

# Statistical Analysis Plan

## (NIVAS Study)

### **Population**

We will perform all the analyses of the trial on the intention-to-treat population. The intention-to-treat population is defined by all randomised patients except patients who would be randomized despite being not eligible for randomisation according to inclusion/exclusion criteria. A modified intention-to-treat analysis will be done on the primary outcome including patients who will not return to operating room for reintervention (i.e, patients in whom trachea will be intubated for return to operating room will not be included in this modified intention-to-treat analysis). Patients who will return to operating room for another surgical procedure and will systematically re-intubated will be considered as a treatment failure (reach primary outcome in intention-to-treat analysis).

### **Sample size**

We estimate that with a sample of 150 patients per group who could be evaluated for the primary efficacy outcome, the study will have at least 90% power to determine both the superiority for the intention-to-treat analysis and for the modified intention-to-treat analysis (excluding the patients that will return to the operating room for reintervention) of non invasive ventilation (NIV-group) as compared with standard-oxygen therapy (oxygen-group). For the intention-to-treat analysis, the following assumptions are made: a 65% event rate in the oxygen-group and a 40% event rate in the NIV-group (absolute risk reduction with NIV of at least 25%). Further assumptions (15% of the included patients) are made relating to patients randomized despite being not eligible for randomisation according to inclusion/exclusion criteria and loss to follow-up for the primary endpoint. For the modified intention-to-treat analysis, the same assumptions are made, with an estimated rate of patients who will return to operating room for reintervention after intubation to be as high as 33% .

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31 **Interim analyses**

32 Two interim analysis will be planned for early stopping of the study owing to safety (mortality  
33 within 90 days) after the first 100 and 200 patients included with the use of a prespecified  
34 Haybittle–Peto efficacy boundary ( $\alpha = 0.001$  for the two interim analysis). These interim  
35 analysis will be performed by an independent data monitoring and safety committee. If an  
36 analysis of the interim data from 100 or 200 patients fulfils the Haybittle-Peto criterion the  
37 inclusion of further patients will be paused and an analysis including patients randomized  
38 during the analysis period will be performed. If this second analysis also fulfils the Haybittle-  
39 Peto criterion the independent data monitoring and safety committee will recommend  
40 stopping the trial. The independent safety monitoring committee included the following  
41 physicians: Pr Karim Asehnoune, Pr Xavier Capdevila and Pr Pierre Michelet.

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43 **Analyses**

44 **Primary analysis:**

45 Unadjusted Chi-square test (or Fisher’s exact test as appropriate) for binary outcome  
46 measures. Unpaired t-test (or Wilcoxon signed-rank testing as appropriate) for continuous  
47 outcome measures. Relative risks will be presented for binary variables and mean  
48 differences for continuous variables with 95% confidence interval.

49 **Secondary analysis:**

50 Multiple (logistic) regression for the primary outcome with the following covariates (variables  
51 will be selected if P value is less than 0.15 in the univariate analysis and a stepwise  
52 procedure will be used to select the final model. Interactions between variables will be  
53 tested):

54 • Patient-specific risk factors

55 - Age

56 - Age  $\geq$  60 years old

- 57 - Male gender
- 58 - Body mass index
- 59 - Body mass index  $\geq 30 \text{ kg/m}^2$
- 60 - Simplified Acute Physiology Score II at entry into the study
- 61 - Simplified Acute Physiology Score II at entry into the study  $> 40$
- 62 - Sequential Organ Failure Assessment score at entry into the study
- 63 - Preexisting conditions : current smoker, alcohol intake, psychotropic use, chronic arterial
- 64 hypertension, ischemic heart disease, chronic heart failure, chronic obstructive
- 65 pulmonary disease, liver cirrhosis, cancer, sepsis
- 66 - Clinical variables : body temperature, heart rate, systolic blood pressure, diastolic blood
- 67 pressure
- 68 - Biochemical variables : hemoglobin, hematocrit, white cell count, white cell count  $>$
- 69  $20000 \text{ n}/\mu\text{liter}$
- 70 • Surgery characteristics-specific risk factors
- 71 - Recent surgical history : elective, emergency
- 72 - Upper abdominal surgery
- 73 - Type of surgery : oesophagectomy, gastrectomy, colorectal resection, liver resection,
- 74 pancreatico-duodenectomy, other procedures
- 75 - Oesophagectomy vs all other types of surgery
- 76 - Laparotomy surgery : vertical midline incision, transverse incision, other
- 77 - Laparoscopic surgery
- 78 - Thoracotomy associated surgery
- 79 - Epidural analgesia
- 80 - Time of surgical procedure
- 81 • Acute respiratory failure-specific risk factors
- 82 - Respiratory rate
- 83 - Time from end of surgery to acute respiratory failure
- 84 - Time from extubation to acute respiratory failure

- 85 - Time from acute respiratory failure to inclusion in the study
- 86 - Causes of acute respiratory failure (atelectasis, copious tracheal secretions, pneumonia,
- 87 pulmonary edema, pleural effusion, pulmonary embolism, others)
- 88 - Arterial blood gases : pH, PaO<sub>2</sub>/FiO<sub>2</sub>, PaCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>

89 We will compare the primary outcome in prespecified subgroups defined by stratification  
90 criteria according to age (less or more 60 years), site of surgery (upper or lower abdominal)  
91 and use or not use of epidural analgesia.

92 The Kaplan-Meier curves for 30-days re-intubation and for 90-days mortality will be plotted  
93 and compared by the log-rank test.

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## 95 **Outcomes**

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### 97 **Primary outcome measure:**

- 98 - Re-intubation within 7 days following randomization.

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### 100 **Secondary outcome measures:**

- 101 - Reintubation within 14 days
- 102 - Reintubation within 30 days
- 103 - ICU-acquired infection within 7, 14 and 30 days
- 104 - Mortality within 30 days and 90-days
- 105 - Duration of Invasive Ventilation within 14 days, 30 days,90 days
- 106 - Invasive ventilatory free days within 14 days, 30 days, 90 days
- 107 - Intensive care unit (ICU) and in hospital lengths of stay within 90 days
- 108 - ICU free days within 14 days, 30 days, 90 days

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110 Tolerance of NIV will also be analyzed separately:

- 111 - leaks around the mask
- 112 - dry mouth and/or nasal congestion

- 113 - copious bronchial secretions
- 114 - ocular irritation
- 115 - skin ulcerations
- 116 - gastric distension
- 117 - anxiety
- 118 - bronchial secretions (no/moderate/excessive)

119 NIV settings and monitored parameters will be presented for reintubated and for non  
120 reintubated patients in the noninvasive ventilation group.

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#### 122 **Missing data**

123 Due to the low rate of predicted missing values, we will not use any imputation method.  
124 Analyses will be performed on the complete cases. We expect to have full data sets on all  
125 patients. If not, we will indicate in each table the number of observed data. In case of  
126 unexpected high rate of missing values (>15%), we will use for the secondary outcomes a  
127 multiple imputation method.

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#### 129 **Software**

130 All data analysis will be conducted with SAS statistical software, version 9.3.