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Study protocol

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

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ABSTRACT

Introduction:

Patients with obesity are considered to be at high risk of acute respiratory failure (ARF) after extubation in intensive care unit (ICU). Compared to oxygen therapy, noninvasive ventilation (NIV) may prevent ARF in high risk patients. However, these strategies have never been compared following extubation of critically ill patients with obesity. Our hypothesis is that NIV is associated with less treatment failure compared to oxygen in patients with obesity after extubation in ICU.

Methods and analysis:

The non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units protocol (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients with obesity defined as a body mass index≥30 kg/m² will be randomly assigned in the "experimental-group" to receive prophylactic NIV applied immediately after extubation combined with high-flow nasal oxygen (HFNO) or standard oxygen between NIV sessions versus in the "control-group" to receive oxygen therapy alone (HFNO or standard oxygen,). The primary outcome is treatment failure within the 72 hours, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention). The single, prespecified, secondary outcome is the incidence of ARF until Day-7. Other outcomes analysed will include tracheal intubation rate at day-7 and day-28, length of ICU and hospital stay, ICU mortality, day-28 and day-90 mortality.

Ethics and dissemination:

The study project has been approved by the appropriate ethics committee "Comité-de-Protection-des-Personnes Ile de FranceV-19.04.05.70025 Cat2 2019-A00956-51". Informed consent is required. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. If use of NIV shows positive effects, teams (medical and surgical) will use NIV following extubation of critically ill patients with obesity.

Trial registration: ClinicalTrials.gov Identifier: NCT 04014920

Strengths and limitations of the study:

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between NIV and oxygen to prevent ARF of critically ill patients with obesity.

- The broad inclusion criteria and the high number of participating ICUs will increase generalisability and the large sample size will provide the opportunity to examine strata and subgroups of interest.
- The double randomization will allow to balance groups limiting the confounding factors and to compare both NIV with oxygen, and HFNO with standard oxygen, and stratification will allow strata analyses.
- The nature of the study intervention does not allow blinding. However, to limit the risk of bias, the methodologist will be blinded to the group.

Keywords: Obesity, noninvasive ventilation, preventive, acute respiratory failure, intensive care unit, high-flow nasal oxygen, NIV, HFNO

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Mechanical ventilation is the artificial support most used in intensive care unit (ICU).[2] If weaning and extubation (removal of the tracheal intubation tube) is successful in approximately 80 to 90% of ICU patients, 10 to 20% will develop acute respiratory failure (ARF) in the days following extubation.[3 4] This incidence is higher in some selected subgroups of patients with underlying lung disease (patients with obesity, chronic obstructive pulmonary disease (COPD), elderly, heart failure, postoperative cardio-thoracic and / or abdominal surgery ...).[5-7]

The management of post-extubation ARF combines etiological treatment associated with ventilatory support which usually requires the use of new endotracheal intubation to deliver "invasive" mechanical ventilation, associated with excess morbidity and mortality.[8 9]

Obesity is associated with excess morbidity and longer length of mechanical ventilation compared to the general population.[7 10] Effect of obesity on mortality is controversial,[11] some studies suggesting a protective or neutral effect of obesity,[12] named “obesity paradox”.[13] At the ventilatory level, several combined pathophysiological changes contribute to an increased incidence of respiratory complications.[7 11]

For over twenty years, non-Invasive Ventilation (NIV) has been used to prevent (“preventive NIV”) and cure (“curative NIV”) ARF in ICU patients.[14 15] An alternative to NIV is the administration of oxygen via standard oxygen or high-flow nasal oxygen (HFNO).[16 17] In an observational study of 124 patients, El Sohl et al.[18] showed a 16% absolute risk reduction of ARF using NIV compared to standard oxygen following extubation.

More recently, HFNO has been developed. High flow rates reduce the dilution of inhaled oxygen and allow precise distribution of FiO2 throughout the inspiratory phase by adapting the peak flow rate to the patient.[17 19] High oxygen flow can also have a washing effect on the dead

space of the nasopharynx. In addition, a flow-dependent effect helps to generate a continuous positive end-expiratory pressure (PEEP).[20] Finally, the use of a high level of humidity could prevent alterations of the ciliated epithelium of the respiratory tract, maintain the activity of the muco-ciliary system, and facilitate the elimination of secretions.[21] In a post-hoc analysis of a large trial of 830 postoperative thoracic patients [22], it was shown that among the 272 patients with obesity (mean BMI of 34 kg/m²), NIV was not superior to HFNO, with treatment failure occurring in 15% and 13% in NIV and HFNO groups respectively. Moreover, in 155 post cardiac surgery patients with obesity, Corley et al.[23] compared HFNO with standard oxygen to prevent ARF, without showing any difference.

However, none of these studies compared simultaneously the most recent devices available: NIV, HFNO and standard oxygen, nor their association.[24] HFNO is now often used,[25] and the PEEP issued by HFNO is much lower than that issued by NIV. The benefit of NIV compared to oxygen therapy (HFNO or standard oxygen) after extubation of critically ill patients with obesity has never been studied.

In this multicentre, randomised, controlled, interventional study in mechanically ventilated critically ill patients with obesity, we will test the hypothesis that NIV (associated with HFNO or standard oxygen between NIV trials) could reduce the rate of treatment failure in comparison with oxygen therapy alone continuously administered (HFNO or standard oxygen) in patients with obesity within 72 hours after extubation in an ICU.

Objectives

Primary objective. To determine whether NIV could reduce the rate of treatment failure in comparison with oxygen within the 72 hours after extubation of critically patients with obesity, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

Secondary objectives. To determine whether NIV could reduce the rate of ARF at Day-7 and other secondary outcomes in comparison with oxygen.

Stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre, and patients characteristics will be done.

The main hypothesis is that NIV (associated with HFNO or standard oxygen) could reduce the rate of treatment failure in comparison with oxygen therapy alone (HFNO or standard oxygen) in patients with obesity within the 72 hours after extubation in ICU.

Trial design

The non-invasive ventilation vs oxygen after extubation in patients with obesity in intensive care units (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomization.

Patients will be randomly assigned (first randomisation) to receive NIV (experimental group) or oxygen (control group). A second randomisation will determine the type of oxygen received in each group: HFNO or standard oxygen. NIV will not be used in the control group. HFNO will not be used in patients of both experimental and control group who will receive standard oxygen after second randomization (Figure 1).

The expected duration of the subject participation is 3 months after inclusion in the study.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the EXTUB-obese trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This study will take place in 35 ICUs in France, belonging to a research network that specializes in the management of critically ill patients and has a particularly high level of expertise in respiratory care strategies.[26]

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU, adult (age ≥ 18 years), covered by public health insurance, with written informed consent from the patient or proxy (if present) before inclusion or once possible if the patient has been included in an emergency context, with obesity defined by a body mass index ≥ 30 kg/m² the day of extubation and require extubation in intensive care unit after a length of mechanical ventilation of more than 6 hours.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: hypercapnia with a formal indication for NIV (PaCO2 ≥ 50 mmHg), isolated cardiogenic pulmonary oedema (formal indication for NIV, patients with pulmonary oedema associated with another ARF aetiology can be included), tracheotomy, home ventilator, end-of-life decision with decision of "do not reintubate", anatomical factors precluding the use of NIV and/or HFNO, previous extubation during the same ICU stay with previous inclusion in the study, duration of mechanical ventilation less than 6 hours, age <18 years, pregnant or breastfeeding woman, protected person, refusal of study participation or to pursue the study by the patient, absence of coverage by the French statutory healthcare insurance system.

Outcomes

Primary outcome

Primary outcome variable is treatment failure within the 72 hours after extubation, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

Main secondary outcome

The single, pre-specified, secondary outcome is incidence of ARF until Day-7.

ARF during the first 7 days will be defined by two criteria among the following:[27]

1) Hypercapnia ($PaCO_2$ > 45 mmHg) with respiratory acidosis (arterial pH ≤ 7.35)

2) Modification of mental state and /or of conscience level (agitation or encephalopathy)

3) Decrease of SpO_2 < 90% or PaO_2 < 55 mmHg despite a FiO_2 > 50% and a flow > 10L/min

4) Hemodynamic instability, with a systolic arterial pressure <70 mmHg during more than 30 minutes despite sufficient fluid loading, and/or the use of vasopressors.

5) Abundant secretions and ineffective cough

6) Respiratory rate > 35/min, with signs of respiratory distress.

These criteria will be collected each day until Day-7.

Exploratory outcomes

Other outcomes will be evaluated as exploratory clinical outcomes:

- Oxygenation evaluated by the PaO2/FiO2 ratio until Day-7
- Organ failure until Day-7 assessed with the SOFA score
- Tracheal intubation rate at Day-7, Day-14 or Day-28
- Length of stay in ICU and in hospital
- ICU, Day-28 and Day-90 mortality rates

A separate analysis of each component of the primary secondary outcome will also be performed.

Interventions

When an extubation is planned by the physician in charge of a patient with obesity, the patient will receive two consecutive randomizations. A first randomisation will be performed to allocate the patient in the experimental group to receive intermittent NIV trials or in the control group to receive continuous oxygen therapy. A second consecutive randomisation will determine the type of oxygen received in each group. For the experimental group, the second randomisation will determine the type of oxygen received between NIV trials (HFNO

or standard oxygen). For the control group, the second randomisation will determine the type of oxygen continuously administered (HFNO or standard oxygen). NIV will not be used in the control group. HFNO will not be used in patients of both experimental and control group who will receive standard oxygen after the second randomization (Figure 1).

In the NIV group, the first NIV session will be offered to the patient within 30 minutes following extubation. The NIV system will first be explained to the patient by the physician or nurse and positioned at bedside. The mask will be chosen according to patient's facial morphology. The mask will be placed and adjusted to avoid leaks. Recommended positive end expiratory pressure (PEEP) value will be set to 10 cmH_2O (and adapted between 5 and 10 cmH_2O depending on tolerance) and value of pressure support (PS) will be set to obtain a respiratory rate between 20 and 30 breaths per minute (bpm) and an expired tidal volume in-between 6 and 8 ml/kg of ideal body weight.

In the experimental group, the recommended length of the intermittent NIV sessions will be standardized as follows: sessions of 30 to 60 minutes spread through the day and night for a cumulated time of at least 4 hours with no upper limit during the first 24 hours. NIV weaning will start 24h after extubation, if respiratory rate is stable and less than 25/minute with a PaO_2/FiO_2 ratio of more than 200 mmHg and a $PaCO_2$ less than 45 mmHg on the blood gases at H24. Between NIV sessions, patients will receive oxygen therapy with the same methods as the control group, with HFNO or standard oxygen.

In both groups, the second randomized device (oxygen device) will be HFNO or standard oxygen.

HFNO will be used at a flow of 50L/min during the first 24 hours (possibly lowered down to 30L/min if needed by the patient), the FiO_2 being set to obtain a $SpO_2 \geq 94\%$. The standard oxygen will be used in case of $SpO_2 < 94\%$ without oxygen.

After 24 hours, the device will be pursued if the patient still needs oxygen, until the discharge from ICU or the absence of need of oxygen. The patient will be followed during his ICU stay and hospital stay until discharge or death. The follow-up will be stopped at 3 months.

Participant timeline

Participant timeline is presented in Table 1 and Figure 2.

Sample size

Two intermediate analyses will be performed after inclusion of 250 and 500 patients (stop for efficacy or safety). Assuming the overall p-value for the trial is 0.05, the p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary). Based on a 12% composite endpoint rate in the oxygen group (Free rea study[4]) and a decrease of 50% of the composite endpoint rate to 6% in the NIV group,[18] with an alpha risk set at 5%, to obtain a 80% power for demonstrating superiority for the primary outcome, we need 954 patients (477 in each group) to demonstrate a superiority of NIV to oxygen therapy. In order to take into account loss of follow-up and intubation for surgical procedures without criteria of ARF, we will include 1000 patients.

Recruitment

Patients are expected to be included during a two years' inclusion period starting October 2019. Among the 35 participating centres, each centre would need to include 1 to 2 patients per month during the 24 months-study period.

March 2019-September 2019: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

October 2019 to September 2021: Inclusion of patients.

October 2021 to December 2021: Cleaning and closure of the database.

January 2022-September 2022: Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clincalt, randomization module). The randomization will

be centralized and available online. It will be stratified on centre,[28 29] length of mechanical ventilation (<48 hours vs ≥ 48 hours) and on type of admission (medical vs surgical), balanced with a 1:1 ratio and minimization.

Blinding

Given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Patients will receive standard ICU monitoring consisting of electrocardiogram analysis, peripheral oxygen saturation, and a noninvasive blood pressure cuff.

The day of extubation (from H0 to H24), the following data will be collected: Socio-demographic data, SAPS II score, length of stay in ICU before inclusion, length of mechanical ventilation before inclusion, reason for intubation, comorbidities, hemodynamic parameters (arterial pressure, heart rate, vasopressors use), ventilatory parameters (respiratory rate and SpO_2), spontaneous breathing trial characteristics (if performed), oxygenation and if performed NIV characteristics and the SOFA score.

From Day-1 to Day-7 the investigator or designated study personnel will record the criteria for the main outcome (reintubation, oxygenation method (continued, stopped, changed)) and for the secondary outcomes (ARF, oxygenation, reintubation, mortality). They will also assess reason for intubation, hemodynamic variables (arterial pressure, heart rate, vasopressors use), ventilatory variables (respiratory rate and SpO_2), oxygenation and if performed NIV characteristics.

Length of stay in ICU will be evaluated. At ICU discharge, day 28 and Day 90, mortality rate will be evaluated.

Statistical methods

The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or worsened just before extubation and were not extubated. Then, a per-protocol analysis will be performed, excluding the reintubation for surgical procedures without criteria of ARF.

All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.4; SAS Institute; Cary, NC, USA, and R, version 3.6.2). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis

Uncorrected chi square test will be used for primary outcome analysis (comparison of the composite criteria at H72 combining reintubation for invasive mechanical ventilation, the switch to the other study treatment or the premature study treatment discontinuation).

A logistic regression will be used for the analysis of the main criteria with odds ratio of failure calculation, before and after adjustment on confounding variables despite the randomization.

A supplementary analysis on the main criteria will be done for the time without treatment failure, per study group, using the log rank test. A Cox model will be performed for the time without treatment failure, before and after adjustment. Covariates will be defined as binary

variables and continuous variables dichotomised according to their median tested in the model, and will be selected in a backward selection procedure if p<0.15 in the univariate analysis and then presented as adjusted odds ratios (ORs) or adjusted Hazard Ratios (HRs) with 95% CIs. A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables will be tested.

Then, stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), center) and patients characteristics will be done.

A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables and time will be tested.

Secondary Analyses

Continuous outcomes will be compared with the Student t test or Mann-Whitney rank-sum test according to the conditions of application and categorical variables with the chi-square test or the Fisher exact test, according to the conditions of application. Then, stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre), type of oxygenation (second randomisation) and patients characteristics will be done.

Interim analysis

This trial will be planned with two interim analyses after the observation of the primary outcome of 250 and 500 patients. The interim analysis will be planned for early stopping of the study owning to safety (as defined by mortality within 7 days) or efficiency on the primary outcome after the first 250 and 500 patients included assuming the overall p-value for the trial is 0.05, p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

Handling of Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. For the exploratory outcomes, a False Discovery Rate method[30] will be used.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

Since the devices used (NIV, HFNO, standard oxygen) are already marketed and used in current clinical practice, the use of these devices does not seem likely to generate a significant risk during this protocol.

Regarding the vigilance of the project, the responsibilities of the investigator and sponsor, the reporting of serious adverse events (AE), annual safety reports will be monitored and carried out in accordance with regulations.

Complete and appropriate data on all AEs experienced during the clinical trial will be recorded on the AE form of the case report form on an ongoing basis for the duration of the study. Each AE report shall include a description of the event, an assessment of its seriousness according to the criteria listed above, its duration, intensity, relationship to the study treatment, other causality factors (if any), any concomitant medication dispensed, actions taken with the study device or other therapeutic interventions and outcome at the end of the observation period.

For each AE, a separate AE form will be filled in.

ETHICS AND DISSEMINATION

Research ethics approval

This research involving humans will be conducted in compliance with French 'Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé), 'Loi N°78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés')

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH).

The study project has been approved by the ethics committee "Comité de Protection des Personnes Ile de France V 19.04.05.70025 Cat 2 2019-A00956-51". The EXTUB obese study is conducted in accordance with the declaration of Helsinki and is registered on at http://www.clinicaltrials.gov (NCT 04014920).

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When possible, after recovery, patients will be retrospectively asked for written consent to continue the trial. Informed consent material is available in Supplemental file 1.

Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment and conduct of the study. The burden of the intervention will not be assessed by patients themselves. The results will be available for study participants on demand. No systematic disseminating of the results for study participants is planned.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

To the best of our knowledge, the EXTUB OBESE trial is the first pragmatic randomised controlled trial powered to investigate if NIV reduces treatment failure at H72 after extubation of ICU patients with obesity, compared to oxygen therapy (HFNO or standard oxygen).

NIV has proven effective in small observational studies in preventing post-extubation ARF in patients with obesity, in an ICU or postoperative setting.[11 18 31-33] The control group was standard oxygen therapy, which was the standard of care a few years ago. Nowadays, HFNO is used more and more, and has proven to be non-inferior to NIV in ARF patients following cardiothoracic surgery and in high risk patients after extubation in the ICU.[5 22]

A published study[6] was designed to assess NIV in a large population of patients older than 65 years or with underlying chronic cardiac or respiratory disease. In this multicentre, randomised, open-label trial, the authors found that HFNO with NIV, compared with HFNO alone, decreased the rate of reintubation within the first 7 days after extubation in the ICU. However, patients with obesity were only included if they had underlying chronic cardiac or respiratory disease, such as obesity hypoventilation syndrome. The current study aims to assess all patients with obesity after a length of invasive mechanical ventilation of at least 6 hours. The stratification of randomization according to the length of mechanical ventilation (less or more than 48 hours) and the type of admission (medical versus surgical), will allow to conclude on several strata of patients with obesity and different severities and profiles.

One of the strengths of the study is that the two consecutive randomizations will allow to balance the groups limiting the confounding factors. Moreover, the double randomization will allow to compare both NIV with oxygen, and HFNO with standard oxygen, and stratification will allow strata analyses.

One other strength is that the team has extensive experience in performing studies about NIV and HFNO or standard oxygen, such as the randomised controlled trials OPERA study[34] and NIVAS study.[35] The research networks involved in the NIVAS study[35] and of the FREE-REA[4],

FRIDA-REA[29] and STYLETO[26 36] study groups will be used. No industry will be involved, and HFNO and NIV are available and widely used in all participating centres, another strength of the study.

One of the limitations is that given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. However, to limit the risk of bias, the methodologist will be blinded to the group.

In conclusion, the EXTUB obese trial is the first investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV is associated with less treatment failure compared to oxygen in patients with obesity within the 72 hours after extubation in an ICU.

Trial status

The trial has started and is actively enrolling since October 2019.

Abbreviations

NIV: Non-Invasive Ventilation; HFNO: High Flow Nasal Humidified Oxygen Therapy; ARF: acute respiratory failure; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score II; AE: Adverse Event

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Author statement

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ, HB, DG and CC. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors (ADJ, MC, YA, GC, HB, DG, CC, NM, SJ) revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Data statement

Technical appendix, statistical code, and dataset available on demand.

Conflicts of interests

Pr. Jaber reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, and Fisher & Paykel. Dr De Jong reports receiving consulting fees from Medtronic. No potential conflict of interest relevant to this article was reported for other authors.

TABLES

Table 1. Participant timeline

Item	Screening/Baseline			Final visit
	Visit 1	Visit 2	Visit 3	Visit 4
Date	H0	H72	Day-28 or ICU discharge	Day-90
Clinical evaluation	X	X	X	
Informed consent	X			
Medical history	X			
Demography	X			
Physical examination	X	X	X	
Vital signs[1]	X	X	X	
Routine laboratory testing[2]	X	X	X	
Experimental treatment	X	X	X	
Endpoints evaluation°	X	X	X	X
Adverse events recording	X	X	X	

[1] include hemodynamic parameters (arterial pressure, heart rate, vasopressors use), respiratory rate, ventilatory parameters (respiratory rate and pulse oxymetry)

[2] arterial blood gases, as usually performed for the daily patient care during the first 72 hours if an arterial catheter was in place. Supplementary blood gases will be done according to the clinical state of the patient. Blood gases will be also done before the re-intubation if an acute respiratory failure following extubation occurs.

FIGURES LEGENDS

Figure 1: Consort diagram of the EXTUB OBESE Trial

NIV = Non Invasive Ventilation; HFNO = high-flow nasal cannula oxygen; BMI = body mass index;

Figure 2: Timeline of data collection

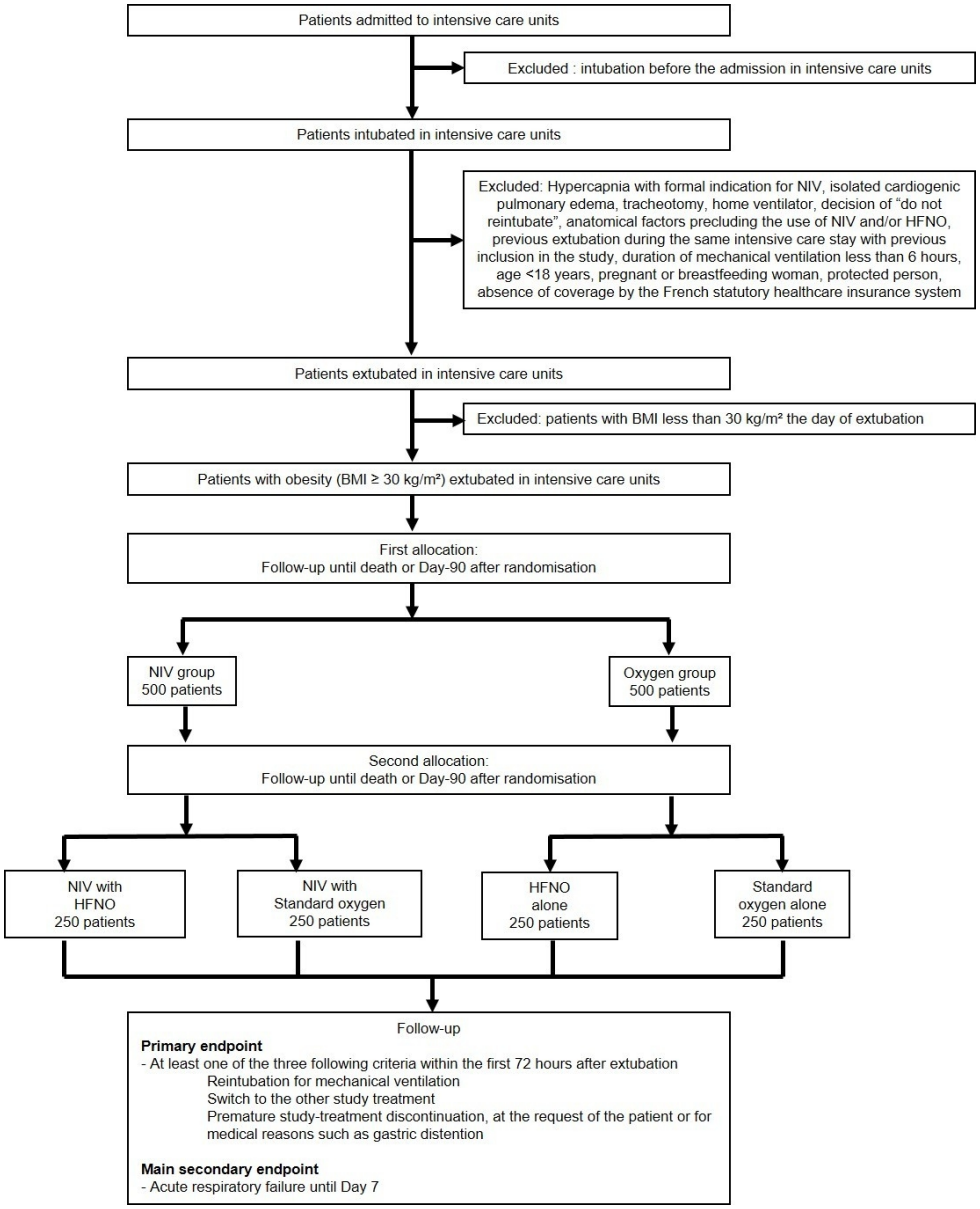

Figure 1

93x115mm (300 x 300 DPI)

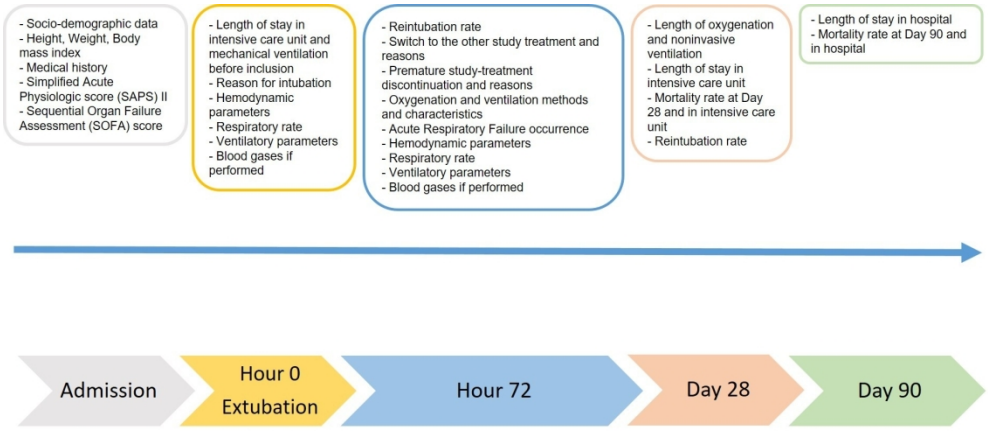

Figure 2: Timeline of data collection

160x75mm (300 x 300 DPI)

INFORMATION NOTE

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

STYLETO Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Pr Samir Jaber*

Madam, Sir,

Your doctor offers you the opportunity to participate in a research project promoted by Montpellier University Hospital. Before making a decision, it is important that you read these pages carefully as they will provide you with the necessary information concerning the different aspects of this research. Don't hesitate to ask your doctor any questions you may have.

Your participation is entirely voluntary. If you do not wish to take part in this research, you will continue to benefit from the best possible medical care in accordance with current knowledge.

WHY THIS RESEARCH?

You are going to be "intubated", which means that you will be put on an intubation tube ("tubing") to connect you to a ventilator to help you breathe.
Sometimes this tube can be difficult to put in place, and can be complicated by a drop in your blood oxygen level.
A "Stylet" can be added to the tube to make it more rigid to make it easier to insert. The addition of this stylet is intended to reduce the difficulty of intubation.
Both methods (with or without a stylet) are performed in routine practice.
To date, no study has evaluated the impact of the addition of a stylet on the difficulty of intubation and its complications.

WHAT IS THE OBJECTIVE OF THIS RESEARCH?

The objective of this study is to determine whether the addition of a stylet to the intubating tube leads to more frequent successful intubation on the first attempt, i.e. to increase the success rate on the first attempt.

HOW IS THIS RESEARCH GOING TO UNFOLD?

This is a so-called randomized (i.e. by drawing lots) comparative study comparing 2 groups: a control group "intubating tube alone" and an intervention group "addition of a stylet to the intubating tube" which will be conducted in 30 centres. 1040 patients will be recruited over a period of 18 months.
After the draw, you will be "intubated" either with an intubating tube alone or with an intubating tube pre-formed by adding a stylet inside.

WHO CAN PARTICIPATE?

Any critically ill patient who needs to be intubated can participate. The latter must be of legal age, must be a beneficiary or be affiliated to a social security scheme.

WHAT YOU WILL BE ASKED?

You will be treated according to the recommendations of good practice, just like any other critically ill patient. You will be monitored until you are discharged from the hospital.
There are no special restrictions.

WHAT ARE THE EXPECTED BENEFITS?

This clinical study has a direct benefit for the patients included. Its aim is to reduce the difficulty of intubation and therefore the complications of intubation.

WHAT ARE THE EXPECTED INCONVENIENTS?

There is no additional risk compared to any intubation performed in critically ill patients.
The addition of a stylet may in exceptional cases, when incorrectly positioned, lead to tracheal injury. Every precaution will be taken to ensure that the stylet is correctly positioned.

WHAT ARE THE POSSIBLE MEDICAL ALTERNATIVES?

An intubating tube is mandatory for intubation. The only two modalities are the presence of an intubating tube alone or with a stylet inside.

WHAT ARE THE MODALITIES OF MANAGEMENT RELATED TO THE STUDY?

Once the intubating tube is in place, no further procedures will be performed. You will be monitored throughout your stay in the intensive care unit and then in hospital.
The end of the search, premature discontinuation or exclusion, does not lead to any particular management modalities.
Participation in this research will not generate any additional costs compared to those you would have for the usual follow-up of this disease.

WHAT ARE YOUR RIGHTS?

Your doctor must provide you with all the necessary explanations concerning this research. If you wish to withdraw at any time, for whatever reason, you will continue to benefit from medical monitoring and this will not affect your future monitoring.
In accordance with the regulations, you must be a beneficiary of a social protection scheme in order to participate in research involving humans.

In accordance with Article L.1111-6 of the Public Health Code, you may designate a trusted person who may be a relative, a close friend or your treating physician and who will be consulted in the event that you are unable to express your wishes and receive the information necessary for this purpose. This person is accountable for your wishes. Her testimony prevails over any other testimony. This designation is made in writing and co-signed by the designated person. It may be revised and revoked at any time.
If you wish, your trusted person can accompany you in your steps and attend medical interviews in order to help you in your decisions.

As part of the research in which the Montpellier University Hospital offers you the opportunity to take part, your personal data will be processed in order to analyse the results of the research with regard to the objective of the research that has been presented to you.
The responsible of this treatment is the *Montpellier University Hospital.*

The study investigator and any other study personnel bound by professional secrecy and under the responsibility of the physician in charge of your treatment will collect medical data about you. This information, called "Personal Information", will be recorded on forms, called case report forms, provided by the sponsor. Only the information strictly necessary for the treatment and the purpose of the research

will be collected on a secure database and then kept at the end of the research, under the responsibility of Prof. Samir Jaber for 15 months.
In order to ensure the confidentiality of your personal information, neither your name nor any other information that would allow you to be directly identified will be entered in the observation notebook or in any other file that the study's medical investigator will provide to the research sponsor or to persons or companies acting on his behalf, in France or abroad.

This data will be identified by a code (inclusion number and initials). The code is used so that the study physician can identify you if necessary. This data may also be transmitted to the French health authorities under conditions that ensure its confidentiality.

In accordance with the provisions of the law on data processing, data files and individual liberties (law no. 78-17 of 6 January 1978 on data processing, data files and individual liberties as amended by law no. 2018-493 of 20 June 2018 on the protection of personal data) and the general regulations on data protection (EU regulation 2016/679), you have the right to access, rectify, delete or limit the information collected about you in the context of this processing.
In certain cases, you may also refuse the collection of your data and object to certain types of data processing being carried out. You also have the right to object to the transmission of data covered by professional secrecy that may be used in the course of such research and processing.
You may also have direct access, or through the intermediary of the doctor of your choice, to all your medical data pursuant to the provisions of Article L1111-7 of the Public Health Code.

You may withdraw your consent to the collection of your data for this processing at any time. Where applicable, in accordance with article L.1122-1-1 of the Public Health Code, the data concerning you that will have been collected prior to your withdrawal of consent may not be deleted and may continue to be processed under the conditions provided for by the research.

Finally, you may request that the personal information collected be provided to you or a third party in digital format (right of portability).

Your rights mentioned above are exercised with the doctor who is following you in the research and who knows your identity.

If you have any further questions about the collection or use of your personal information or the rights associated with this information, you can contact the Data Protection Officer of Montpellier University Hospital (Tel: 04 67 33 72 71) or the investigating physician at your centre, Dr. Samir Jaber.

If, despite the measures put in place by the sponsor, you feel that your rights are not being respected, you may file a complaint with the competent data protection supervisory authority in France, the Commission Nationale de l'Informatique et des Libertés (CNIL).

If the data controller wishes to further process your personal data for a purpose other than that for which your personal data were collected, you will be informed in advance about this other purpose, the length of time your data will be kept, and any other relevant information to ensure fair and transparent processing.

Searches mentioned in 1° of article L. 1121-1 relating to the products mentioned in article L. 5311-1 :

We inform you that you will be registered in the national file of persons who lend themselves to research provided for in Article L.1121-16 of the Public Health Code. You have the possibility to check with the Minister

in charge of Health the accuracy of the data concerning you in this file and the destruction of the data at the end of the period provided for by law.

In accordance with the law n°2012-300 of 5 March 2012 relating to research involving the human person :

- this research has obtained a favourable opinion from the Committee for the Protection of Persons of name of the CPP (category 2)

- The promoter of this research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out a civil liability insurance policy with Newline Syndicate 1218 at Lloyd's. (Category 2)

- persons who have suffered harm as a result of participation in research involving humans may assert their rights before regional conciliation and medical injury compensation commissions

- When this search is completed, you will be kept personally informed of the overall results by your doctor as soon as they are available, if you wish.

After reading this information note, do not hesitate to ask your doctor any questions you may have. After a period of reflection, if you agree to participate in this research, you must complete and sign the consent to participate form. A copy of the complete document will be given to you.

Thank you.

CONSENT FORM

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

STYLETO Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Pr Samir Jaber*

I .....*(name, surname)* certify that I have read and understood the briefing note provided to me.

I had the opportunity to ask all the questions I wished to the Pr/Dr ..... *(name, surname)* who explained to me the nature, objectives, potential risks and constraints associated with my participation in this research.

I am aware of the possibility that I may interrupt my participation in this research at any time without having to justify my decision and I will do my best to inform the doctor who is following me in the research. This will of course not affect the quality of subsequent care.

I have been assured that the decisions that are necessary for my health will be taken at any time, in accordance with the current state of medical knowledge.

I am aware that this research has received a favourable opinion from the Committee for the Protection of Individuals (category 2) and has obtained compliance with the General Data Protection Regulations.

The promoter of the research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out civil liability insurance with Newline Syndicate 1218 at Lloyd's (Category 2).

I accept that the persons collaborating in this research or mandated by the promoter, as well as possibly the representative of the Health Authorities, have access to the information in the strictest respect of confidentiality.

I accept that the data recorded in the course of this research may be subject to computerised processing under the responsibility of the promoter.

I have noted that, in accordance with the provisions of the law relating to data processing, files and freedoms, I have the right to access, rectify, limit the processing of my data and make a complaint to the Commission Nationale de l'Informatique et des Libertés (CNIL): https://www.cnil.fr/. I also have the right to oppose the transmission of data covered by professional secrecy

Having had sufficient time for reflection before making my decision, I freely and voluntarily agree to participate in the research "Determination of optimal spontaneous ventilation testing during mechanical ventilation withdrawal: a physiological cross-over study in the resuscitation patient and perioperative medicine".

I may at any time ask for further information from the doctor who proposed me to participate in this research, telephone number:

STYLETO Study

Done in .....the b c Done in .....the b c

Patient signature :

Physician signature :

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

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Study protocol

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

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Abstract word counts: 295 (max 300)
Total word counts:3967 (max 4000)
References, n=35
Table, n=1
Figure, n=2
Supplemental File 1: Patient consent form

ABSTRACT

Introduction:

Patients with obesity are considered to be at high risk of acute respiratory failure (ARF) after extubation in intensive care unit (ICU). Compared to oxygen therapy, noninvasive ventilation (NIV) may prevent ARF in high risk patients. However, these strategies have never been compared following extubation of critically ill patients with obesity. Our hypothesis is that NIV is associated with less treatment failure compared to oxygen therapy in patients with obesity after extubation in ICU.

Methods and analysis:

The non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units protocol (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients with obesity defined as a body mass index≥30 kg/m² will be randomly assigned in the "NIV-group" to receive prophylactic NIV applied immediately after extubation combined with high-flow nasal oxygen (HFNO) or standard oxygen between NIV sessions versus in the "oxygen therapy-group" to receive oxygen therapy alone (HFNO or standard oxygen,). The primary outcome is treatment failure within the 72 hours, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention). The single, prespecified, secondary outcome is the incidence of ARF until Day-7. Other outcomes analysed will include tracheal intubation rate at day-7 and day-28, length of ICU and hospital stay, ICU mortality, day-28 and day-90 mortality.

Ethics and dissemination:

The study project has been approved by the appropriate ethics committee "Comité-de-Protection-des-Personnes Ile de FranceV-19.04.05.70025 Cat2 2019-A00956-51". Informed consent is required. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. If use of NIV shows positive effects, teams (medical and surgical) will use NIV following extubation of critically ill patients with obesity.

Trial registration: ClinicalTrials.gov Identifier: NCT 04014920

Strengths and limitations of the study:

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between NIV and oxygen therapy to prevent ARF of critically ill patients with obesity.

- The broad inclusion criteria and the high number of participating ICUs will increase generalisability and the large sample size will provide the opportunity to examine strata and subgroups of interest.
- The double randomization will allow to balance groups limiting the confounding factors and to compare both NIV with oxygen therapy, and HFNO with standard oxygen, and stratification will allow strata analyses.
- The nature of the study intervention does not allow blinding. However, to limit the risk of bias, the methodologist will be blinded to the group.

Keywords: Obesity, noninvasive ventilation, preventive, acute respiratory failure, intensive care unit, high-flow nasal oxygen, NIV, HFNO

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Mechanical ventilation is the artificial support most used in intensive care unit (ICU).[2] If weaning and extubation (removal of the tracheal intubation tube) is successful in approximately 80 to 90% of ICU patients, 10 to 20% will develop acute respiratory failure (ARF) in the days following extubation.[3 4] This incidence is higher in some selected subgroups of patients with underlying lung disease (patients with obesity, chronic obstructive pulmonary disease (COPD), elderly, heart failure, postoperative cardio-thoracic and / or abdominal surgery ...).[5-7]

The management of post-extubation ARF combines etiological treatment associated with ventilatory support which usually requires the use of new endotracheal intubation to deliver "invasive" mechanical ventilation, associated with excess morbidity and mortality.[8 9]

Obesity is associated with excess morbidity and longer length of mechanical ventilation compared to the general population.[7 10] Effect of obesity on mortality is controversial,[11] some studies suggesting a protective or neutral effect of obesity,[12] named “obesity paradox”.[13] At the ventilatory level, several combined pathophysiological changes contribute to an increased incidence of respiratory complications.[7 11]

For over twenty years, non-Invasive Ventilation (NIV) has been used to prevent (“preventive NIV”) and cure (“curative NIV”) ARF in ICU patients.[14 15] An alternative to NIV is the administration of oxygen therapy via standard oxygen or high-flow nasal oxygen (HFNO).[16 17] In an observational study of 124 patients, El Sohl et al.[18] showed a 16% absolute risk reduction of ARF using NIV compared to standard oxygen following extubation.

More recently, HFNO has been developed. High flow rates reduce the dilution of inhaled oxygen and allow precise distribution of FiO2 throughout the inspiratory phase by adapting the peak flow rate to the patient.[17 19] High oxygen flow can also have a washing effect on the dead

space of the nasopharynx. In addition, a flow-dependent effect helps to generate a continuous positive end-expiratory pressure (PEEP).[20] Finally, the use of a high level of humidity could prevent alterations of the ciliated epithelium of the respiratory tract, maintain the activity of the muco-ciliary system, and facilitate the elimination of secretions.[21] In a post-hoc analysis of a large trial of 830 postoperative thoracic patients [22], it was shown that among the 272 patients with obesity (mean BMI of 34 kg/m²), NIV was not superior to HFNO, with treatment failure occurring in 15% and 13% in NIV and HFNO groups respectively. Moreover, in 155 post cardiac surgery patients with obesity, Corley et al.[23] compared HFNO with standard oxygen to prevent ARF, without showing any difference.

However, none of these studies compared simultaneously the most recent devices available: NIV, HFNO and standard oxygen, nor their association.[24] HFNO is now often used,[25] and the PEEP issued by HFNO is much lower than that issued by NIV. The benefit of NIV compared to oxygen therapy (HFNO or standard oxygen) after extubation of critically ill patients with obesity has never been studied.

In this multicentre, randomised, controlled, interventional study in mechanically ventilated critically ill patients with obesity, we will test the hypothesis that NIV (associated with HFNO or standard oxygen between NIV trials) could reduce the rate of treatment failure in comparison with oxygen therapy alone continuously administered (HFNO or standard oxygen) in patients with obesity within 72 hours after extubation in an ICU.

Objectives

Primary objective. To determine whether NIV could reduce the rate of treatment failure in comparison with oxygen therapy within the 72 hours after extubation of critically patients with obesity, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

Secondary objectives. To determine whether NIV could reduce the rate of ARF at Day-7 and other secondary outcomes in comparison with oxygen therapy.

Stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre, and patients characteristics will be done.

The main hypothesis is that NIV (associated with HFNO or standard oxygen) could reduce the rate of treatment failure in comparison with oxygen therapy alone (HFNO or standard oxygen) in patients with obesity within the 72 hours after extubation in ICU.

Trial design

The non-invasive ventilation vs oxygen after extubation in patients with obesity in intensive care units (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomization.

Patients will be randomly assigned (first randomisation) to receive NIV (experimental group) or oxygen therapy (control group). A second randomisation will determine the type of oxygen received in each group: HFNO or standard oxygen. (Figure 1).

The expected duration of the subject participation is 3 months after inclusion in the study.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the EXTUB-obese trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This study will take place in 35 ICUs in France, belonging to a research network that specializes in the management of critically ill patients and has a particularly high level of expertise in respiratory care strategies.[26]

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU, adult (age ≥ 18 years), covered by public health insurance, with written informed consent from the patient or proxy (if present) before inclusion or once possible if the patient has been included in an emergency context, with obesity defined by a body mass index ≥ 30 kg/m² the day of extubation and require extubation in intensive care unit after a length of mechanical ventilation of more than 6 hours.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: hypercapnia with a formal indication for NIV ($PaCO_2$ ≥ 50 mmHg), isolated cardiogenic pulmonary oedema (formal indication for NIV, patients with pulmonary oedema associated with another ARF aetiology can be included), tracheotomy, home ventilator, end-of-life decision with decision of "do not reintubate", anatomical factors precluding the use of NIV and/or HFNO, previous extubation during the same ICU stay with previous inclusion in the study, duration of mechanical ventilation less than 6 hours, age <18 years, pregnant or breastfeeding woman, protected person, refusal of study participation or to pursue the study by the patient, absence of coverage by the French statutory healthcare insurance system.

Outcomes

Primary outcome

Primary outcome variable is treatment failure within the 72 hours after extubation, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

For the primary analysis, comparing NIV to oxygen therapy, switch to the other study treatment will be defined as switch from oxygen therapy to NIV. Premature study-treatment discontinuation will be defined as discontinuation of NIV or HFNO at the request of the patient

before completion of one session of NIV of at least 30 minutes in the NIV group or before 12 hours of HFNO in the oxygen therapy group or for medical reasons such as gastric distention.

For the secondary analysis, comparing also HFNO to standard oxygen, switch to the other study treatment will also be defined as switch from oxygen therapy to HFNO.

Main secondary outcome

The single, pre-specified, secondary outcome is incidence of ARF until Day-7.

ARF during the first 7 days will be defined by two criteria among the following:[27]

1) Hypercapnia ($PaCO_2$ > 45 mmHg) with respiratory acidosis (arterial pH ≤ 7.35)

2) Modification of mental state and /or of conscience level (agitation or encephalopathy)

3) Decrease of SpO_2 < 90% or PaO_2 < 55 mmHg despite a FiO_2 > 50% and a flow > 10L/min

4) Hemodynamic instability, with a systolic arterial pressure <70 mmHg during more than 30 minutes despite sufficient fluid loading, and/or the use of vasopressors.

5) Abundant secretions and ineffective cough

6) Respiratory rate > 35/min, with signs of respiratory distress.

These criteria will be collected each day until Day-7.

Exploratory outcomes

Other outcomes will be evaluated as exploratory clinical outcomes:

- Oxygenation evaluated by the PaO2/FiO2 ratio until Day-7
- Organ failure until Day-7 assessed with the SOFA score
- Tracheal intubation rate at Day-7, Day-14 or Day-28
- Length of stay in ICU and in hospital
- ICU, Day-28 and Day-90 mortality rates

Safety/adverse outcomes

- Death during the NIV, HFNO or standard oxygen sessions
- Cardiac arrest during the NIV, HFNO or standard oxygen sessions

A separate analysis of the component « reintubation » of the primary outcome will also be performed.

Interventions

All consecutive extubation procedures will be screened for inclusion. A spontaneous breathing trial before extubation will not be mandatory and will be left at the clinician appreciation. The decision of extubation will be left to the appreciation of the physician. When an extubation is planned by the physician in charge of a patient with obesity, the patient will receive two consecutive randomizations. A first randomisation will be performed to allocate the patient in the experimental group to receive intermittent NIV trials or in the oxygen therapy group to receive continuous oxygen therapy. A second consecutive randomisation will determine the type of oxygen received in each group. For the experimental group, the second randomisation will determine the type of oxygen received between NIV trials (HFNO or standard oxygen). For the oxygen therapy group, the second randomisation will determine the type of oxygen continuously administered (HFNO or standard oxygen). NIV will not be used in the oxygen therapy group, excepted in case of rescue because of ARF at the physician request. HFNO will not be used in patients of both NIV and oxygen therapy group who will receive standard oxygen after the second randomization (Figure 1), excepted in case of rescue because of ARF at the physician request.

In the experimental group, the first NIV session will be offered to the patient within 30 minutes following extubation. The NIV system will first be explained to the patient by the physician or nurse and positioned at bedside. The mask will be chosen according to patient's facial morphology. The mask will be placed and adjusted to avoid leaks. Recommended positive end expiratory pressure (PEEP) value will be set to 10 cmH_2O (and adapted between 5 and 10 cmH_2O depending on tolerance) and value of pressure support (PS) will be set to obtain a respiratory rate between 20 and 30 breaths per minute (bpm) and an expired tidal volume in-between 6 and 8 ml/kg of ideal body weight. The recommended length of the intermittent NIV sessions will be standardized as follows: sessions of 30 to 60

minutes spread through the day and night for a cumulated time of at least 4 hours with no upper limit during the first 24 hours. NIV weaning will start 24h after extubation, if respiratory rate is stable and less than 25/minute with a PaO_2/FiO_2 ratio of more than 200 mmHg and a $PaCO_2$ less than 45 mmHg on the blood gases at H24. Between NIV sessions, patients will receive oxygen therapy with the same methods as the oxygen therapy group, with HFNO or standard oxygen.

In both groups, the second randomized device (oxygen therapy device) will be HFNO or standard oxygen.

HFNO will be used at a flow of 50L/min during the first 24 hours (possibly lowered down to 30L/min if needed by the patient), the FiO_2 being set to obtain a SpO_2≥94%. HFNO will be used during the first 24 hours whatever the percentage of SpO2, the FiO2 being set at 21% in case of SpO2≥94% without oxygen. The standard oxygen will be used only in case of SpO_2<94% without oxygen.

After 24 hours, the device will be pursued if the patient still needs oxygen, until the discharge from ICU or the absence of need of oxygen. The patients will be followed during their ICU stay and hospital stay until discharge or death. The follow-up will be stopped at 3 months.

Final decision of re-intubation will be taken by the physician according to prespecified criteria[28] : respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, massive aspiration, persistent inability to clear respiratory secretions, heart rate of less than 50/min with loss of alertness, and severe hemodynamic instability without response to fluid and vasoactive drugs.

Participant timeline

Participant timeline is presented in Table 1 and Figure 2.

Sample size

Two intermediate analyses will be performed after inclusion of 250 and 500 patients (stop for efficacy or safety). Assuming the overall p-value for the trial is 0.05, the p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

Based on a 12% composite endpoint rate in the oxygen group (Free rea study[4]) and a decrease of 50% of the composite endpoint rate to 6% in the NIV group,[18] with an alpha risk set at 5%, to obtain a 80% power for demonstrating superiority for the primary outcome, we need 954 patients (477 in each group) to demonstrate a superiority of NIV to oxygen therapy. In order to take into account loss of follow-up and intubation for surgical procedures without criteria of ARF, we will include 1000 patients.

Recruitment

Patients are expected to be included during a two years' inclusion period starting October 2019. Among the 35 participating centres, each centre would need to include 1 to 2 patients per month during the 24 months-study period.

March 2019-September 2019: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

October 2019 to September 2021: Inclusion of patients.

October 2021 to December 2021: Cleaning and closure of the database.

January 2022-September 2022: Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clincalt, randomization module). The randomization will be centralized and available online. It will be stratified on centre,[29 30] length of mechanical ventilation (<48 hours vs ≥ 48 hours) and on type of admission (medical vs surgical), balanced with a 1:1 ratio and minimization. The randomization will be performed from one hour before extubation to 30 minutes after extubation.

Blinding

Given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Patients will receive standard ICU monitoring consisting of electrocardiogram analysis, peripheral oxygen saturation, and a noninvasive blood pressure cuff.

The day of extubation (from H0 to H24 beginning from the time of extubation), the following data will be collected: demographic data, SAPS II score, length of stay in ICU before inclusion, length of mechanical ventilation before inclusion, reason for intubation, comorbidities, hemodynamic parameters (arterial pressure, heart rate, vasopressors use), ventilatory parameters (respiratory rate and SpO_2), spontaneous breathing trial characteristics (t-tube or pressure support, if performed), oxygenation and if performed NIV characteristics and the SOFA score.

From Day-1 to Day-7 the investigator or designated study personnel will record the criteria for the main outcome (reintubation and main reason for re-intubation, oxygenation method (continued, stopped, changed)) and for the secondary outcomes (ARF, oxygenation, mortality). They will also assess reason for intubation, hemodynamic variables (arterial pressure, heart rate, vasopressors use), ventilatory variables (respiratory rate and SpO_2), oxygenation and if performed NIV characteristics.

Length of stay in ICU will be evaluated. At ICU discharge, day 28 and Day 90, mortality rate will be evaluated.

Statistical methods

The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or worsened just before extubation and were not extubated. Then, a per-protocol analysis will be performed, excluding the reintubation for surgical procedures without criteria of ARF.

All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.4; SAS Institute; Cary, NC, USA, and R, version 3.6.2). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis

Uncorrected chi square test will be used for primary outcome analysis (comparison of the composite criteria at H72 combining reintubation for invasive mechanical ventilation, the switch to the other study treatment or the premature study treatment discontinuation).

A logistic regression will be used for the analysis of the primary outcome with odds ratio of failure calculation, before and after adjustment on confounding variables despite the randomization. A supplementary analysis on the primary outcome will be done for the time without treatment failure, per study group, using the log rank test. Unadjusted Kaplan Meier curves with respect to the primary outcome for the two groups will be performed to see if both curves do not cross each other ie the assumption of proportionality of the Cox model is not breached. In this case, a Cox model will be performed for the time without treatment failure, before and after adjustment. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected a priori and limited according to the number of events of primary outcome (reason

for intubation, previous respiratory disease and SOFA score) and then presented as adjusted odds ratios (ORs) or adjusted Hazard Ratios (HRs) with 95% CIs. A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables will be tested.

Then, unadjusted stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), center) and patients characteristics will be done on the primary outcome and reintubation rate.

A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables and time will be tested.

Secondary Analyses

Continuous outcomes will be compared with the Student t test or Mann-Whitney rank-sum test according to the conditions of application and categorical variables with the chi-square test or the Fisher exact test, according to the conditions of application. Then, stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre), type of oxygenation (second randomisation) and patients characteristics will be done.

Interim analysis

This trial will be planned with two interim analyses after the observation of the primary outcome of 250 and 500 patients. The interim analysis will be planned for early stopping of the study owning to safety (as defined by mortality within 7 days) or efficiency on the primary outcome after the first 250 and 500 patients included assuming the overall p-value for the trial is 0.05, p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

Handling of Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. For the exploratory outcomes, a False Discovery Rate method[31] will be used.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

Since the devices used (NIV, HFNO, standard oxygen) are already marketed and used in current clinical practice, the use of these devices does not seem likely to generate a significant risk during this protocol.

Regarding the vigilance of the project, the responsibilities of the investigator and sponsor, the reporting of serious adverse events (AE), annual safety reports will be monitored and carried out in accordance with regulations.

Complete and appropriate data on all AEs experienced during the clinical trial will be recorded on the AE form of the case report form on an ongoing basis for the duration of the study. Each AE report shall include a description of the event, an assessment of its seriousness according to the criteria listed above, its duration, intensity, relationship to the study treatment, other causality factors (if any), any concomitant medication dispensed, actions taken with the study device or other therapeutic interventions and outcome at the end of the observation period.

For each AE, a separate AE form will be filled in.

ETHICS AND DISSEMINATION

Research ethics approval

This research involving humans will be conducted in compliance with French 'Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé), 'Loi N°78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés')

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH).

The study project has been approved by the ethics committee "Comité de Protection des Personnes Ile de France V 19.04.05.70025 Cat 2 2019-A00956-51". The EXTUB obese study is conducted in accordance with the declaration of Helsinki and is registered on at http://www.clinicaltrials.gov (NCT 04014920).

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When possible, after recovery, patients will be retrospectively asked for written consent to continue the trial. Informed consent material is available in Supplemental file 1.

Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment and conduct of the study. The burden of the intervention will not be assessed by patients themselves. The results will be available for study participants on demand. No systematic disseminating of the results for study participants is planned.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

To the best of our knowledge, the EXTUB OBESE trial is the first pragmatic randomised controlled trial powered to investigate if NIV reduces treatment failure at H72 after extubation of ICU patients with obesity, compared to oxygen therapy (HFNO or standard oxygen).

NIV has proven effective in small observational studies in preventing post-extubation ARF in patients with obesity, in an ICU or postoperative setting.[11 18 32-34] The control group was standard oxygen, which was the standard of care a few years ago. Nowadays, HFNO is used more and more, and has proven to be non-inferior to NIV in ARF patients following cardiothoracic surgery and in high risk patients after extubation in the ICU.[5 22]

However, a recent published study[6] was performed to assess NIV in a large population of patients older than 65 years or with underlying chronic cardiac or respiratory disease. In this multicentre, randomised, open-label trial, the authors found that HFNO with NIV, compared with HFNO alone, decreased the rate of reintubation within the first 7 days after extubation in the ICU. It is worth noting that patients with obesity were only included if they had underlying chronic cardiac or respiratory disease, such as obesity hypoventilation syndrome. The current study aims to assess all patients with obesity after a length of invasive mechanical ventilation of at least 6 hours. In this setting of previous studies comparing NIV and standard oxygen showing superiority of NIV, [11 18 31-33] and according to the recent study of Thille et al., [6] we chose to design the trial as a superiority trial of NIV over oxygen therapy (including HFNO and standard oxygen). The stratification of randomization according to the length of mechanical ventilation (less or more than 48 hours) and the type of admission (medical versus surgical), will allow to conclude on several strata of patients with obesity and different severities and profiles.

One of the strengths of the study is that the two consecutive randomizations will allow to balance the groups limiting the confounding factors. Moreover, the double randomization will

allow to compare both NIV with oxygen therapy, and HFNO with standard oxygen, and stratification will allow strata analyses.

One other strength is that the team has extensive experience in performing studies about NIV and HFNO or standard oxygen, such as the randomised controlled trials OPERA study[35] and NIVAS study.[28] The research networks involved in the NIVAS study[28] and of the FREE-REA[4], FRIDA-REA[30] and STYLETO[26 36] study groups will be used. No industry will be involved, and HFNO and NIV are available and widely used in all participating centres, another strength of the study.

One of the limitations is that given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. However, to limit the risk of bias, the methodologist will be blinded to the group.

In conclusion, the EXTUB obese trial is the first investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV is associated with less treatment failure compared to oxygen therapy in patients with obesity within the 72 hours after extubation in an ICU.

Trial status

The trial has started and is actively enrolling since October 2019.

Abbreviations

NIV: Non-Invasive Ventilation; HFNO: High Flow Nasal Humidified Oxygen Therapy; ARF: acute respiratory failure; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score II; AE: Adverse Event

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Author statement

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM, HB and ADJ wrote the statistical analysis plan and estimated the sample size. All authors (ADJ, HB, NM, SJ) revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is National Ministry of Health, France (PHRCN-18-0078 Finess 340780477). There is no industry support or involvement in the trial.

Data statement

Technical appendix, statistical code, and dataset available on demand.

Conflicts of interests

Pr. Jaber reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, and Fisher & Paykel. Dr De Jong reports receiving consulting fees from Medtronic. No potential conflict of interest relevant to this article was reported for other authors.

TABLES

Table 1. Participant timeline

Item	Screening/Baseline			Final visit
	Visit 1	Visit 2	Visit 3	Visit 4
Date	H0	H72	Day-28 or ICU discharge	Day-90
Clinical evaluation	X	X	X	
Informed consent	X			
Medical history	X			
Demography	X			
Physical examination	X	X	X	
Vital signs[1]	X	X	X	
Routine laboratory testing[2]	X	X	X	
Experimental treatment	X	X	X	
Endpoints evaluation°	X	X	X	X
Adverse events recording	X	X	X	

[1] include hemodynamic parameters (arterial pressure, heart rate, vasopressors use), respiratory rate, ventilatory parameters (respiratory rate and pulse oxymetry)

[2] arterial blood gases, as usually performed for the daily patient care during the first 72 hours if an arterial catheter was in place. Supplementary blood gases will be done according to the clinical state of the patient. Blood gases will be also done before the re-intubation if an acute respiratory failure following extubation occurs.

FIGURES LEGENDS

Figure 1: Consort diagram of the EXTUB OBESE Trial

NIV = Non Invasive Ventilation; HFNO = high-flow nasal cannula oxygen; BMI = body mass index;

Figure 2: Timeline of data collection

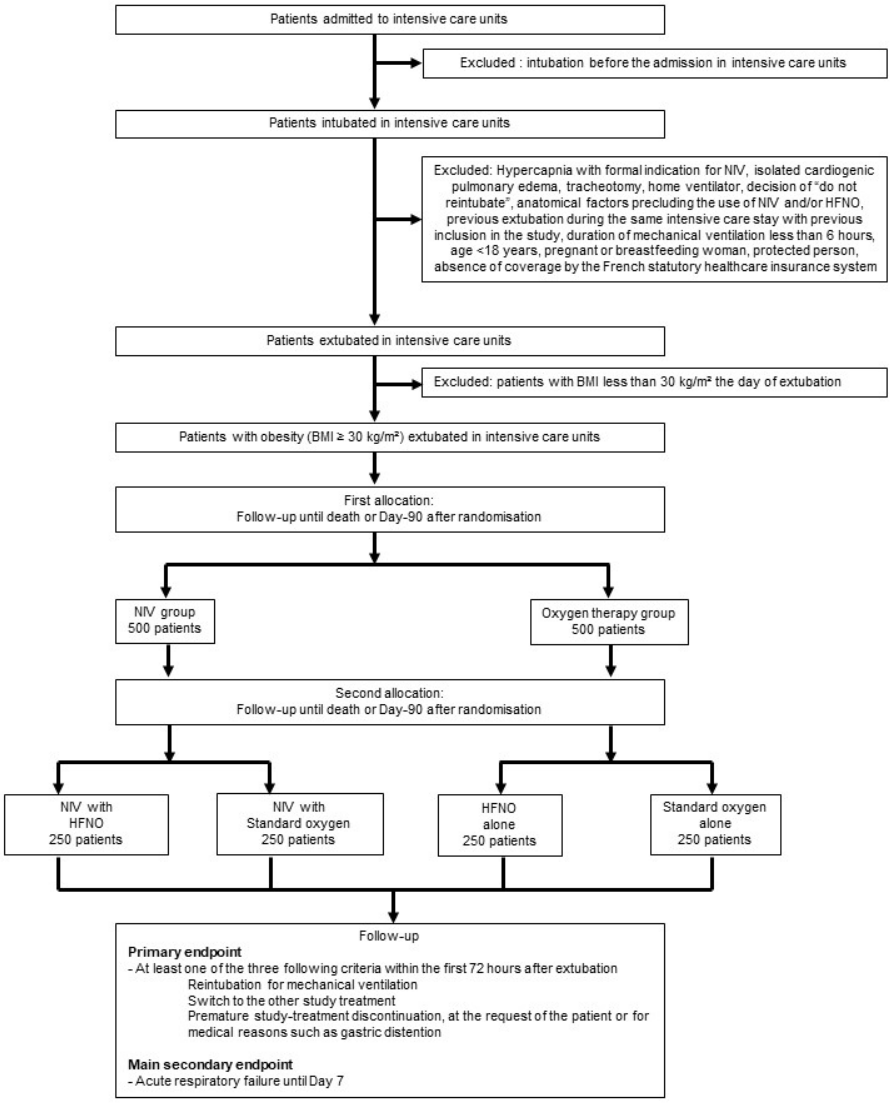

Figure 1

190x254mm (96 x 96 DPI)

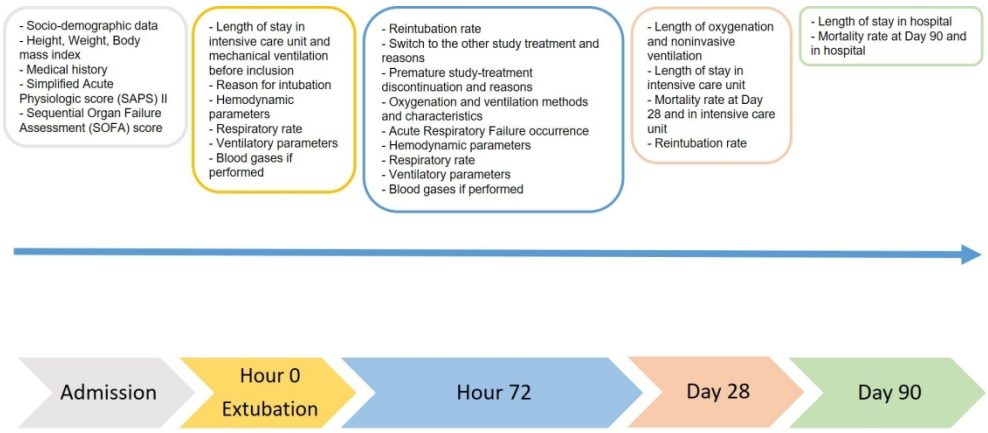

Figure 2

160x75mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

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Primary Subject Heading:	Intensive care
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Study protocol

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

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Abstract word counts: 295 (max 300)
Total word counts:3967 (max 4000)
References, n=35
Table, n=1
Figure, n=2
Supplemental File 1: Patient consent form

ABSTRACT

Introduction:

Patients with obesity are considered to be at high risk of acute respiratory failure (ARF) after extubation in intensive care unit (ICU). Compared to oxygen therapy, noninvasive ventilation (NIV) may prevent ARF in high risk patients. However, these strategies have never been compared following extubation of critically ill patients with obesity. Our hypothesis is that NIV is associated with less treatment failure compared to oxygen therapy in patients with obesity after extubation in ICU.

Methods and analysis:

The non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units protocol (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomisation. Patients with obesity defined as a body mass index≥30 kg/m² will be randomly assigned in the "NIV-group" to receive prophylactic NIV applied immediately after extubation combined with high-flow nasal oxygen (HFNO) or standard oxygen between NIV sessions versus in the "oxygen therapy-group" to receive oxygen therapy alone (HFNO or standard oxygen,). The primary outcome is treatment failure within the 72 hours, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention). The single, prespecified, secondary outcome is the incidence of ARF until Day-7. Other outcomes analysed will include tracheal intubation rate at day-7 and day-28, length of ICU and hospital stay, ICU mortality, day-28 and day-90 mortality.

Ethics and dissemination:

The study project has been approved by the appropriate ethics committee "Comité-de-Protection-des-Personnes Ile de FranceV-19.04.05.70025 Cat2 2019-A00956-51". Informed consent is required. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. If use of NIV shows positive effects, teams (medical and surgical) will use NIV following extubation of critically ill patients with obesity.

Trial registration: ClinicalTrials.gov Identifier: NCT 04014920

Strengths and limitations of the study:

- The broad inclusion criteria and the high number of participating ICUs will increase generalisability of the study.

- The large sample size will provide the opportunity to examine strata and subgroups of interest.
- The double randomisation with stratification will allow to balance groups limiting the confounding factors and to compare both NIV with oxygen therapy, and HFNO with standard oxygen.
- The main endpoint is a composite criterion that has been previously validated in one large multicentre randomized controlled trial.
- A limitation of this study is that the nature of the study intervention does not allow blinding.

Keywords: Obesity, noninvasive ventilation, preventive, acute respiratory failure, intensive care unit, high-flow nasal oxygen, NIV, HFNO

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Mechanical ventilation is the artificial support most used in intensive care unit (ICU).[2] If weaning and extubation (removal of the tracheal intubation tube) is successful in approximately 80 to 90% of ICU patients, 10 to 20% will develop acute respiratory failure (ARF) in the days following extubation.[3 4] This incidence is higher in some selected subgroups of patients with underlying lung disease (patients with obesity, chronic obstructive pulmonary disease (COPD), elderly, heart failure, postoperative cardio-thoracic and / or abdominal surgery ...).[5-7]

The management of post-extubation ARF combines etiological treatment associated with ventilatory support which usually requires the use of new endotracheal intubation to deliver "invasive" mechanical ventilation, associated with excess morbidity and mortality.[8 9]

Obesity is associated with excess morbidity and longer length of mechanical ventilation compared to the general population.[7 10] Effect of obesity on mortality is controversial,[11] some studies suggesting a protective or neutral effect of obesity,[12] named “obesity paradox”.[13] At the ventilatory level, several combined pathophysiological changes contribute to an increased incidence of respiratory complications.[7 11]

For over twenty years, non-Invasive Ventilation (NIV) has been used to prevent (“preventive NIV”) and cure (“curative NIV”) ARF in ICU patients.[14 15] An alternative to NIV is the administration of oxygen therapy via standard oxygen or high-flow nasal oxygen (HFNO).[16 17] In an observational study of 124 patients, El Sohl et al.[18] showed a 16% absolute risk reduction of ARF using NIV compared to standard oxygen following extubation.

More recently, HFNO has been developed. High flow rates reduce the dilution of inhaled oxygen and allow precise distribution of FiO2 throughout the inspiratory phase by adapting the peak flow rate to the patient.[17 19] High oxygen flow can also have a washing effect on the dead

space of the nasopharynx. In addition, a flow-dependent effect helps to generate a continuous positive end-expiratory pressure (PEEP).[20] Finally, the use of a high level of humidity could prevent alterations of the ciliated epithelium of the respiratory tract, maintain the activity of the muco-ciliary system, and facilitate the elimination of secretions.[21] In a post-hoc analysis of a large trial of 830 postoperative thoracic patients [22], it was shown that among the 272 patients with obesity (mean BMI of 34 kg/m²), NIV was not superior to HFNO, with treatment failure occurring in 15% and 13% in NIV and HFNO groups respectively. Moreover, in 155 post cardiac surgery patients with obesity, Corley et al.[23] compared HFNO with standard oxygen to prevent ARF, without showing any difference.

However, none of these studies compared simultaneously the most recent devices available: NIV, HFNO and standard oxygen, nor their association.[24] HFNO is now often used,[25] and the PEEP issued by HFNO is much lower than that issued by NIV. The benefit of NIV compared to oxygen therapy (HFNO or standard oxygen) after extubation of critically ill patients with obesity has never been studied.

In this multicentre, randomised, controlled, interventional study in mechanically ventilated critically ill patients with obesity, we will test the hypothesis that NIV (associated with HFNO or standard oxygen between NIV trials) could reduce the rate of treatment failure in comparison with oxygen therapy alone continuously administered (HFNO or standard oxygen) in patients with obesity within 72 hours after extubation in an ICU.

Objectives

Primary objective. To determine whether NIV could reduce the rate of treatment failure in comparison with oxygen therapy within the 72 hours after extubation of critically patients with obesity, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

Secondary objectives. To determine whether NIV could reduce the rate of ARF at Day-7 and other secondary outcomes in comparison with oxygen therapy.

Stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre, and patients characteristics will be done.

The main hypothesis is that NIV (associated with HFNO or standard oxygen) could reduce the rate of treatment failure in comparison with oxygen therapy alone (HFNO or standard oxygen) in patients with obesity within the 72 hours after extubation in ICU.

Trial design

The non-invasive ventilation vs oxygen after extubation in patients with obesity in intensive care units (EXTUB-obese) trial is an investigator-initiated, multicentre, stratified, parallel-group unblinded trial with an electronic system–based randomisation.

Patients will be randomly assigned (first randomisation) to receive NIV (experimental group) or to receive oxygen therapy (control group). A second randomisation of both groups will determine the type of oxygen received in each group: (a) NIV with HFNO between sessions, or NIV with standard oxygen between sessions (experimental group) or (b) HFNO or standard oxygen (control group, Figure 1).

The expected duration of the subject participation is 3 months after inclusion in the study.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the EXTUB-obese trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This study will take place in 35 ICUs in France, belonging to a research network that specializes in the management of critically ill patients and has a particularly high level of expertise in respiratory care strategies.[26]

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU, adult (age ≥ 18 years), covered by public health insurance, with written informed consent from the patient or proxy (if present) before inclusion or once possible if the patient has been included in an emergency context, with obesity defined by a body mass index ≥ 30 kg/m² the day of extubation and require extubation in intensive care unit after a length of mechanical ventilation of more than 6 hours.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: hypercapnia with a formal indication for NIV (PaCO2 ≥ 50 mmHg), isolated cardiogenic pulmonary oedema (formal indication for NIV, patients with pulmonary oedema associated with another ARF aetiology can be included), tracheotomy, home ventilator, end-of-life decision with decision of “do not reintubate”, anatomical factors precluding the use of NIV and/or HFNO, previous extubation during the same ICU stay with previous inclusion in the study, duration of mechanical ventilation less than 6 hours, age <18 years, pregnant or breastfeeding woman, protected person, refusal of study participation or to pursue the study by the patient, absence of coverage by the French statutory healthcare insurance system.

Outcomes

Primary outcome

Primary outcome variable is treatment failure within the 72 hours after extubation, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).[5]

For the primary analysis, comparing NIV to oxygen therapy, switch to the other study treatment will be defined as switch from oxygen therapy to NIV. Premature study-treatment discontinuation will be defined as discontinuation of NIV or HFNO at the request of the patient before completion of one session of NIV of at least 30 minutes in the NIV group or before 12 hours of HFNO in the oxygen therapy group or for medical reasons such as gastric distention.

For the secondary analysis, comparing also HFNO to standard oxygen, switch to the other study treatment will also be defined as switch from oxygen therapy to HFNO.

Main secondary outcome

The single, pre-specified, secondary outcome is incidence of ARF until Day-7.

ARF during the first 7 days will be defined by two criteria among the following:[27]

1) Hypercapnia ($PaCO_2$ > 45 mmHg) with respiratory acidosis (arterial pH ≤ 7.35)

2) Modification of mental state and /or of conscience level (agitation or encephalopathy)

3) Decrease of SpO_2 < 90% or PaO_2 < 55 mmHg despite a FiO_2 > 50% and a flow > 10L/min

4) Hemodynamic instability, with a systolic arterial pressure <70 mmHg during more than 30 minutes despite sufficient fluid loading, and/or the use of vasopressors.

5) Abundant secretions and ineffective cough

6) Respiratory rate > 35/min, with signs of respiratory distress.

These criteria will be collected each day until Day-7.

Exploratory outcomes

Other outcomes will be evaluated as exploratory clinical outcomes:

- Oxygenation evaluated by the PaO2/FiO2 ratio until Day-7
- Organ failure until Day-7 assessed with the SOFA score
- Tracheal intubation rate at Day-7, Day-14 or Day-28
- Length of stay in ICU and in hospital
- ICU, Day-28 and Day-90 mortality rates

Safety/adverse outcomes

- Death during the NIV, HFNO or standard oxygen sessions

- Cardiac arrest during the NIV, HFNO or standard oxygen sessions

Sub-analysis of reintubation occurrences according to prespecified criteria[28] will be performed.

Interventions

All consecutive extubation procedures will be screened for inclusion. A spontaneous breathing trial before extubation will not be mandatory and will be left at the clinician discretion. The decision of extubation will be left to the discretion of the physician. When an extubation is planned by the physician in charge of a patient with obesity, the patient will receive two consecutive randomisations. A first randomisation will be performed to allocate the patient in the experimental group to receive intermittent NIV trials or in the oxygen therapy group to receive continuous oxygen therapy. A second consecutive randomisation will determine the type of oxygen received in each group. For the experimental group, the second randomisation will determine the type of oxygen received between NIV trials (HFNO or standard oxygen). For the oxygen therapy group, the second randomisation will determine the type of oxygen continuously administered (HFNO or standard oxygen). NIV will not be used in the oxygen therapy group, except in the case of rescue therapy in the case of ARF and at the physician's request. HFNO will not be used in patients of both NIV and oxygen therapy group who will receive standard oxygen after the second randomisation (Figure 1), except in the case of rescue therapy in the case of ARF and at the physician's request.
In the experimental group, the first NIV session will be offered to the patient within 30 minutes following extubation. The NIV system will first be explained to the patient by the physician or nurse and positioned at bedside. The mask will be chosen according to patient's facial morphology. The mask will be placed and adjusted to avoid leaks. Recommended positive end expiratory pressure (PEEP) value will be set to 10 cmH_2O (and adapted between 5 and 10 cmH_2O depending on tolerance) and value of pressure support (PS) will be set to obtain a respiratory rate between 20 and 30 breaths per minute (bpm) and an expired tidal volume in-between 6 and 8 ml/kg of ideal body weight. The recommended

length of the intermittent NIV sessions will be standardized as follows: sessions of 30 to 60 minutes spread through the day and night for a cumulated time of at least 4 hours with no upper limit during the first 24 hours. NIV weaning will start 24h after extubation, if respiratory rate is stable and less than 25/minute with a PaO_2/FiO_2 ratio of more than 200 mmHg and a $PaCO_2$ less than 45 mmHg on the blood gases at H24. Between NIV sessions, patients will receive oxygen therapy with the same methods as the oxygen therapy group, with HFNO or standard oxygen.

In both groups, the second randomised device (oxygen therapy device) will be HFNO or standard oxygen.

HFNO will be administered at a flow of 50L/min during the first 24 hours (can be reduced with patient improvement/tolerance to 30L/min if required), with an FiO2 set to target SpO2 ≥94%, which may in some patients reduce to an FiO2 of 21%. Patients administered standard oxygen will receive this therapy only in the case where SpO2 ≤94%. We chose the SpO2 threshold of 94% as it is "standard practices" in the majority of the hospitals participating to the study.

After 24 hours, the device will be pursued if the patient still needs oxygen, until the discharge from ICU or the absence of need of oxygen. The patients will be followed during their ICU stay and hospital stay until discharge or death. The follow-up will be stopped at 3 months.

Final decision of re-intubation will be taken by the physician according to prespecified criteria[28] : respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, massive aspiration, persistent inability to clear respiratory secretions, heart rate of less than 50/min with loss of alertness, and severe hemodynamic instability without response to fluid and vasoactive drugs.

Participant timeline

Participant timeline is presented in Table 1 and Figure 2.

Sample size

Two intermediate analyses will be performed after inclusion of 250 and 500 patients (stop for efficacy or safety). Assuming the overall p-value for the trial is 0.05, the p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary). Based on a 12% composite endpoint rate in the oxygen group (Free rea study[4]) and a decrease of 50% of the composite endpoint rate to 6% in the NIV group,[18] with an alpha risk set at 5%, to obtain a 80% power for demonstrating superiority for the primary outcome, we need 954 patients (477 in each group) to demonstrate a superiority of NIV to oxygen therapy. In order to take into account loss of follow-up and intubation for surgical procedures without criteria of ARF, we will include 1000 patients.

Recruitment

Patients are expected to be included during a two years' inclusion period starting October 2019. Among the 35 participating centres, each centre would need to include 1 to 2 patients per month during the 24 months-study period.

March 2019-September 2019: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

October 2019 to September 2021: Inclusion of patients.

October 2021 to December 2021: Cleaning and closure of the database.

January 2022-September 2022: Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clincalt, randomisation module). The randomisation will be centralized and available online. It will be stratified on centre,[29 30] length of mechanical ventilation (<48 hours vs ≥ 48 hours) and on type of admission (medical vs surgical), balanced with a 1:1 ratio and minimization. The randomisation will be performed from one hour before

extubation to 30 minutes after extubation. It was decided to authorize the physician to perform randomisation in the 30 minutes following extubation in order to be still able to include patients if the physician had forgotten before extubation.

Blinding

Given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Patients will receive standard ICU monitoring consisting of electrocardiogram analysis, peripheral oxygen saturation, and a noninvasive blood pressure cuff.

The day of extubation (from H0 to H24 beginning from the time of extubation), the following data will be collected: demographic data, SAPS II score, length of stay in ICU before inclusion, length of mechanical ventilation before inclusion, reason for intubation, comorbidities, hemodynamic parameters (arterial pressure, heart rate, vasopressors use), ventilatory parameters (respiratory rate and SpO_2), spontaneous breathing trial characteristics (t-tube or pressure support, if performed), oxygenation and if performed NIV characteristics and the SOFA score.

From Day-1 to Day-7 the investigator or designated study personnel will record the criteria for the main outcome (reintubation and main reason for re-intubation, oxygenation method (continued, stopped, changed)) and for the secondary outcomes (ARF, oxygenation, mortality). They will also assess reason for intubation, hemodynamic variables (arterial pressure, heart rate, vasopressors use), ventilatory variables (respiratory rate and SpO_2), oxygenation and if performed NIV characteristics.

Length of stay in ICU will be evaluated. At ICU discharge, day 28 and Day 90, mortality rate will be evaluated.

Statistical methods

The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, were protected or not covered by the French statutory healthcare insurance system, worsened just before extubation and were not extubated, or had no main outcome recorded on electronic case report form.

Then, a per-protocol analysis will be performed, excluding the patients with reintubation for surgical procedures without criteria of ARF, with BMI less than 30 kg/m² or with home ventilator.

All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.4; SAS Institute; Cary, NC, USA, and R, version 3.6.2). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis

Uncorrected chi square test will be used for primary outcome analysis (comparison of the composite criteria at H72 combining reintubation for invasive mechanical ventilation, the switch to the other study treatment or the premature study treatment discontinuation).

A logistic regression will be used for the analysis of the primary outcome with odds ratio of failure calculation, before and after adjustment on confounding variables despite the

randomisation. A supplementary analysis on the primary outcome will be done for the time without treatment failure, per study group, using the log rank test. Unadjusted Kaplan Meier curves with respect to the primary outcome for the two groups will be performed to see if both curves do not cross each other ie the assumption of proportionality of the Cox model is not breached. In this case, a Cox model will be performed for the time without treatment failure, before and after adjustment. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected a priori and limited according to the number of events of primary outcome (reason for intubation, previous respiratory disease and SOFA score) and then presented as adjusted odds ratios (ORs) or adjusted Hazard Ratios (HRs) with 95% CIs. A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables will be tested.

Then, unadjusted stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), center) and patients characteristics will be done on the primary outcome and reintubation rate.

A centre effect will be checked using a mixed effect model, considering the centre both as a random and then a fixed variable. Interactions between variables and time will be tested.

Secondary Analyses

Continuous outcomes will be compared with the Student t test or Mann-Whitney rank-sum test according to the conditions of application and categorical variables with the chi-square test or the Fisher exact test, according to the conditions of application. Then, stratified and subgroups analyses according to variable of stratification (length of mechanical ventilation < 48 hours vs ≥ 48 hours, type of admission (medical vs surgical), centre), type of oxygenation (second randomisation) and patients characteristics will be done.

Interim analysis

This trial will be planned with two interim analyses after the observation of the primary outcome of 250 and 500 patients. The interim analysis will be planned for early stopping of the study owning to safety (as defined by mortality within 7 days) or efficiency on the primary outcome after the first 250 and 500 patients included assuming the overall p-value for the trial is 0.05, p-value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

Handling of Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. For the exploratory outcomes, a False Discovery Rate method[31] will be used.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

Since the devices used (NIV, HFNO, standard oxygen) are already marketed and used in current clinical practice, the use of these devices does not seem likely to generate a significant risk during this protocol.

Regarding the vigilance of the project, the responsibilities of the investigator and sponsor, the reporting of serious adverse events (AE), annual safety reports will be monitored and carried out in accordance with regulations.

Complete and appropriate data on all AEs experienced during the clinical trial will be recorded on the AE form of the case report form on an ongoing basis for the duration of the study. Each AE report shall include a description of the event, an assessment of its seriousness according to the criteria listed above, its duration, intensity, relationship to the study treatment, other causality factors (if any), any concomitant medication dispensed, actions taken with the study device or other therapeutic interventions and outcome at the end of the observation period.

For each AE, a separate AE form will be filled in.

ETHICS AND DISSEMINATION

Research ethics approval

This research involving humans will be conducted in compliance with French 'Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé), 'Loi N°78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés')

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH).

The study project has been approved by the ethics committee "Comité de Protection des Personnes Ile de France V 19.04.05.70025 Cat 2 2019-A00956-51". The EXTUB obese study is conducted in accordance with the declaration of Helsinki and is registered on at http://www.clinicaltrials.gov (NCT 04014920).

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When possible, after recovery, patients will be retrospectively asked for written consent to continue the trial. Informed consent material is available in Supplemental file 1.

Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment and conduct of the study. The burden of the intervention will not be assessed by patients themselves. The results will be available for study participants on demand. No systematic disseminating of the results for study participants is planned.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

To the best of our knowledge, the EXTUB OBESE trial is the first pragmatic randomised controlled trial powered to investigate if NIV reduces treatment failure at H72 after extubation of ICU patients with obesity, compared to oxygen therapy (HFNO or standard oxygen).

NIV has proven effective in small observational studies in preventing post-extubation ARF in patients with obesity, in an ICU or postoperative setting.[11 18 32-34] Standard oxygen (control group) was the standard practice in past years, however, currently HFNO has become the more common practice, and has proven to be non-inferior to NIV in ARF patients following cardiothoracic surgery and in high risk patients after extubation in the ICU.[5 22]

However, a recent published study[6] was performed to assess NIV in a large population of patients older than 65 years or with underlying chronic cardiac or respiratory disease. In this multicentre, randomised, open-label trial, the authors found that HFNO with NIV, compared with HFNO alone, decreased the rate of reintubation within the first 7 days after extubation in the ICU. It is worth noting that patients with obesity were only included if they had underlying chronic cardiac or respiratory disease, such as obesity hypoventilation syndrome. The current study aims to assess all patients with obesity after a length of invasive mechanical ventilation of at least 6 hours. In this setting of previous studies comparing NIV and standard oxygen showing superiority of NIV, [11 18 31-33] and according to the recent study of Thille et al., [6] we chose to design the trial as a superiority trial of NIV over oxygen therapy (including HFNO and standard oxygen). The stratification of randomisation according to the length of mechanical ventilation (less or more than 48 hours) and the type of admission (medical versus surgical), will allow to conclude on several strata of patients with obesity and different severities and profiles.

One of the strengths of the study is that the two consecutive randomisations will allow to balance the groups limiting the confounding factors. Moreover, the double randomisation will

allow to compare both NIV with oxygen therapy, and HFNO with standard oxygen, and stratification will allow strata analyses.

One other strength is that the team has extensive experience in performing studies about NIV and HFNO or standard oxygen, such as the randomised controlled trials OPERA study[35] and NIVAS study.[28] The research networks involved in the NIVAS study[28] and of the FREE-REA[4], FRIDA-REA[30] and STYLETO[26 36] study groups will be used. No industry will be involved, and HFNO and NIV are available and widely used in all participating centres, another strength of the study.

One of the limitations is that given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. However, to limit the risk of bias, the methodologist will be blinded to the group.

In conclusion, the EXTUB obese trial is the first investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV is associated with less treatment failure compared to oxygen therapy in patients with obesity within the 72 hours after extubation in an ICU.

Trial status

The trial has started and is actively enrolling since October 2019.

Abbreviations

NIV: Non-Invasive Ventilation; HFNO: High Flow Nasal Humidified Oxygen Therapy; ARF: acute respiratory failure; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score II; AE: Adverse Event

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Author statement

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM, HH and ADJ wrote the statistical analysis plan and estimated the sample size. All authors (ADJ, HH, NM, SJ) revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is National Ministry of Health, France (PHRCN-18-0078 Finess 340780477). There is no industry support or involvement in the trial.

Data statement

Technical appendix, statistical code, and dataset available on demand.

Conflicts of interests

Pr. Jaber reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, and Fisher & Paykel. Dr De Jong reports receiving consulting fees from Medtronic. No potential conflict of interest relevant to this article was reported for other authors.

TABLES

Table 1. Participant timeline

Item	Screening/Baseline			Final visit
	Visit 1	Visit 2	Visit 3	Visit 4
Date	H0	H72	Day-28 or ICU discharge	Day-90
Clinical evaluation	X	X	X	
Informed consent	X			
Medical history	X			
Demography	X			
Physical examination	X	X	X	
Vital signs[1]	X	X	X	
Routine laboratory testing[2]	X	X	X	
Experimental treatment	X	X	X	
Endpoints evaluation°	X	X	X	X
Adverse events recording	X	X	X	

[1] include hemodynamic parameters (arterial pressure, heart rate, vasopressors use), respiratory rate, ventilatory parameters (respiratory rate and pulse oxymetry)

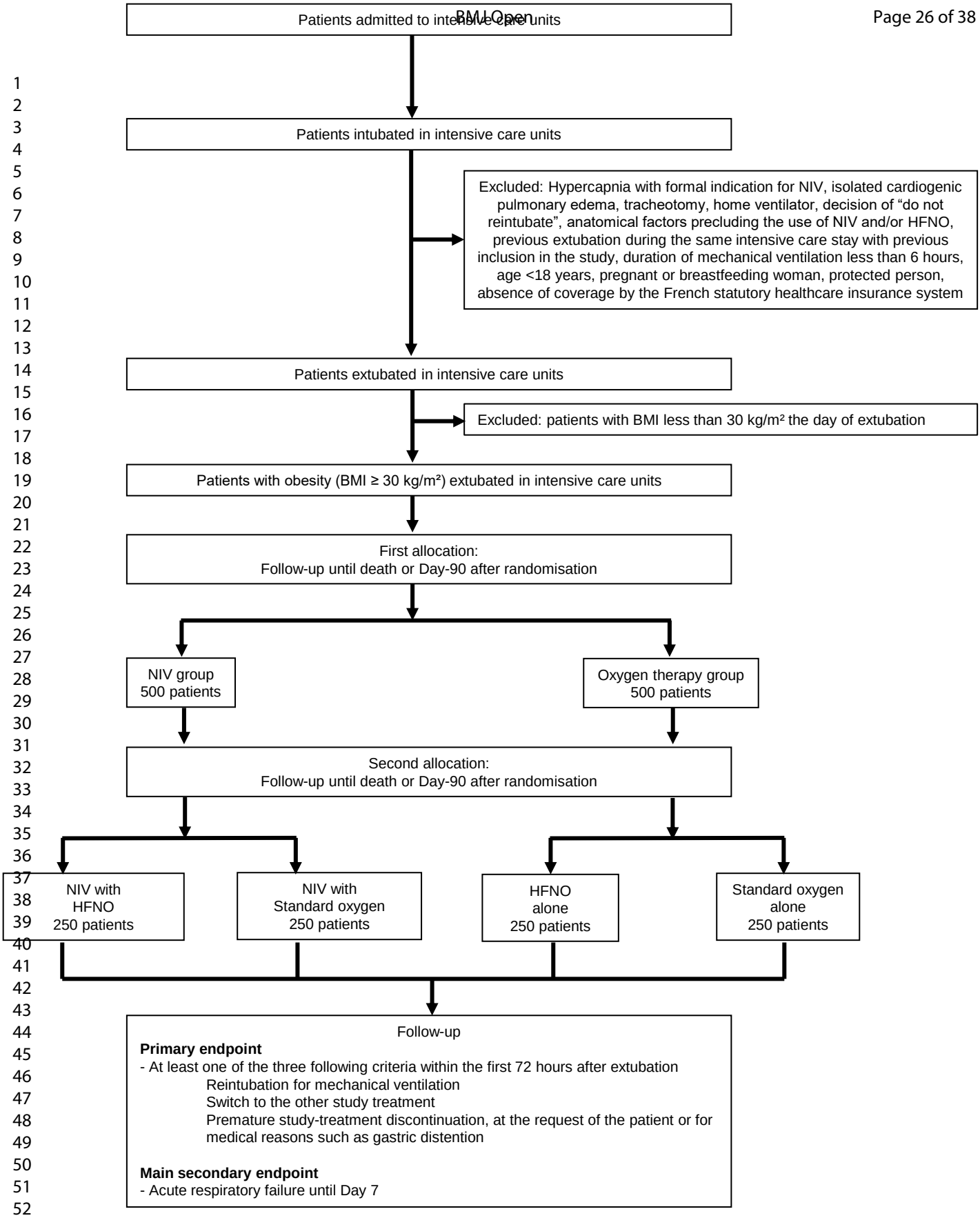
[2] arterial blood gases, as usually performed for the daily patient care during the first 72 hours if an arterial catheter was in place. Supplementary blood gases will be done according to the clinical state of the patient. Blood gases will be also done before the re-intubation if an acute respiratory failure following extubation occurs.

FIGURES LEGENDS

Figure 1: Consort diagram of the EXTUB OBESE Trial

NIV = Non Invasive Ventilation; HFNO = high-flow nasal cannula oxygen; BMI = body mass index;

Figure 2: Timeline of data collection


Patients admitted to intensive care units
Patients intubated in intensive care units
Excluded: Hypercapnia with formal indication for NIV, isolated cardiogenic pulmonary edema, tracheotomy, home ventilator, decision of "do not reintubate", anatomical factors precluding the use of NIV and/or HFNO, previous extubation during the same intensive care stay with previous inclusion in the study, duration of mechanical ventilation less than 6 hours, age <18 years, pregnant or breastfeeding woman, protected person, absence of coverage by the French statutory healthcare insurance system
Patients extubated in intensive care units
Excluded: patients with BMI less than 30 kg/m² the day of extubation
Patients with obesity (BMI ≥ 30 kg/m²) extubated in intensive care units
First allocation:
Follow-up until death or Day-90 after randomisation
NIV group
500 patients
Oxygen therapy group
500 patients
Second allocation:
Follow-up until death or Day-90 after randomisation
NIV with
HFNO
250 patients
NIV with
Standard oxygen
250 patients
HFNO
alone
250 patients
Standard oxygen
alone
250 patients
Follow-up
Primary endpoint
- At least one of the three following criteria within the first 72 hours after extubation
Reintubation for mechanical ventilation
Switch to the other study treatment
Premature study-treatment discontinuation, at the request of the patient or for medical reasons such as gastric distention
Main secondary endpoint
- Acute respiratory failure until Day 7

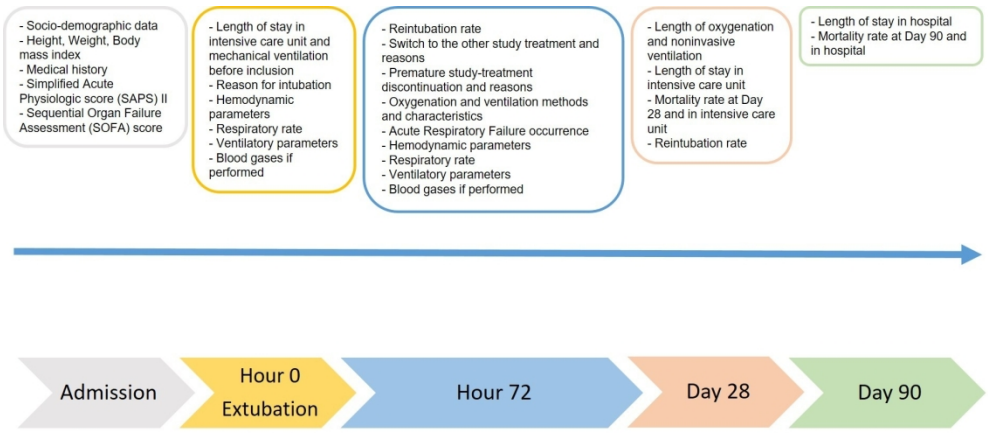


Figure 2: Timeline of data collection

160x75mm (300 x 300 DPI)

INFORMATION NOTE

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

EXTUB-OBESE Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Dr Audrey DE JONG*

Madam, Sir,

Your doctor offers you the opportunity to participate in a research project promoted by Montpellier University Hospital. Before making a decision, it is important that you read these pages carefully as they will provide you with the necessary information concerning the different aspects of this research. Don't hesitate to ask your doctor any questions you may have.

Your participation is entirely voluntary. If you do not wish to take part in this research, you will continue to benefit from the best possible medical care in accordance with current knowledge.

WHAT IS THE OBJECTIVE OF THIS RESEARCH?

You have been intubated and put on invasive mechanical ventilation. The objective of the research is to study the best method of oxygenation following the removal of the tube connecting it to the ventilator (so-called extubation maneuver). Following extubation in intensive care, the main risk is the development of acute respiratory failure, which occurs in 10 to 20% of cases. This acute respiratory failure can lead to reintubation. The objective is thus to show that the addition of non-invasive ventilation sessions following extubation can prevent the onset of acute respiratory failure and therefore reduce the need for re-intubation. The use of non-invasive ventilation would be particularly appropriate in patients with a body mass index ≥ 30 kg / m², defining "obesity", due to their morphological characteristics. Between sessions of non-invasive ventilation, two oxygen therapy methods will also be compared: so-called "standard" oxygen therapy by Venturi mask versus high-flow nasal oxygen therapy.

WHAT IS THE METHODOLOGY OF THE STUDY?

This is a therapeutic trial that will be conducted in around 40 healthcare establishments in France where 1,000 patients will be recruited over a period of 3 years. As part of this project, a computer draw (this is called randomization) will be performed to determine whether or not you will receive non-invasive ventilation in addition to the oxygen therapy following extubation. If you receive non-invasive ventilation, it will be administered in sessions of 30 minutes to 1 hour every 3 to 6 hours. If you do not receive non-invasive ventilation, you will be treated according to good practice recommendations. The management of your illness will thus be the same regardless of whether or not non-invasive ventilation is administered. The oxygen administered continuously or between sessions of non-invasive ventilation will be administered in two ways (second randomization): so-called "standard" oxygen therapy by mask or high-flow nasal oxygen therapy.

WHAT IS THE MANAGEMENT AND FOLLOWING?

If you agree that you continue the study, you will be followed for the duration of your stay in intensive care. You will receive adjuvant treatment by non-invasive ventilation or not in addition to the specific therapeutic management provided by the doctor.

Your state of health and laboratory parameters will be monitored throughout your stay in intensive care and in hospital.

WHAT ARE THE EXPECTED BENEFITS?

Regardless of the group, this study allows you to have close monitoring by the healthcare team and optimal management of the disease.
If you are included in the so-called “experimental group (non-invasive ventilation + high-flow nasal oxygen therapy or standard oxygenation), the advantage that you could expect by participating in this study is a reduction in the work of breathing and therefore a reduction in blood pressure. risk of onset of acute respiratory failure post extubation. Conversely, if you do not have treatment with non-invasive ventilation, you will have treatment with high-flow nasal oxygen therapy or standard oxygenation, both of which are used in routine practice.

WHAT ARE THE EXPECTED INCONVENIENTS?

Insofar as the devices used (standard oxygen therapy, high-flow nasal oxygen therapy or non-invasive ventilation) are already marketed, placed on the market and used in routine clinical practice, and insofar as these devices have shown very satisfactory results in In terms of oxygenation, the use of these devices does not seem to be able to generate a significant risk during this protocol. The main risk remains the discomfort associated with the device.

WHAT ARE THE POSSIBLE MEDICAL ALTERNATIVES?

Following extubation in intensive care, the need for reintubation following the onset of acute respiratory failure occurs in 10 to 20% of cases. In order to prevent this reintubation, we will study the systematic use of non-invasive ventilation, without waiting for acute respiratory failure to appear. Between the "preventive" sessions of non-invasive ventilation, oxygen will be administered in two possible ways: either in a so-called "standard" way through a mask, or with high-flow nasal oxygen therapy, which could also make it possible to reduce episodes of acute respiratory failure and therefore reintubation. If you do not want to continue participating, you will have "standard" oxygen at all times, which is the usual treatment following extubation of intensive care patients.

WHAT ARE YOUR RIGHTS?

Your doctor must provide you with all the necessary explanations concerning this research. If you wish to withdraw at any time, for whatever reason, you will continue to benefit from medical monitoring and this will not affect your future monitoring.
In accordance with the regulations, you must be a beneficiary of a social protection scheme in order to participate in research involving humans.

In accordance with Article L.1111-6 of the Public Health Code, you may designate a trusted person who may be a relative, a close friend or your treating physician and who will be consulted in the event that you are unable to express your wishes and receive the information necessary for this purpose. This person is accountable for your wishes. Her testimony prevails over any other testimony. This designation is made in writing and co-signed by the designated person. It may be revised and revoked at any time.
If you wish, your trusted person can accompany you in your steps and attend medical interviews in order to help you in your decisions.

As part of the research in which the Montpellier University Hospital offers you the opportunity to take part, your personal data will be processed in order to analyse the results of the research with regard to the objective of the research that has been presented to you.
The responsible of this treatment is the *Montpellier University Hospital.*

The study investigator and any other study personnel bound by professional secrecy and under the responsibility of the physician in charge of your treatment will collect medical data about you. This information, called "Personal Information", will be recorded on forms, called case report forms, provided by the sponsor. Only the information strictly necessary for the treatment and the purpose of the research will be collected on a secure database and then kept at the end of the research, under the responsibility of Dr Audrey DE JONG for 15 months.
In order to ensure the confidentiality of your personal information, neither your name nor any other information that would allow you to be directly identified will be entered in the observation notebook or in any other file that the study's medical investigator will provide to the research sponsor or to persons or companies acting on his behalf, in France or abroad.

This data will be identified by a code (inclusion number and initials). The code is used so that the study physician can identify you if necessary. This data may also be transmitted to the French health authorities under conditions that ensure its confidentiality.

In accordance with the provisions of the law on data processing, data files and individual liberties (law no. 78-17 of 6 January 1978 on data processing, data files and individual liberties as amended by law no. 2018-493 of 20 June 2018 on the protection of personal data) and the general regulations on data protection (EU regulation 2016/679), you have the right to access, rectify, delete or limit the information collected about you in the context of this processing.
In certain cases, you may also refuse the collection of your data and object to certain types of data processing being carried out. You also have the right to object to the transmission of data covered by professional secrecy that may be used in the course of such research and processing.
You may also have direct access, or through the intermediary of the doctor of your choice, to all your medical data pursuant to the provisions of Article L1111-7 of the Public Health Code.

You may withdraw your consent to the collection of your data for this processing at any time. Where applicable, in accordance with article L.1122-1-1 of the Public Health Code, the data concerning you that will have been collected prior to your withdrawal of consent may not be deleted and may continue to be processed under the conditions provided for by the research.

Finally, you may request that the personal information collected be provided to you or a third party in digital format (right of portability).

Your rights mentioned above are exercised with the doctor who is following you in the research and who knows your identity.

If you have any further questions about the collection or use of your personal information or the rights associated with this information, you can contact the Data Protection Officer of Montpellier University Hospital (Tel: 04 67 33 72 71) or the investigating physician at your centre, Dr. Samir Jaber.

If, despite the measures put in place by the sponsor, you feel that your rights are not being respected, you may file a complaint with the competent data protection supervisory authority in France, the Commission Nationale de l'Informatique et des Libertés (CNIL).

If the data controller wishes to further process your personal data for a purpose other than that for which your personal data were collected, you will be informed in advance about this other purpose, the length of time your data will be kept, and any other relevant information to ensure fair and transparent processing.

Searches mentioned in 1° of article L. 1121-1 relating to the products mentioned in article L. 5311-1 :

We inform you that you will be registered in the national file of persons who lend themselves to research provided for in Article L.1121-16 of the Public Health Code. You have the possibility to check with the Minister in charge of Health the accuracy of the data concerning you in this file and the destruction of the data at the end of the period provided for by law.

In accordance with the law n°2012-300 of 5 March 2012 relating to research involving the human person:

- this research has obtained a favourable opinion from the Committee for the Protection of Persons of name of the CPP (category 2)

- The promoter of this research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out a civil liability insurance policy with Newline Syndicate 1218 at Lloyd's. (Category 2)

- persons who have suffered harm as a result of participation in research involving humans may assert their rights before regional conciliation and medical injury compensation commissions

- When this search is completed, you will be kept personally informed of the overall results by your doctor as soon as they are available, if you wish.

After reading this information note, do not hesitate to ask your doctor any questions you may have. After a period of reflection, if you agree to participate in this research, you must complete and sign the consent to participate form. A copy of the complete document will be given to you.

Thank you.

EXTUB-OBESE Study

CONSENT FORM

Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol

EXTUB-OBESE Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Dr Audrey DE JONG*

I .....*(name, surname)* certify that I have read and understood the briefing note provided to me.

I had the opportunity to ask all the questions I wished to the Pr/Dr ..... *(name, surname)* who explained to me the nature, objectives, potential risks and constraints associated with my participation in this research.

I am aware of the possibility that I may interrupt my participation in this research at any time without having to justify my decision and I will do my best to inform the doctor who is following me in the research. This will of course not affect the quality of subsequent care.

I have been assured that the decisions that are necessary for my health will be taken at any time, in accordance with the current state of medical knowledge.

I am aware that this research has received a favourable opinion from the Committee for the Protection of Individuals (category 2) and has obtained compliance with the General Data Protection Regulations.

The promoter of the research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out civil liability insurance with Newline Syndicate 1218 at Lloyd's (Category 2).

I accept that the persons collaborating in this research or mandated by the promoter, as well as possibly the representative of the Health Authorities, have access to the information in the strictest respect of confidentiality.

I accept that the data recorded in the course of this research may be subject to computerised processing under the responsibility of the promoter.

I have noted that, in accordance with the provisions of the law relating to data processing, files and freedoms, I have the right to access, rectify, limit the processing of my data and make a complaint to the Commission Nationale de l'Informatique et des Libertés (CNIL): https://www.cnil.fr/. I also have the right to oppose the transmission of data covered by professional secrecy

Having had sufficient time for reflection before making my decision, I freely and voluntarily agree to participate in the research " Non-invasive ventilation vs oxygen therapy after extubation in patients with obesity in intensive care units: The multicentre randomised EXTUB-OBESE study protocol ".

I may at any time ask for further information from the doctor who proposed me to participate in this research, telephone number:

Done in.....the ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Patient signature :

Done in .....the ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Physician signature :

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.