arrest, intubation difficulty score (IDS) ≥ 5, hypotension or oesophageal intubation) - Total hospital costs and cost consequence analysis (truncated at 28 days)

Design of the study	This is a superiority multicenter randomized controlled trial. Patients will be included and randomized either in pre-hospital setting by the emergency physician of the mobile intensive care unit (MICU) or in the ED. In the control group, the decision of intubation will be left to the discretion of the treating emergency physician of the mobile intensive care unit (MICU) or in the ED. In the intervention group, a conservative management will be implemented where the patient will be closely monitored, and the decision of intubation will be initially withheld, with safety intubation performed in case of regurgitation, seizure, shock, or sign of respiratory distress.
Population of study participants	ED Adult patients with acute poisoning and decreased level of consciousness (GCS ≤ 8)
Inclusion criteria	1. Age ≥ 18 years 2. Clinical suspicion of acute poisoning (either alcohol, drug, or médication 3. Decreased level of consciousness with a GCS ≤ 8 assessed by an emergency physician either in the ED or in the out of hospital field with the mobile intensive care unit (MICU). 4. Written informed consent signed by the trustworthy person / family member / close relative or inclusion in case of emergency 5. Patients affiliated to French social security (“AME” excepted)
Exclusion criteria	1. Respiratory failure (SaO2 < 90% with oxygen, clinical signs of respiratory distress) 2. Sustained Systolic blood pressure < 90 mmHg despite fluid resuscitation of 1 liter of critalloid 3. Witnessed generalized seizure 4. Acute cerebral aggression (Traumatic brain injury, intracranial hematoma, stroke) 5. Suspected Cardiotropic drugs poisoning (beta blockers, calcium channel inhibitor, angiotensin conversion enzyme), QRS or QT enlargement on ECG. 6. Suspected sole intoxication with toxic for which there is a reversal antidote e. 7. Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom 8. Known Pregnant women and breast feeding woman 9. Participation in another intervention trial
Interventions under investigation	<u>Conservative airway management</u> Decision to intubate will be withheld as long as the patient’s state allows it. The patient will be closely monitored and decision of intubation will be made upon presence of regurgitation, seizure, shock, or sign of respiratory distress.
Comparator arm	Routine practice - decision of intubation left at the discretion of the emergency physician
Interventions added by the study	Blood pressure, SpO2, respiratory rate, heart rate and GCS every 30 minutes until the patient recovers a GCS>8 or responds adequately to a simple order
Expected benefits for the participants and for society	Acute poisoning is a frequent reason for presentation to the ED or MICU intervention. These patients are often intubated, when their GCS is below 8, in order to protect their airways. Intubated patients need subsequent intensive care unit admission and monitoring, and this can be associated with increased risk of

	pulmonary complications, length of hospital-stay and cost. In a context of expenditures control in health care, appropriate intensive care resource utilization is an important issue. Thus, if our hypothesis is demonstrated, the results of NICO study, less exposure to the complications related to endotracheal intubation, associated with decrease of ICU stay and reduction of their health costs, will change practice and national and international guidelines for management of acute come poisoned patients.
Risks and burdens added by the study	The risk added by the research is the one of potential complications following a decreased level of consciousness and no invasive airway protection. This includes a risk of regurgitation and aspiration pneumonia. This risk has never been formally evaluated and equipoise remains on the benefit-risk balance of a conservative airway management (no intubation) compared to invasive one (sedation, intubation and mechanical ventilation). The risk level of the study is C.
Practical implementation	After a comatose patient has been screened and fulfil inclusion criteria with no exclusion criteria, the patient will be included and randomized. This inclusion can occur either in the pre hospital setting or in the ED Patients randomized in the control group will be treated according to routine care regarding their airway management. Patients randomized in the intervention group will be conservatively managed and closely monitored: sedation and intubation will be withheld as long as the patient's state allows it (no signs of respiratory distress, no seizure, no shock and no regurgitation) until he recovers a satisfactory level of consciousness.
Number of participants included	Up to 240 patients
Number of centres	26 Emergency Departments /SMUR and reanimation in France
Duration of the study	24 months of inclusion Each participant will be included and followed-up until hospital discharge (truncated at 28 days) Total duration of the study: 25 months
Number of enrolments expected per site and per month	1 patient per center per month
Statistical analysis	No interim analysis is planned. Principal criterion will be analyzed using the Finkelstein model according to ITT principle. Sensitivity analysis will be performed using the win ratio method.
Funding sources	Ministry of Health, 2019 national PHRC program
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

A conservative management without immediate endotracheal intubation of adult patients with acute poisoning and a decreased level of consciousness (defined by a Glasgow Coma Scale ≤ 8) is effective and associated with fewer complications at 28 days.

2.2 Description of knowledge relating to the condition in question

A decreased level of consciousness is a common reason for presentation to the emergency department (ED) and is often the result of intoxication (up to 1% of all ED visits and 3% of intensive care unit (ICU) admission).[1,2] In France, approximately 165 000 poisoned patients are managed each year.[1] Originally developed in head injured patients, the Glasgow Coma Scale (GCS) is a validated reproducible score evaluating the level of consciousness – a GCS ≤ 8 is associated with reduced gag reflex and increased incidence of aspiration pneumonia (with an adjusted odds ratio of 2.32, 95%CI =1.60 to 3.33).[3] However, whether this risk of aspiration pneumonia (AP) may be decreased by early intubation is unknown, and no difference in the risk of AP was reported between patients that were intubated early and patients who were not.[3]

2.3 Summary of relevant pre-clinical experiments and clinical trials

Although it is well established that in trauma patients, a GCS ≤ 8 mandates airway management by endotracheal intubation, it remains unknown whether this strategy should be applied to other etiologies of coma, in particular for acute poisoned patients. Tracheal intubation and mechanical ventilation allow to prevent aspiration pneumonia, to optimize oxygenation and gas exchange.

Endotracheal intubation in poisoned patients

In poisoned patients, a decreased GCS has been associated to the use of endotracheal intubation in a recent retrospective study in 882 patients (OR 2.1 per point lost in GCS, IC 95% [1.8 – 2.5]).[1] In the US, 5 to 20% of poisoned patients are intubated,[4] whereas, in France, several studies and the EPITOX cohort analysis showed that the proportion of poisoned patients with a GCS≤ 8 that are intubated ranges from 20% to 46%.[1,5,6]. This confirms that this practice is frequently used in routine practice. This procedure is used in order to avoid the 5 to 15% (depending on the definition used and the targeted population) risk of pulmonary aspiration,[3,7] although there is no proven reduced risk from intubation.

Nevertheless, invasive airway management is related with an incidence more than 10% of morbidity and mortality in emergency setting.[8–10] Furthermore, more than one third of aspiration pneumonia occurred in patients that were intubated.[3] Thus, the benefit-risk ratio of intubation is not well established. It is noteworthy that, intubation is associated with substantial risk for poisoned patients, including difficult intubation (20%), aspiration pneumonia (3%), arythenoid subluxation (2%), and prolonged ICU stay (median of > 36h).[10,11].

Conservative management of poisoned patients

On the other hand, observational studies with small series of patients reported that a conservative management of poisoned patients including simple observation may be safe with no reported need of mechanical ventilation and no reported increased aspiration risk.[2,12] Therefore, equipoise remains on the indication of intubation for these patients.[2,12].

Finally, the benefit/risk ratio concerning tracheal intubation in comatose poisoned patient remains widely unknown and warrant a solid randomized trial.

Thus, we wish to assess whether a conservative airway management of comatose poisoned patients with no emergent intubation can be safely conducted in the ED with no increased risk of aspiration, ICU admission or mechanical ventilation) and thus a lower rate of ICU admission and length of hospital stay.

2.4 Description of the population to be studied and justification for the choice of participants

We will include patients with a decreased level of consciousness (defined by a GCS of 8 or less) caused by acute intoxication (alcohol, recreative drugs, or other prescription drugs (with the exception intoxication with cardiotropic drugs, e.g. beta blockers, calcium channel inhibitor, angiotensin conversion enzyme)). These patients will be included at the initial stage of their management: in the ED, or out of hospital with a pre-hospital emergency physician. We will exclude patients with clear proven benefit of intubation: patients in shock, patients with suspicion of brain lesion, seizure related with poisoning, visualization of regurgitation of gastric content or sign of respiratory distress.

2.5 Succinct description of the intervention

Conservative airway management. Patients will be conservatively managed, i.e. close monitoring and no intubation and mechanical ventilation unless the patient presents a clinical event that needs intubation (shock, sign of respiratory distress, visualization of regurgitation or seizure).

2.6 Summary of the known and foreseeable benefits and risks for the research participants

Acute poisoning is a common reason for presentation to the ED or MICU intervention (up to 1% of all ED visits and 3% of intensive care unit (ICU) admission). These patients are often intubated (reported rate ranging from 20 to 50% in different cohort studies), when their GCS is below 8, in order to protect their airways. However there is currently no clear demonstration of its efficacy in this specific target population, while it is known that intubation is associated with morbidity and mortality.[8–10]
Intubated patients need subsequent intensive care unit admission and invasive monitoring, and this can be associated with increased risk of pulmonary complications, length of hospital-stay, nosocomial infections and cost. In a context of expenditures control in health care, appropriate intensive care resource utilization is an important issue. When considering the increasing demand for intensive care among emergency patients, the importance of health care resource allocation and expenditure control, and the possible absence benefit of intubation and intensive care, an endotracheal airway management of poisoned coma patients might be detrimental.
Thus, if our hypothesis is demonstrated, the results of NICO study will change practice and guidelines for management of acute come poisoned patients, with less exposure to the morbidity of endotracheal intubation and associated with decrease of ICU stay, and reduction of their health costs.

3 OBJECTIVES

3.1 Primary objective

To compare, between conservative management and routine practice, a composite hierarchical outcome of in-hospital mortality and morbidity truncated at 28 days, in comatose poisoned patients.

3.2 Secondary objectives

Secondary objectives include the comparison between groups of each component of the composite endpoints and, in-hospital adverse events and the total hospital costs.

4 STUDY DESIGN

4.1 Study endpoints.

4.1.1 Primary endpoint

Hierarchical composite endpoint of:
- In hospital death (truncated at 28 days)
- Length of ICU stay
- Length of hospital stay

This endpoint will be reported using both the Finkelstein model (Finkelstein Stat med 1999; Beitler JAMA 2019) and the win ratio methods (Pocok Eur H J 2016), with priority listed in this order from highest to lowest.
Patients will be followed until hospital discharge (or truncated at 28 days if still hospitalized) and data collected in the electronic health record the investigator with the help of a clinical research technician.

4.1.2 Secondary endpoints

- In-hospital death (truncated at 28 days)
- ICU length of stay (truncated at 28 days)
- Hospital length of stay (truncated at 28 days)
- Proportion of patient with Mechanical ventilation at day28
- Length of mechanical ventilation until hospital discharge or at day28
- Proportion of ICU admission
- Proportion of Rapid onset pneumonia
- Adverse events from intubation (hypoxemia, dental trauma, regurgitation, cardiac arrest, intubation difficulty score (IDS) ≥ 5, hypotension or oesophageal intubation)
- Total hospital costs and cost consequence analysis (truncated at 28 days)

4.2 Description of research methodology

4.2.1 Design of the study

This is an open superiority randomized controlled trial, in two parallel arms.
Patients will be randomized and subsequently allocated in the control group (routine practice) or intervention group. In the control group, the decision of immediate intubation will be left to the discretion of the treating emergency physician of the mobile intensive care unit (MICU) or in the ED. In the intervention group, a conservative management will be implemented where the patient will be closely monitored, and the decision of intubation will be initially withheld, with safety intubation performed in case of regurgitation, seizure, shock, or sign of respiratory distress.

4.2.2 Number of participating sites

25 EDs and SMUR in France
Recruitment centres: emergency department or physician-staffed EMS ambulance (SMUR)
1 reanimation service: for the patients follow up

4.2.3 Identification of participants

The participants in this research will be identified as follows: site number (3 digits) - sequential enrolment number for the site (4 digits) - surname initial - first name initial.
This reference number is unique and will be used for the entire duration of the study.

A randomisation number will also be assigned when the participant is randomised. This number will have the following format: RXXXX.

4.2.4 Randomisation

Randomization list will be assessed by URC-Est. Randomisation in a 1 : 1 ratio, will be stratified by centre and block balanced. The width of the blocks will not be communicated to the investigators.
Randomization process will use sealed envelopes, since patients can be randomized in mobile intensive care unit in which access to Internet can be limited.

4.2.5 Blinding methods and measures put in place to protect blinding

Due to the nature of intervention, this study is an open trial.

5 IMPLEMENTATION OF THE STUDY

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
Patient as soon as his/her condition allows it (due to the extreme emergency situation not allowing the collection of prior consent of the patient or relative)	The investigator of each centre or collaborating emergency physicians declared and trained in the study	As soon as the patient's state allows it	As soon as the patient's state allows it

5.1 Baseline visit / randomisation visit

After confirmation of all inclusion criteria and absence of exclusion criteria (that includes systematic ECG), the patient will be included and randomized in the control group or in the intervention group. As allowed by the French Law and after approval by the CPP, due to the decreased level of consciousness, a delayed informed signed consent will be sought as soon as the patient' state allows it. The signed consent of the next of kin will be sought when available.
A paper CRF will be available to collect in the ED details regarding intubation and adverse events related to intubation procedure (hypoxemia, dental trauma, regurgitation, cardiac arrest, intubation difficulty, hemodynamic instability or oesophageal intubation).

5.2 Follow-up visits

Followed until hospital discharge, the follow up will occur at hospital discharge (or truncated at 28 days after inclusion if still hospitalized). The local investigator with the help of clinical research technician will collect and implement the data in the CRF.

5.3 Expected length of participation and description of the chronology and duration of the study

Duration of enrolment period :	24months
Duration of follow-up period :	28 days maximum
Total study duration:	25 months

5.4 Table or diagram summarising the chronology of the study :

Actions	Day 0	As soon as the patient's state allows it	Hospital Discharge (truncated at 28 days if still hospitalized)
Information		X	
Informed consent		X	
Verification of inclusion and non-inclusion criteria	X		
Pregnancy test	X		
Randomization	X		
Clinical exam	X		
Airway management (conservative or intubation)	X		
Clinical surveillance and close monitoring of mental status, respiratory rate and vital parameters	X		
Record of adverse events and endpoints	X	X	X

5.5 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Airway management	Endotracheal intubation performed at the discretion of the emergency physician	No immediate intubation
Monitoring for vital parameters	Blood pressure, SpO2, respiratory rate, heart rate	Blood pressure, SpO2, respiratory rate, heart rate and GCS every 30 minutes until the patient recovers a GCS>8 or responds adequately to a simple order

6 <u>ELIGIBILITY CRITERIA</u>

6.1 Inclusion criteria

1- Age ≥ 18 years
2- Clinical suspicion of acute poisoning (either alcohol, drug or medication)
3- Decreased level of consciousness with a GCS ≤ 8 assessed by an emergency physician either in the ED or in the out of hospital field with the mobile intensive care unit (MICU).
4- Written informed consent signed by the patient / the trustworthy person / family member / close relative or inclusion in case of emergency
5- Patients affiliated to French social security (“AME” excepted)

6.2 Exclusion criteria

1- Respiratory failure (SpO2 < 90% with oxygen provided by nasal cannula (≤ 4 l/min.), clinical signs of respiratory distress)
2- Sustained systolic blood pressure < 90 mmHg despite fluid resuscitation of 1 liter of critalloid
3- Witnessed seizure
4- Acute cerebral aggression (Traumatic brain injury, intracranial hematoma, stroke)
5- Suspected Cardiotropic drugs poisoning (beta blockers, calcium channel inhibitor, angiotensin conversion enzyme), QRS or QT enlargement on ECG.
6- Suspected sole intoxication with toxic for which there is an antidote
7- Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom
8- Known Pregnant women and breast feeding woman
9- Participation in another intervention trial

6.3 Recruitment procedure

	Number of participants
Total number of participants to be included	Un to 240
Number of recruiting centres	25
Enrolment period (months)	24
Number of participants/centre	Between 09 and 10

Number of participants/centre/month	1

All of the participating centers have already participated in large prospective trials conducted by the primary investigators of the present trial, with high recruitment targets that were always reached in the planned time schedule in the ED (PROPER NCT02375919 JAMA 2018, SCREEN NCT02738164 JAMA 2017, ELISABETH NCT03683212) or in the out-of-hospital medical ICU (CAAM NCT 02327026 JAMA 2018, PRESENCE NCT01009606 NEJM 2013).

The EPITOX observational study conducted in French EDs in 2016 suggested that a median of 8 patients per month per center would fulfilled our inclusion criteria. Therefore, our inclusion target of 2 patients/per center/per month is highly reachable within the timeframe.

6.4 Termination rules

6.4.1 Criteria and methods for premature discontinuation of study-related interventions/procedures/strategies

Several situations are possible:
- Temporary suspension of study-related interventions/procedures/strategies used, the investigator must document the reason for suspending and resuming the procedure in the participant's source file and the case report form (CRF)
- Premature discontinuation of study-related interventions/procedures/strategies used but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of study-related interventions/procedures/strategies used and withdrawal from the study

The investigator must:
- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for the hospital following the premature discontinuation of study-related procedures used.
Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study procedure must be discontinued but the participant will continue to be monitored for the study.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

The case report form must list the various reasons why the participant has discontinued the study :
- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue

- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of study-related interventions/procedures/strategies used and participation of the patient in the study; see section 6.4.1.

6.4.4 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSAR) are observed in one of the study arms or if there is a discrepancy in the serious adverse reactions between the study arms, requiring a reassessment of the benefit-risk ratio for the study.

Similarly, AP-HP as the sponsor or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the intervention performed, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the procedure required to conduct the study

The procedure under investigation is the conservative management of patient's airways, with close patient's monitoring and withholding the decision of immediate intubation if patient has no complication. Once the patient is included and randomized in the intervention group, he will be closely monitored in the resuscitation room in the ED (SAUV) or in the MICU and transported to an ED participating to this trial and monitored there. Continuous monitoring includes blood pressure, heart rate, respiratory rate and SpO2 checked every 30 minutes, Clinical reevaluation every 30 minutes with new GCS assessment will performed by local investigator. In the resuscitation room, patients benefit from the continuous physical presence of a nurse or physician, who can therefore detect any potential sign of respiratory distress, regurgitation, seizure, or other adverse events.
If the patient recovers a sufficient level of consciousness (evaluated by a GCS > 8 for more than 30 minutes or a correct state of consciousness defined by appropriate verbal or motor response to a simple order), then he can be discharged from the resuscitation area and managed in the main major ED room for routine monitoring and care.
If the patient presents at any time any sign of respiratory distress, regurgitation, shock or other events that mandates an endotracheal intubation, he will be immediately sedated with rapid sequence intubation and intubated.
All intubation will be performed following the guidelines of the French society of intensive care medicine for rapid sequence intubation. Drugs of choice for induction combine an hypnotic drug (either ketamine, hypnomidate or propofol) and a short term curare (Succynilcholine). A pre-oxygenation aiming at maintaining a 100% SpO2 for 2 minutes will be sought. In case of hypoxia, non invasive ventilation should be used. The choice of direct or video laryngoscopy will be left to the discretion of the physician. The post-intubation measurement of CO2 with capnography is recommended when available.

7.2 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including rescue medications

Not applicable

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoint assessment parameters

The local investigator with the help of the clinical research technician will collect vital status, length of ICU and hospital stay, and other secondary endpoints).
Any suspicion of pneumonia reported in the health record will be analyzed by the local investigator and confronted to US CDC definition of pneumonia [13].

Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

(i) New or progressive and persistent infiltrates, (ii) consolidation, (iii) cavitation AND at least one of the following:

(a) fever (>38°C) with no other recognised cause,

(b) leucopaenia (white cell count $<4\times10^9$ litre−1) or leucocytosis (white cell count $>12\times10^9$ litre−1),

(c) for adults >70 year old, altered mental status with no other recognised cause;

AND at least two of the following:

(a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements,

(b) new onset or worsening cough, or dyspnoea, or tachypnoea,

(c) rales or bronchial breath sounds,

(d) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy assessment parameters

All data regarding adjudication of primary and secondary endpoint will be collected at patient's discharge (or truncated at day 28).

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

Members of the committee: Pr Frédéric Adnet, Pr Yonathan Freund, Marine Cachanado, Pr Tabassome Simon.
Missions: design the study, define target population, define primary and secondary assessment criteria, monitor inclusion rate and follow up of the patients

10 SAFETY ASSESSMENT - RISKS AND BURDENS ADDED BY THE STUDY

10.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

Adverse event occurring in a person enrolled in a study involving human participants, when this event is related to the study or to the product being studied.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the research participant, requires hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction**

Any adverse reaction for which the nature, severity or progression are not consistent with information pertaining to the products, acts practiced and methods used during the study.

Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor not relating to a health product (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

For example, this concerns:

- any clinically significant increase in the frequency of an expected serious adverse reaction;
- early termination or a temporary halt for safety reasons for a trial carried out in another country with the same product (act or method) as the one being studied in France;
- recommendations from the Data Monitoring Committee, if applicable, if they are relevant to the safety of the participants;
- suspected unexpected serious adverse reactions in participants who have terminated the trial and of which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.

10.2 The role of the investigator

For each adverse event, the investigator must assess its severity and report all serious and non-serious adverse events in the case report form (e-CRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:
- either by using general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: prevents daily activities*

The investigator must **assess the causal relationship between** a serious adverse events and interventions/procedures added by the study.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre Method), and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC: causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
**Or study procedures

10.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per Article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies informs the sponsor without delay on the day he become aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the *Code de la Santé Publique*, with the exception except any event which is listed in the protocol (see section 10.2.2) and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.2.2 Specific features of the protocol

Other events that require the investigator to notify the sponsor without delay

- Adverse events deemed "medically significant":

- Evidence of moderate or severe Acute respiratory distress syndrome, as defined by the Berlin definition Occurrence of regurgitation leading to intubation
- Occurrence of shock leading to intubation

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

Notify using a special form appended to the protocol.

10.2.3 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms

- *Normal and natural course of the condition* :

Evidence of mild Acute respiratory distress syndrome, as defined by the Berlin definition, Sedation, intubation, mechanical ventilation, aspiration pneumonia, Ventilator Associated Pneumonia, ICU admission and all complication expected with intubation and extubation (laryngeal complication, cardiac complication, traumatism etc…) are frequent in routine practice for ED poisoned patients and decreased level of consciousness. Therefore, these events will not mandate a forma report to the sponsor except those leading to death. These events will be collected and analyzed as secondary endpoints.

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

10.2.3.1 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date of the inclusion
- throughout the whole follow-up period required for the trial *(28 days),*
- Indefinitely, if the SAE is likely to be due to procedures performed by the study

10.2.3.2 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99, only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies using e-CRFs:

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr

10.3 Role of the sponsor

The sponsor, represented by its Safety Department, continuously, throughout the trial, assesses participant safety throughout the study.

10.3.1 Analysis and declaration of serious adverse events

The sponsor assesses :
- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific intervention/procedure/examination added by the study,
  All serious adverse events which the investigator and/or the sponsor believe could have a causal relationship with the conservative airway management, specifically added by the study that could reasonably be considered as having suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the interventions/procedures/practiced acts and/or administered products over the course of the study.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

Serious adverse events likely to be related to the conservative airway management are as follows*:*
- acute respiratory distress requiring emergent intubation and subsequent acute respiratory distress syndrome, as defined by the Berlin definition
- seizure
- regurgitation, inhalation/aspiration pneumonia
- shock

Serious adverse events likely to be related to the intubation/extubation:
Severe hypoxemia, severe collapsus cardio-vascular , cardiac arrest , difficult intubation, difficult extubation, rhythm disorders, œsophageal intubation, inhalation, Agitation, dental breakage, traumatism and laryngeal complications (hematoma of vocal cords, cartilaginous stripping, granulom, arytenoid sub luxation), oedema

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency) :
- The sponsor must send the initial report immediately upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of monitoring reports within a period of 8 calendar days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.2 Analysis and declaration of other safety data

Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend or halt or modify the study protocol or similar studies.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issues, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 7 days from learning of the information.

10.3.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (ASR or annual safety report), which includes, in particular:
- a safety analysis for the research participants,
- a list of all the suspected serious adverse reactions that occurred in France in the concerned study during the period covered by the report,
- summary tables including all of the SAEs that have occurred since the start of the study.

The annual safety report must be sent no later than 60 days after the anniversary of the date on which the first participant was included in the study.

10.4 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled. All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
- Dr Anne-Laure FERAL (Hôpital Européen Georges Pompidou, Paris) : Emergency medicine
- Pr Elie Azoulay (Hôpital Saint-Louis, Paris) : Intensive care medicine
- Pr Patrick Goldstein (CHU de Lille) : Emergency medicine

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

Data will be collected first in a paper CRF filled in the MICU or in the ED by the treating emergency physicians, then in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-EST. Data will be completed by the investigators for each visit of follow up with the help of a Clinical Research Technician (CRT) of URC-Est for AP-HP centers and of each center for others centers.

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

For each recruited patient, besides usual clinical and biological data, we will collect the following specific items :
- Time to recover a GCS > 8
- Need for intubation
- Evidence of aspiration
- Primary and secondary endpoints

11.3 Right to access data and source documents

11.3.1 Data access

In accordance with GCPs :
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

Data management will be performed by a data manager from URC-Est under the responsibility of Pr T. Simon. Statistical analysis will be performed by a biostatistician from URC-Est under the responsibility of Pr T. Simon.

11.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

A detailed analysis plan will be a priori defined. Analysis will be performed by a statistician from URC-Est after data review and data base lock. Therefore, no interim analysis is planned. Analyses will be performed using SAS® software (version 9.4 or updated version).
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 intent to treat (ITT) population.
This endpoint will be analyzed by:

A) Using first the Finkelstein model (Finkelstein et al., Statistics in medicine, 1999) (cf. **Erreur ! Source du renvoi introuvable.**) 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 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	Reduced	Not used	+1 (win)	-1 (lose)
No	No	Increased	Not used	-1 (lose)	+1 (win)
No	No	Same	Reduced	+1 (win)	-1 (lose)
No	No	Same	Increased	-1 (lose)	+1 (win)

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
No	No	Same	Same	0 (tie)	0 (tie)

B) A sensitivity analysis will be performed using the win ratio methods (Pocok Eur H J 2016).

Others sensitivity analyses will also be performed on per protocol population using the same methods.

Secondary criteria analysis:

Proportion of in-hospital death will be compared between groups by a Pearson Chi² test or a Fisher exact test, as appropriate. Proportion difference between groups and its 95% confidence interval will be calculated.

ICU length of stay, free-days for mechanical ventilation at day 28 and hospital length of stay will be compared between groups by a Student t test or a Wilcoxon rank sum test, as appropriate.

Proportion of: mechanical ventilation, ICU admission and rapid onset pneumonia (as defined by the US CDC definition of pneumonia, Abbott et al. BJA 2018) will be compared between groups by a Pearson Chi² test or a Fisher exact test, as appropriate. For each criterion proportion difference between groups and its 95% confidence interval will be calculated.

Proportion of adverse events from intubation (hypoxemia, dental trauma, regurgitation or oesophageal intubation) will be compared between groups by a Pearson Chi² test or a Fisher exact test, as appropriate. Proportion difference between groups and its 95% confidence interval will be calculated overall and for each kind of adverse event.

12.2 Calculation hypotheses for the number of participants required and the result

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.

12.3 Anticipated level of statistical significance

All tests will be two-sided, and a P value of <0.05 will be considered significant.

12.4 Statistical criteria for termination of the study

Not applicable. No interim analysis data planned.

12.5 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. No replacement of other missing data is planned.

12.6 Management of modifications made to the analysis plan for the initial strategy

All modification made to the analysis plan for the initial strategy will be documented in the analysis report.

12.7 Choice of individuals to be included in the analyses

Intent to treat population (ITT): all randomized patients regardless of the strategy received by the patient.
The “per protocol” (PP) population is defined as all patients randomized and treated without major protocol violations/deviations. Pre-defined major protocol violations/deviations are:

- Non-respect of all selection criteria
- 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 endpoints
- Inclusion in another interventional study

Major protocol deviation identified during a blinded data review before data base lock.

12.8 Economic evaluation analysis

The economic analysis will be performed by URC-Eco, Pr Isabelle Durand Zaleski.
The components of the economic study are: 1) costs calculations and comparisons, 2) a cost consequence analysis.
We will estimate the 28-day total costs of conservative vs standard management and the consequences measured by mortality, severe adverse events including mechanical ventilation, ICU admission, rapid onset pneumonia. Costs and consequences will not be aggregated. Due to the short duration of the follow up, QALYs will not be calculated (the anticipated difference in utilities is small and will be divided by 12 since the follow up is only 28 days).
The cost analysis will be undertaken from the viewpoint of the healthcare system restricted to the hospital since all relevant resources are hospital-based, over a 28-day time horizon, without discounting.
Resources used during the index admission and during repeat admissions over a 28-day period will be recorded prospectively. Hospital resources will be valued using the production costs associated with the patients’ DRGs, adjusted for actual use of life support systems and actual length of stay. Repeat hospital admissions during the 28-day follow up period will be included in the cost computation, based upon DRG costs following the same calculation rules. Non hospital resources will not be included.
Outcomes (consequences) are medical events, other endpoints used in the trial such as ICU stay are already included in the cost calculations and will not be double counted. The consequence analysis will compare cumulated mortality and the adverse events listed above at 28 days between groups. The cost consequence analysis will compare total 28-days hospital costs and outcomes between groups. We will estimate the uncertainty using bootstrap replications and calculate the probability that the conservative management is both cost saving and outcome improving using the cost effectiveness plane.
Baseline results will be presented as mean ± SD, median interquartile ranges (IQR), or as frequencies with percentages. Resource use data will be presented as means with standard error of the mean despite non-normal distribution because they better represent per patient data than median values and compared using nonparametric testing. Costs, survival, and adverse events will be presented as means with 2.5 to 97.5% bootstrapped intervals.

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

13.1.2 Scope of centre monitoring

In the case of this **C** risk study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level **high**.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.).

13.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the

data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.
These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code. The person will be given granted a short reflection period between receiving the information and being asked to sign the consent form.
Emergency procedure, Article L1122-1-3 of the Code de la Santé Publique (French Public Health Code): if the person is unable to express his will and the next-of-kin is unidentified and/or unreachable

at time of inclusion, the investigator may proceed to the inclusion of the person without any consent. The investigator must supply any document demonstrating that he has extensively tried to identify and/or to reach the next-of-kin. In this case of emergency procedure, the next-of-kin gives his consent as soon as he is identified and reachable; the person gives his consent to continue his participation to the study when he has recovered his ability to express his will.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consentor the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP, as well as the methods used for providing information with a view to obtain consent. The investigator will retain the original signed and dated consent form.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 28 days later the inclusion.
The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

14.3 Compensation for participants

No compensation will be given to participants.

14.4 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.5 Legal obligations

14.5.1 Role of the sponsor

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique* (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.5.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants not concerning a health product mentioned in Article L5311-1, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory provisions in force.

14.5.3 Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants not concerning a health product, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.5.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation - GDPR) regulations.

- Request for authorisation by the CNIL (French Data Protection Agency)

This research is not governed by the CNIL "Reference Method" (MR-001) because inclusion due to an emergency situation without collection of consent at the time of inclusion.
The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.

14.5.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.5.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.5.7 Archiving

Specific documents for an interventional study involving human participants not concerning a health product will be archived by the investigator and the sponsor for 15 years after the end of the research. This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents.

15 FUNDING AND INSURANCE

15.1 Funding sources

This is a research funded by the 2019 national PHRC program, French ministry of health.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and

their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period (0100518814033 200112), which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from Programme Hospitalier de Recherche Clinique – National PHRC 2019 (French Ministry of Health)"

This study has been registered on the website http://clinicaltrials.gov/ under number:

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18 LIST OF ADDENDA

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version

18.1 List of investigators

18.2 Serious Adverse Events notification form

18.3 Pregnancy notification form