SYNOPSIS
PROTOCOL AnticipUSC – N°ICO 2016-A-04

A) Clinical Trial Identification			
TITLE OF THE TRIAL: ***Multicenter, open-label, randomized study comparing early postoperative prophylactic non-invasive ventilation in the intensive care unit versus standard postoperative follow-up in patients at high risk of postoperative pulmonary complications according to the preoperative ARISCAT score, undergoing surgery under general or regional anesthesia (ANTICIPUSC)***			
SHORT TITLE:	ANTICIPUSC		
COORDINATOR:	Dr Denis DUPOIRON		
ESTIMATED NUMBER OF CENTERS:	3	**NUMBER OF PATIENTS**:	266

B) Sponsor Identification	
NAME OF THE ORGANIZATION:	ICO, DRCI-Cellule de Promotion
CONTACT PERSON: TEL : 02 41 35 28 21 FAX : 02 40 67 97 87	MME MARINE TIGREAT

C) General Information About the Trial

Indication:

This study will focus on a selected population at high risk of postoperative pulmonary complications (PPC) according to the ARISCAT score, among all surgical patients in the participating centers, whether undergoing surgery under General Anesthesia (GA) or Regional Anesthesia (RA), who may benefit from preventive postoperative management.

Primary objective:

The primary objective of the study is to compare the effectiveness of a preventive postoperative management strategy using non-invasive ventilation (NIV) in the intensive care unit versus standard care, on the incidence of acute respiratory failure within 7 postoperative days during hospitalization, in patients at high risk according to the ARISCAT score.

Secondary objectives:

- The safety and tolerability of the strategy under study
- The cause of acute respiratory failure (arf) among the different postoperative pulmonary complications (ppc)
- Mortality during hospitalization for surgery, up to a maximum of 7 days
- Any effect on patient reintubation (cause and timing)
- Any effect on the length of stay in the icu/intensive care unit and on invasive or non-invasive mechanical ventilation
- Any effect on the incidence of healthcare-associated infections, defined according to the centers for disease control (cdc) criteria.

Inclusion criteria:

1. Patient aged 18 years or older
2. Patient scheduled for elective surgery or considered semi-urgent (pre-anesthesia consultation < 48 hours before the surgical procedure), under General Anesthesia (GA) or Regional Anesthesia (RA)
3. Patient with an ARISCAT score greater than or equal to 45 (high risk of PPC)
4. Written informed consent signed by the patient
5. Patient affiliated with a social security system

Exclusion criteria:

1. Minors, pregnant or breastfeeding women
2. Obstetric procedures
3. Surgeries under Local Anesthesia (LA) or peripheral nerve block
4. Procedures performed outside an interventional room (e.g., operating theater or interventional radiology)
5. Procedures related to previous surgical complications
6. Patients reoperated during follow-up (no double inclusion for the second surgery)
7. Organ transplantation
8. Patients already intubated preoperatively
9. Outpatient surgery
10. Refusal to participate or inability to provide informed consent
11. Persons deprived of liberty or adults under guardianship
12. Participation in another interventional study.

Primary endpoint:

Occurrence of acute respiratory failure (ARF) within 7 postoperative days during hospitalization, validated by the blinded adjudication committee with respect to the randomization arm.

Secondary endpoints:

Assessment of the safety and tolerability of the strategy under study:

- Discomfort or intolerance to NIV, defined as the inability to achieve the target of 6 to 8 hours per day due to premature termination of sessions caused by intolerance, despite proper implementation of NIV, including excessive leaks when these are the reason for stopping sessions
- Skin lesions at contact points between the interface and the patient's skin
- Anastomotic suture dehiscence (digestive or bronchial) when caused by a total pressure (PEEP + IPAP) > 20 cmH_2O
- Gastric distension defined as aeric distension of the gastric air pocket evidenced by imaging or gastric tube aspiration
- Occurrence of aspiration of secretions or vomit whose evacuation was hindered by the NIV mask

Any ARF must lead to investigation of its etiology using appropriate examinations:

Infectious pneumonia defined by a Modified Clinical Pulmonary Infection Score (CPIS) > 6, with microbiological thresholds of culture concentrations >10^3 CFU/ml for a protected distal sample, >10^4 CFU/ml for bronchoalveolar lavage, and >10^6 CFU/ml for tracheal aspiration

The Modified Clinical Pulmonary Infection Score (modified CPIS)

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	≥36.5 and ≤38.4	≥38.5. and ≤38.9	≥39 or ≤36.4
Leukocytes count, per mm^3	≥4,000 and ≤11,000	<4,000 or >11,000	<4,000 or >11,000 + band forms ≥500
P_{aO2}/F_{IO2}, mmHg	>240 or ARDS		≤240 and no evidence of ARDS
Microbiology	Negative		Positive

Figure 1 - Score CPIS

- Upper airway obstruction (aspiration or pulmonary congestion, altered consciousness defined by a Glasgow score ≤ 12)
- Heart failure with hydrostatic pulmonary edema
- Pulmonary embolism confirmed by contrast-enhanced pulmonary imaging during the arterial phase, or venous thrombosis confirmed and associated with ARF
- Pleural effusion: on chest X-ray, obliteration of the costophrenic angle or Damoiseau line in upright position, evidence of displacement of adjacent anatomical structures, opacity in one hemithorax with preservation of vascular shadows, or confirmed by thoracic CT scan
- Atelectasis: pulmonary opacity with mediastinal, hilar, or diaphragmatic shift toward the affected area and compensatory hyperinflation of the non-atelectatic lung, or confirmed by thoracic CT scan showing areas of atelectasis or derecruitment
- Pneumothorax: presence of air in the pleural space without vascular bed adjacent to the visceral pleura
- Bronchospasm: onset of expiratory wheezing treated with bronchodilators
- Aspiration pneumonia: pneumonia following inhalation of regurgitated gastric fluid
- Other etiology (e.g., other surgical complications)

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Assessment of mortality during hospitalization for surgery

- Death from any cause during hospitalization for surgery

Assessment of an effect on patient reintubation:

- Reintubation due to respiratory failure (ARF)
- Reintubation due to non-respiratory failure, excluding reintubations specifically for a new surgical or interventional radiology procedure
- Time to reintubation to assess delayed reintubation (characterized by a non-significant difference in reintubation rate between groups but a longer delay in the NIV group)

Assessment of an effect on length of stay in ICU and duration of invasive or non-invasive mechanical ventilation:

- Number of days of invasive mechanical ventilation (intubated or tracheostomized) during hospitalization for surgery, including episodes of reintubation
- Number of days of non-invasive mechanical ventilation (NIV) during hospitalization for surgery, including prophylactic and therapeutic NIV.

Assessment of an effect on the incidence of healthcare-associated infections, defined according to Centers for Disease Control (CDC) criteria:

- Infectious pneumonia: see secondary endpoint criteria
- Urinary tract infection: fever > 38°C and urine culture showing no more than two microbial species, at least one with a concentration $>10^5$ CFU/ml, in a patient with no other obvious source of infection
- Catheter-related infection: fever > 38°C, positive catheter culture or sample, and resolution of fever within 48 hours after catheter removal without antibiotic change and no other identified source of infection
- Bacteremia: fever > 38°C and at least one positive blood culture (two or more if coagulase-negative staphylococcus)
- Surgical site infection

Data collection is performed prospectively throughout the first 7 days of hospitalization for surgery.

D) Description of Investigational Medicinal Products

MEDICAMENTS :

Name of the Medicinal Product (INN)	Brand Name	Pharmaceutical Form	Route of Administration	Dosage per Administration
Medical Liquid Oxygen	N/A	Gas	N/A	

Therapeutic regimen:
The ventilatory mode used will be an assisted mode (PSV or BiPAP), as these have shown a stronger (86) and more sustained effect (29) than CPAP alone.
The interface—nasal mask, face mask, or helmet—is chosen according to the unit's usual practice.
NIV sessions of 1 hour are repeated every 2 to 3 hours, aiming for a daily assistance duration of 6 to 8 hours for a minimum of 24 hours. Weaning from NIV is managed by the clinician within a maximum of 48 hours.

Initially set between +5 and +8 cmH_2O, IPAP is gradually increased in increments of 2 to 3 cmH_2O for patient comfort, until achieving an inspiratory peak allowing an expired tidal volume (Vte) between 6–8 ml/kg of predicted body weight, according to current ventilation recommendations (84, 112), with a respiratory rate < 30/min.
PEEP is set between +5 and +10 cmH_2O, and FiO_2 adjusted to maintain SpO_2 > 92% or PaO_2 > 70 mmHg on blood gas analysis. Care is taken to ensure that total pressure (PEEP + IPAP) remains ≤ 20 cmH_2O to avoid gastric distension (airway pressure lower than the lower esophageal sphincter pressure) (42) and to minimize the theoretical risk of bronchial suture dehiscence in thoracic surgery.

The ventilator's inspiratory trigger is set to the minimum value allowing the most sensitive detection of inspiratory efforts without causing auto-triggering.
The clinician may adjust IPAP based on the patient's blood gas results.

Duration of Treatment:
Each prophylactic NIV session lasts 1 hour. Sessions are repeated every 2 to 3 hours, separated by 2-hour periods without assisted ventilation to allow the patient to rest, eat, and receive care, including physiotherapy sessions. This schedule may be adapted to the unit's activity, with the goal of achieving a daily assistance duration of 6 hours without exceeding 8 hours, for a minimum of 24 hours.
Weaning from NIV is managed by the clinician within a maximum of 48 hours.

Expected outcomes:
Prevent the occurrence of PPCs and the complications they cause:

- Infectious pneumonia and aspiration pneumonia
- Pleural effusions
- Atelectasis
- Bronchospasm
- Acute respiratory failure (ARF) and hypoxemia, and consequently:
  - o Prevent patient reintubation
  - o Prevent surgical site infections and anastomotic suture dehiscence
  - o Reduce morbidity and mortality related to reintubation, and shorten length of stay
  - o Avoid the need for invasive mechanical ventilation and all associated complications:
    - ▪ Nosocomial infections, including ventilator-associated pneumonia (VAP) due to micro-aspirations linked to the endotracheal tube
    - ▪ Delayed rehabilitation
    - ▪ Communication difficulties
    - ▪ Discomfort

E) CONSIDERATIONS STATISTIQUES

Statistical analyses will be performed using R software and IBM SPSS.
A total of 266 patients are planned for inclusion, divided into two balanced groups.

DESCRIPTION OF PLANNED STATISTICAL METHODS:

Research Protocol

Patients will be analyzed on an intention-to-treat basis and then per-protocol.

Intention-to-treat analysis: all patients included in the study for whom outcome data are available will be considered in the analysis according to their randomization group. No imputation method will be used in case of missing data.
If organizational constraints prevent the patient from receiving prophylactic NIV (despite inclusion in the corresponding intervention arm), the patient will remain in their randomization arm for the entire study duration, and their data will be analyzed on an intention-to-treat basis.

Per-protocol analysis excludes patients for whom the initial protocol was not fully adhered to. Only patients who followed the protocol will be considered in the analyses, within the arm to which they were originally randomized.

The analysis will focus on the primary endpoint to determine whether randomization to the "PPC prevention strategy" arm leads to a reduction in PPC frequency compared to the control group. Effect size and number needed to treat will be calculated.
Similarly, for secondary endpoints, significant differences between the two groups will be sought in terms of:
a) Safety and tolerability of the strategy under study (see safety assessment parameters)
b) Mortality during hospitalization
c) Patient reintubation
d) Length of stay and duration of invasive or non-invasive mechanical ventilation

Description of the overall analysis method

The significance threshold is set at 0.05, and all tests will be two-sided. For qualitative variables, results will be reported as counts and percentages. For quantitative variables, results will be reported as means and standard deviations in case of normal distribution, and as medians with 25th and 75th percentiles in the absence of a Gaussian distribution. Normality of continuous variables will be assessed using the Kolmogorov-Smirnov test.
A simple descriptive analysis will be performed on the entire study population and by subgroups. This description will include sociodemographic data, medical history, ongoing treatments, etc.
A qualitative and quantitative analysis of missing data will be performed. No imputation of missing data is planned for the endpoints.

Study of Associations (Qualitative and/or Quantitative Variables):
For each parameter of interest, a bivariate analysis will be performed, possibly complemented by a multivariate analysis adapted to the outcome variable to explore potential associations.
For bivariate analyses, the use of parametric or non-parametric tests will depend on sample size and/or variable distribution. The significance threshold is set at 0.05, and all tests will be two-sided.
The statistical test used will be Pearson's Chi-square test (or Fisher's exact test) for qualitative variables. For quantitative variables, the statistical tests used will be ANOVA or the non-parametric Kruskal-Wallis test.
The association between each presumed risk factor and the parameter of interest will be estimated using the relative risk (RR) and its 95% confidence interval.
A multivariate logistic regression analysis will estimate the adjusted RR and its 95% confidence interval for each retained factor (conservative threshold of 0.20 in univariate analysis).

Early Mortality:
Overall survival is defined as the time between the date of operating room discharge and the date of death if the patient dies within 7 days, or the end of study follow-up at Day 7. The Kaplan-Meier method will be used to estimate survival rates and plot survival curves. The Log-Rank test will be used to compare survival curves. Event-free survival is defined as the time between operating room discharge and the date of occurrence of the event (PPC) or the date of last follow-up if censored.
A semi-parametric Cox proportional hazards regression model will estimate for each variable the crude association (Hazard Ratio, HR) between the factor studied and death (bivariate analysis), then the adjusted HR in multivariate analysis.
The significance threshold for including other variables in the multivariate analysis will be 0.20. If several candidate variables are redundant, the most representative variable will be retained for the model.

Subgroup Analyses (Exploratory):
Subgroup analyses will address the occurrence of endpoints:

- According to patient characteristics at inclusion (medical history, ARISCAT score components, type of surgery, and planned anesthetic technique).
- The subgroup of patients receiving NIV as curative (under conditions noted at session start) will be compared to the group receiving NIV only prophylactically in terms of outcome at Day 7.
- Identification of factors associated with failure of prophylactic NIV in the subgroup where NIV was prematurely discontinued.

Statistical Justification for Sample Size:
Previously described data indicate that the expected effect size is approximately a 50% reduction in events:

- In studies on medical populations, the effect of prophylactic NIV was observed even on harder endpoints than ours: -66% reduction in reintubation, -51% reduction in ARF incidence, and -50% reduction in reintubations, and again -69% reduction in ARF incidence.

- In surgical populations, prophylactic NIV has led to a reduction in restrictive syndrome of about 50%, an improvement in pulmonary function tests (PFTs) of +30%, and a decrease in length of stay by 7 days.
- In curative use after abdominal surgery—a more unfavorable situation since ARF is more advanced—Squadrone reported favorable outcomes in 90% of cases with CPAP, and reintubations were reduced by 30%.

Given that the expected incidence of ARF in the high-risk group is 30–50%, a sample size of at least 121 subjects per arm is required to demonstrate, under a two-sided hypothesis, a relative reduction of 50% in ARF between a group managed with prophylactic NIV (15%) and a group managed with standard care (30%), with an alpha risk of 5% and a beta power of 90%. We anticipate 10% of patients will be non-evaluable.
The required sample size is therefore 242 + 24 = 266 high-risk subjects evaluated for PPC.

STATISTICAL STOPPING RULES:
No interim analysis is planned in the protocol. However, if during the review of safety and efficacy data provided to the independent monitoring committee (raw, descriptive, and summarized data without pre-established statistics by the investigator or sponsor), a highly significant difference is identified for the primary endpoint or one of the safety parameters when comparing the two groups blinded to treatment allocation, the committee may decide to stop the study.

METHOD FOR HANDLING MISSING, UNUSED, OR INVALID DATA:
Patients included in the study for whom an endpoint is not available will not be considered in the analysis for that missing endpoint. No imputation method will be used for missing data.

MANAGEMENT OF CHANGES TO THE INITIAL ANALYSIS PLAN:
Modifications to the initial analysis plan may be proposed by the monitoring committee (interim analysis, statistical tests, adverse events, secondary objectives) if new literature data justify them.
Protocol deviations will be identified and measured. Dual analysis—intention-to-treat and per-protocol—will assess the impact of protocol deviations on study results.

SELECTION OF PATIENTS FOR ANALYSIS:
All patients included in the study, meeting all inclusion criteria and presenting no exclusion criteria, will be included in the analyses of available endpoints according to their case report forms.

See Criteria for Premature Discontinuation of a Participant's Involvement in the Study:

- **Withdrawal of consent:** Data collected will not be included in the intention-to-treat analysis.
- **Discontinuation by the investigator:** Data already collected will be used in the analyses unless the subject withdraws consent.
- **Lost to follow-up:** Data collected for subjects lost to follow-up will be used in the analyses unless the subject withdraws consent.
- **Organizational impossibility to receive prophylactic NIV (inclusion in the corresponding intervention arm):** The patient will be included in the intention-to-treat analysis and followed under the same conditions as in the control arm.

RANDOMIZATION

High-risk patients with an ARISCAT score ≥ 45 will be randomized upon inclusion in the study during the preoperative period (consultation or pre-anesthesia visit, and no later than the day of surgery before anesthesia begins).

Treatment allocation will be performed through centralized computerized electronic randomization by minimization into two groups (1:1), with stratification by center, sex, age, preoperative SpO_2, presence of respiratory infection within the previous month, anemia, surgical incision (upper abdominal or intrathoracic), expected surgery duration (≤2h, 2–3h, >3h), and procedure urgency.

F) Planned Duration of the Trial	
Inclusion period:	30 months
Treatment period:	48 hours
Follow-up period:	7 days
Total duration of the trial (including follow-up):	30.5 months