Statistical Analysis Plan (SAP)

HElmet NonInvasive Ventilation versus high-flow Oxygen Therapy in acute hypoxemic respiratory failure

Administrative Information

Title, registration, versions, and revisions

Acronym:	HENIVOT
Protocol Identification number:	3503 Fondazione Policlinico A. Gemelli IRCCS
Clinical Trial.gov identifier:	NCT04502576
Clinical Trial protocol version:	5.3
Document type:	SAP Documentation
SAP data and version:	23 September 2020 / Version 1.0
SAP revision history:	None

Signatures

We the undersigned, certify that we read this SAP and approve it is adequate in scope of the analyses.

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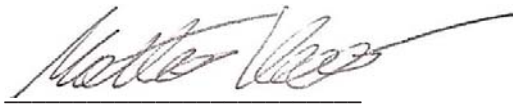

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1. Introduction

1.1. Purpose of the Statistical Analysis Plan

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for Clinical Trial Protocol (CTP). Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP may be included in any regulatory submissions and/or manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

1.2. Background

Non-invasive positive pressure ventilation (NIV) has been convincingly shown to be safe and effective as first line treatment in patients with acute hypercapnic respiratory failure and acute cardiogenic pulmonary oedema. Despite some data suggest NIV may also avoid intubation in heterogeneous categories of patients with acute hypoxemic respiratory failure (AHRF), its safety and efficacy in such a context is still debated, given the high failure rate and the possible detrimental effect on the clinical outcome.

Nasal high flow oxygen (NHF) is a new and promising tool for oxygen therapy in critically ill patients: NHF allows accurate delivery of the set FiO2, anatomical dead space clearance due to a washout effect in the upper airways and provides a small, variable amount of positive end end-expiratory pressure. Different studies have investigated its safety and efficacy in several clinical settings and a multicentre randomized controlled trial showed that NHF, as compared to NIV sessions delivered via a face mask, may reduce the intubation rate, and improve clinical outcome in severely hypoxemic patients with de novo AHRF [1]. As patients' comfort is crucial for NIV success, over the last years a great effort has been made to optimize NIV tolerability. Different interfaces are available for non-invasive ventilation: despite face masks being more commonly used, helmet has been shown to improve patients' comfort, allowing patients' interaction, speech, feeding and not limiting cough. Nonetheless, skin necrosis, gastric distension, or eye irritation are seldom observed during helmet NIV, while may be consequences of long-term treatments with face masks.

Moreover, differently from face masks, helmets permit longer-term treatments and allow the setting of higher levels of PEEP without causing air leaks. Interestingly, higher PEEP during fully controlled mechanical ventilation in the early phase of the disease improves mortality in ARDS patients and raising evidence indicates that it may exert beneficial effects also if spontaneous breathing is maintained. In this sense, a recent randomized controlled trial comparing continuous NIV delivered with helmet or face-mask in patients with ARDS showed a lower intubation rate and a lower 90-day mortality in patients in the helmet group who, accordingly, underwent treatments with higher PEEP and lower FiO2[2].

We previously showed that helmet NIV may provide physiological benefits over NHF [3], but whether first-line treatment with helmet NIV as compared to NHF may improve clinical outcome in acute hypoxemic respiratory failure remains uncertain.

1.3. Objectives

1.3.1. Primary objective

The primary outcome will be the number of ventilatory support-free days at day 28 from enrolment. Ventilatory support will include invasive positive pressure ventilation (through endotracheal tube or tracheostomy), non-invasive ventilation and NHF.

1.3.2. Secondary objectives

1. The proportion of patients who require endotracheal intubation within 28 days from study enrolment
2. 28-day and 60-day invasive-ventilation free days
3. 28-day, 60-day mortality, 90-day mortality
4. 'In-ICU' and 'In-hospital' mortality
5. Days of ICU stay after randomization
6. Days of hospital stay after randomization
7. 6- and 12-month quality of life

The main safety endpoints will be:

1. In patients meeting the primary endpoint, time (hours) from randomization to intubation.
2. Among patients meeting the primary endpoint, proportion of patients requiring 'emergency intubation', defined according to the judgement of the attending physician.
3. Among patients meeting the primary endpoint, the cause of non-invasive treatment failure (as defined by the intubation criteria).

1.3.3. Explorative objectives

• PaO2/FiO2 ratio at 1-6-12-24-48-72 hours after randomization
• PaCO2 1-6-12-24-48-72 hours after randomization
• Respiratory rate 1-6-12-24-48-72 hours after randomization
• Discomfort related to the device 1-6-12-24-48-72 hours after randomization
• Dyspnoea 1-6-12-24-48-72 hours after randomization at the different timepoints.
• Daily measured SOFA
• Rate of hospital acquired pneumonia, ICU acquire infections, need for extracorporeal membrane oxygenation, pneumothorax, barotrauma, subcutaneous emphysema, tracheostomy, acute kidney injury requiring renal replacement therapy, septic shock, liver failure, upper limber thrombosis.
• Catecholamine-free days/days of ICU stay

2. Study Design

2.1. General study design and plan

The HENIVOT pilot study is designed as an open-label, multicentre randomized trial to assess first-line treatment with helmet NIV as compared to NHF may increase the amount of 28-day ventilatory support-free days of patients admitted to the intensive care unit due to acute hypoxemic respiratory failure.

Assessment of the oxygenation criteria:

Nonhypercapnic patients with a PaO2/FiO2≤200 mmHg will be enrolled. In the absence of exclusion criteria, and if all others inclusion criteria are met, patients showing PaO2/FiO2≤300 and >200 mmHg will be treated according to the clinical practice of each institution and eventually reassessed for the presence of oxygenation criterion up to 72 hours from ICU admission.

Randomization:

Enrolled patients will be randomized in a 1:1 ratio to receive helmet PSV or NHF as first-line treatment for AHRF. A computer-generated permuted block randomization scheme with varying block sizes ranging from 3 to 9 managed by a centralized web-based system will be used to allocate patients to each group. Randomization will be stratified according to the presence of SARS-CoV-2 infection (diagnosed with a positive polymerase chain reaction (PCR) testing of the nasopharyngeal or tracheal sample) Patients will have to undergo the allocated treatment within 1 hour from the moment of enrolment criteria validation.

2.2. Sample size, power, and detectable difference

Systematic data about the total duration of respiratory support in patients affected by hypoxemic respiratory failure with PaO_2/FiO_2 lower than 200 mmHg and treated solely with high-flow nasal oxygen are lacking. Data from a single-center exploratory report indicate that the mean 28-day respiratory support-free days of patients receiving first line treatment with high-flow nasal oxygen is 11.6 days. We hypothesized that this parameter would be 25% higher in patients receiving helmet non-invasive ventilation (14.6 days).

Assuming a normal distribution of the primary endpoint, we calculated that the enrolment of 50 patients per group would provide 80% power to detect a 25%-increase in the number of ventilatory-support free days on a 28-day basis in the helmet group, with an alpha level of 0.05. The attrition rate was expected to be smaller than 10% and likely due to protocol violations, absence of objective criteria to define the need for endotracheal intubation, cross-over and drop-outs. We planned to enrol a total of 110 patients.

2.3. Analysis Populations

The patients included/excluded in each analysis will be agreed as follows:

2.3.1. Intention-To-Treat [ITT] Population

The intention to treat (ITT) population will contain all patients enrolled in the study. The ITT will be used for primary, secondary and explorative outcomes analysis.

2.3.2. Per-Protocol [PP] Population

The per protocol (PP) population will contain all ITT patients who do not have any major protocol deviation. The PP will be used of primary and secondary outcome analysis.

Major protocol deviation will include the following:

- Cross-over between study protocols;
- Assigned treatment not provided due to any reason;

3. Statistical analysis

The R software version 4.0.2 will be used to perform all data analyses and to generate tables and figures. All data collected will be tabulated descriptively by study group and analysed on an intention-to-treat basis. In addition, a per protocol analysis will be conducted on the patients who successfully underwent the allocated treatments for the time defined by the study protocol.

3.1. General analysis conventions

Quantitative data will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum). Results will be expressed as mean ± SD or median [interquartile rage]. Qualitative data will be summarized by absolute and relative frequency distribution and expressed as number of events [%]. Kolmogorov-Smirnov and Shapiro-Wilk normality tests will be used to test if data are well modelled by a normal distribution.

3.2. Comparisons between groups

3.2.1. Qualitative variables

Comparisons between groups regarding qualitative variables will be performed with the Chi-Squared test or the Fisher's exact test, as appropriate in agreement with tests assumptions.

3.2.2. Time to event data

Analysis of intubation and mortality rate will be performed using time-to-event data. Categorical variables will be analysed using the log-rank test and continuous variables will be assessed using a univariable Cox proportional hazard regression analysis. Analysis of mortality and intubation proportion for significant results will be presented by Kaplan-Meier survival curves when independent variables are dichotomous or categorical.

3.2.3. Quantitative variables

Quantitative normal variables will be compared with the ANOVA and T-student tests. Inter-group differences in quantitative variables distribution at different timepoints will be assessed with ANOVA for repeated measures. Prespecified subgroup analyses according to the following characteristics will be performed:

- Patients with AHRF due to COVID-19
- Patients with bilateral pulmonary infiltrates at study inclusion
- History or no history of cardiac failure
- Patients older than 65 years.
- Patients with PaCO2≥40 at study inclusion
- Respiratory rate≥35 at study inclusion (measure at the moment of the oxygenation criteria validation while receiving 50 L/min of 50% oxygen via a face mask).
- P/F≤120 at study inclusion.
- Immunocompromised patients. All analyses will be performed applying a bilateral hypothesis.

3.2.4. Ordinal qualitative and non-normal quantitative variables

Ordinal qualitative variables or non-normal quantitative variables will be compared Mann-Whitney and Kruskal-Wallis tests.

4. References

1. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, et al.: **High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure.** *N Engl J Med* 2015, **372**:2185–96.

2. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP: **Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial.** *JAMA* 2016, **315**:2435–41.

3. Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, Bocci MG,Mercurio G, Dell'Anna AM, Eleuteri D, et al.: **Physiological Comparison of High-Flow Nasal Cannula and Helmet Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure**. *Am J Respir Crit Care Med* 2020, **201**:303–312.