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High-flow nasal oxygen therapy alone or with noninvasive ventilation in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure: the randomised multicentre controlled FLORALI-IM protocol

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Contributors

RC, J-PF and AWT, in collaboration with all authors and the REVA Network designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with RC.

All authors contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

The firm Fisher & Paykel provided the high-flow oxygen therapy equipment and masks for noninvasive ventilation to all the participating centres but has no other involvement in the study.

Competing interests

RC reports travel expense coverage to attend scientific meetings from Fisher & Paykel and MSD.

JPF reports travel expense coverage to attend scientific meetings and personal fees from Fisher & Paykel and SOS Oxygène.

SE reports consulting fees from Aerogen, La diffusion technique française, Baxter, Bayer, lecture fees from Aerogen, Fisher & Paykel, unrestricted research grants / research support from from Fisher & Paykel, Hamilton medical, Aerogen, La diffusion technique française.

Chr G reports travel expense coverage to attend scientific meetings, personal fees and logistic support from Fisher & Paykel, Resmed and Lowenstein Medical.

AWT reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel, Covidien, Maquet-Getinge, General Electric Healthcare.

SJ reports personal fees for lectures from Hamilton Medical and Nihon Kohden.

GG reports payment for lectures from Getinge, Draeger Medical, Pfizer, Fisher&Paykel, and travel/accommodation/congress registration support from Biotest and Getinge.

FP, NT, MD, GP, Cha G, DC, JB, AG, JD, DM, GL, JPQ, AH, JD, DB, EV, SN, GC, DT, MA, Cl G, DB, TL, AK, SR and report no conflict of interest.

Ethics approval

The first version of the study protocol has been approved by the central ethics committee (Ethics Committee Ouest III, Poitiers, France) with the registration number 2016-A00834-47 (23 March 2016).

Provenance and peer review

Not commissioned; externally peer reviewed.

ABSTRACT (271 words)

Introduction: Recent practice guidelines suggest applying noninvasive ventilation (NIV) as first-line therapy in management of immunocompromised patients admitted to intensive care unit (ICU) for acute hypoxemic respiratory failure. By pooling all randomised controlled trials, application of NIV is associated with decreased intubation and mortality rates as compared to standard oxygen. However, recent studies including large sample size trials have found similar outcomes with or without NIV or even deleterious effects of NIV in patients with acute hypoxemic respiratory failure. Therefore, given the uncertainty in the evidence, application of NIV is only a conditional recommendation.

All previous studies have compared NIV to standard oxygen and not to high-flow nasal oxygen therapy (HFOT). Several studies have found lower mortality rates using HFOT alone than using HFOT with NIV sessions in patients with de novo respiratory failure, and even in immunocompromised patients. We are hypothesizing that HFOT alone is more effective than HFOT with NIV sessions and reduces mortality of immunocompromised patients with acute hypoxemic respiratory failure.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing HFOT alone or with NIV in immunocompromised patients admitted to ICU for severe acute hypoxemic respiratory failure. Around 280 patients will be randomised with a 1:1 ratio in two groups. The primary outcome is the mortality rate at day 28 after enrolment. Secondary outcomes include the rate of intubation in each group, length of ICU and hospital stay, and mortality up to day 180.

Ethics and dissemination: The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT02978300

Keywords: immunosuppression, acute respiratory failure, noninvasive ventilation, high-flow nasal cannula oxygen therapy, clinical trial, mortality

Strengths and limitations of the study

- This trial is the first to compare high-flow nasal oxygen therapy (HFOT) alone versus HFOT with non-invasive ventilation (NIV) sessions for treatment of acute hypoxemic respiratory failure in immunocompromised patients admitted to ICU.
- This trial is empowered to compare mortality rates in patients with severe acute hypoxemic respiratory failure.
- Settings of each oxygenation technique will be protocolised to optimise their efficiency according to physiological studies.
- Limitation: The individual study assignments of the patients will not be masked. Given the nature of the two strategies under evaluation, a double-blind trial is not possible.

Word count: 3582

INTRODUCTION

Background and rationale

Acute hypoxemic respiratory failure is the leading cause of admission to intensive care units (ICU) in immunocompromised patients.[1] Intubation and subsequent invasive mechanical ventilation are needed in about two-thirds of cases and are associated with particularly high mortality reaching 50-70% of cases.[1–3] Therefore, it is crucial to assess the best strategy of oxygenation with the aim of avoiding the need for intubation in immunocompromised patients.

The recent European/American clinical practice guidelines have recommended noninvasive ventilation (NIV) as first-line therapy for management of acute hypoxemic respiratory failure in immunocompromised patients.[4] Indeed, by pooling all randomised controlled trials, NIV was associated with decreased intubation and mortality rates as compared to standard oxygen (**Table 1**).[5–8] However, the largest randomised controlled trial comparing NIV versus standard oxygen found no difference in intubation or mortality rates and, application of NIV was consequently only a conditional recommendation.[5]

All previous studies have compared NIV to standard oxygen and not versus high-flow nasal oxygen therapy (HFOT).[4] More recently, better outcomes have been reported with HFOT than with standard oxygen, and even as compared to HFOT with NIV in patients with acute hypoxemic respiratory failure, thereby suggesting potential deleterious effects of NIV.[9–11] NIV may be associated with harmful effects in *de novo* respiratory failure,[12] especially in patients generating strong inspiratory efforts and subsequent large tidal volumes due to high transpulmonary pressures.[13,14] It could be argued that NIV protocol was not protective enough, *i.e.* by applying low levels of pressure-support to avoid large tidal volumes that may worsen underlying lung injury,[15] by applying high levels of positive end-expiratory pressure (PEEP) to promote alveolar recruitment as is the case in patients invasively ventilated for acute respiratory distress syndrome (ARDS),[16,17] and by applying prolonged sessions of NIV to avoid derecruitment during NIV breakoffs .[18,19] Indeed, while most of these patients meet the clinical criteria for ARDS,[20] optimisation of ventilator settings during NIV could lead to better outcomes as it is the case in patients under invasive mechanical ventilation.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing HFOT alone or with optimised NIV sessions in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure. Our hypothesis is that HFOT alone may reduce mortality rate at day 28 as compared to HFOT with NIV, despite application of NIV with protective ventilator settings.

Primary objective

To compare the mortality rate at day 28 after inclusion between HFOT alone and HFOT with NIV in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure.

Secondary objectives

- To compare the rates of intubation, and of mortality in ICU, in hospital, at day 90 and at day 180 after inclusion between the 2 strategies.
- To compare length of stay in ICU, in hospital, and the number of ventilator-free days (invasive or noninvasive mechanical ventilation) within the 28 days following inclusion.
- To compare tolerance between the 2 strategies.

Trial design

The FLORALI-IM study is an investigator-initiated, prospective, multicentre, randomised, controlled, open trial comparing 2 strategies of oxygenation using HFOT alone or with NIV in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure. Patients will be randomly assigned to the HFOT alone group or HFOT with NIV group with a 1:1 ratio.

METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The FLORALI-IM study is taking place in 29 ICUs in France and 1 ICU in Italy.

Eligibility criteria

Inclusion criteria

Adult immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure are considered eligible.

Acute hypoxemic respiratory failure is defined by respiratory rate ≥ 25 breaths/min, and a PaO_2/FiO_2 ≤ 300 mm Hg while spontaneously breathing under standard oxygen with oxygen flow rate of at least 10 l/min, under HFOT, or under NIV. For patients under standard oxygen, FiO_2 is calculated according to the following formula: FiO_2 = 0.21 + 0.03 per supplemental litre of oxygen.[12]

Immunosuppression is defined by one of the following criteria[21]: hematologic malignancy (active or remitting for less than 5 years), allogenic stem cell transplantation in the last 5 years, active solid cancer, leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l induced by chemotherapy, solid organ transplantation, acquired immunodeficiency syndrome, systemic steroids ≥ 0.5 mg/kg/day of prednisone equivalent for at least 3 weeks, immunosuppressive or immunomodulatory drugs.

Exclusion criteria

Patients fulfilling one of the following criteria will not be included: $PaCO_2$ above 50 mm Hg, patients who could strongly benefit from NIV *i.e.* with underlying chronic lung disease, cardiogenic pulmonary oedema or postoperative patients; severe shock defined as vasopressor dose > 0.3 µg/kg/min of norepinephrine-equivalent to maintain systolic blood pressure > 90 mm Hg or with impaired consciousness with a Glasgow coma score ≤ 12; patients with urgent need for intubation or with do-not-intubate order at time of inclusion; or patients with contraindication to NIV according to the French consensus conference,[22] *i.e.* patient refusal, cardiorespiratory arrest, coma, non-drained pneumothorax, unresolved vomiting, upper airway obstruction, hematemesis, or severe facial trauma.

Intervention

Patients eligible for inclusion will be informed, asked for consent and then randomised within the first 6 hours after they meet inclusion criteria to be assigned to one of the 2 following groups: 1) The patients assigned to control group will receive HFOT with NIV sessions; 2) The patients assigned to interventional group will receive HFOT alone.

As NIV may be more effective in hematologic or neutropenic patients,[6] randomization will be stratified according to the existence of underlying hematologic malignancy, leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l induced by chemotherapy.

Interventional group: HFOT alone

Immediately after randomisation, patients assigned to the interventional group will be continuously treated by HFOT (Optiflow or AIRVO2, Fisher & Paykel, Auckland, New Zealand) with a flow of 60 l/min and FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$) through a heated humidifier (MR 850, Fisher & Paykel, Auckland, New Zealand) set to the 'intubation' position.

Control group: HFOT with NIV

Immediately after randomisation, NIV will be initiated with a first session of at least 4h until clinical improvement and then applied by sessions of at least 1h for a minimal duration of at least 12 hours a day. NIV will be carried out with a ventilator dedicated for NIV (ICU ventilator after activation of NIV mode or NIV bi-level ventilator) in pressure-support (PS) ventilatory mode with a minimal PS level of 5 cm H_2O targeting a tidal volume of 6 ml/kg of predicted body weight and avoiding tidal volumes exceeding 8 ml/kg, a PEEP level of at least 8 cm H_2O, and FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$). Between NIV sessions, HFOT will be delivered as in the interventional group.

Duration of treatment

In the 2 groups, strategies of oxygenation will be applied for a minimal duration of 48h. After that, continuation of the treatment will be decided according to patient respiratory status **(Figure 1)**.

Criteria for weaning oxygenation strategies

As there is no consensual method of weaning from HFOT or NIV, we propose a standardised weaning protocol to mitigate differences between centres. From 48h after enrolment, weaning from both oxygenation strategies will be assessed twice a day during the investigator's round.

In the HFOT alone group, HFOT will be stopped and switched to standard oxygen when respiratory rate is < 25 breaths/min and $SpO_2 \geq 92\%$ with $FiO_2 \leq 50\%$ and flow ≤ 50 L/min.

In the NIV group, NIV will be stopped first when respiratory rate is < 25 breaths/min and SpO_2 ≥ 92% with FiO_2 ≤ 50%, and then HFOT will be stopped and switched to standard oxygen as in the HFOT alone group.

At any time after weaning of oxygenation techniques, if respiratory rate is ≥ 25 breaths/min or SpO_2 < 92% HFOT or HFOT with NIV sessions will be resumed according to the randomisation group.

Prespecified intubation criteria

In order to avoid harmful effects of delayed intubation in patients treated with NIV [23,24] and HFOT, [25] intubation will be performed if at least one of the following criteria is fulfilled: neurological failure defined as agitation or altered consciousness defined as a Glasgow coma scale below 12 points, hemodynamic failure defined as the need for a dose of norepinephrine greater than 0.3 µg/kg/min of norepinephrine-equivalent to maintain systolic blood pressure greater than 90 mm Hg, persisting or worsening respiratory failure defined by the presence of at least 2 criteria among the following: respiratory rate > 40 /min, lack of improvement of high respiratory muscle workload, severe hypoxemia defined as a need for FiO_2 of 100% to maintain SpO_2 ≥ 92% or PaO_2/FiO_2 ≤ 100 mm Hg, and acidosis defined as pH < 7.35 units.

Outcomes

Primary outcome

The primary outcome is mortality at day 28 after randomization.

Secondary outcomes

Secondary outcome variables include the following:

1. Mortality in ICU, in hospital, at day 90 and at day 180,
2. Intubation at day 28 from randomization.
3. Length of stay in ICU and in hospital,
4. Number of ventilator-free days, and number of oxygenation techniques-free days within the 28 days following randomization,
5. Tolerance of oxygenation techniques.

Sample size

We determined that enrolment of 280 analysable patients would provide a power of 80% to show an absolute difference of 15% in the rate of mortality at day 28 after randomization between the control group using HFOT with NIV (mortality rate estimated of 35%) and the intervention group using HFOT alone (mortality rate estimated of 20%). As NIV may be more effective according to the type of immunosuppression, stratification will be performed in order to have the same number of patients with hematologic malignancy, leukopenia or neutropenia induced by chemotherapy in each group.

Estimated rates of mortality in the two groups

The estimated mortality rates in the two groups are based on the recent literature. Mortality rates at day 28 reported in patients treated with HFOT and NIV are particularly homogeneous: 37% in a retrospective monocentre study,[26] 38% in a post-hoc analysis of a randomized trial,[9] and 36% in our preliminary study.[10] A lower mortality rate (24%) has been reported in patients treated with NIV in a randomised trial.[5] However, this difference could be explained by the lower severity of respiratory failure at admission. According to our previous studies, we can estimate a mortality rate of 20% in the interventional group.[9,10] A recent trial reported a mortality rate of 36% in patients treated with HFOT alone.[27] However, a high proportion of patients died without prior intubation in the HFOT alone group (55 patients, 40%), *i.e.* with a do-not-intubate order, and the actual mortality rate was closer to 25% after exclusion of these patients.

Recruitment

Initial expected duration of patient enrolment is 2 years, starting in January 2017.

- End of 2015: grant award;
- 2016: approval by an independent ethics committee;
- 2017: inclusion of patients;
- 2019: end of inclusions, monitoring of participating centres and queries to investigators; overseeing by the steering committee at the REVA Network meetings; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;
- 2020-2021: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNEMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

A computer-generated randomization is performed with stratification according to centre and the type of immunosuppression (haematological malignancy or leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l vs. the others types of immunosuppression) in a 1:1 ratio and by blocks, using a centralized web-based management system (Clinfile). After randomization, the strategy assigned to the patient (HFOT alone or with NIV) will be initiated immediately.

Data collection and management

Data will be collected on an electronic-Case Report Form by a trained investigator or research assistant at each centre (**Figure 2**). At time of inclusion, the following data will be collected: informed consent, demographic characteristics, Charlson score, [28] vital signs, current oxygenation settings (oxygen flow under standard oxygen, FiO_2 and gas flow under HFOT, and FiO_2, pressure-support levels and PEEP under NIV), tolerance to oxygenation devices using a visual analogic scale, arterial blood gases and analysis of chest X-ray. Similar data and an evaluation of dyspnoea using a 5-point Likert scale will be recorded at H1, between H6 and H12, at H24 ± 6h, H48 ± 6h and H72 ± 6h after randomization. Duration of the first NIV session and total duration of NIV within the first 24h, between H24 and H48 and between H48 and H72 will be collected to ensure adherence to the protocol. The type of ventilator used for NIV and the NIV interface will be collected. For intubated patients, time and reason for intubation will be documented according to the above-mentioned criteria. Invasive ventilatory settings, arterial blood gases and chest X-ray will be recorded during the first 3 days following intubation. At day 28, vital status, need for intubation, total duration of invasive ventilation and of each oxygenation technique studied will be recorded. At ICU and hospital discharge, vital status and length of stay will be collected. At day 90 and day 180, vital status and Eastern Cooperative Oncology Group score will be recorded. [29]

As the absence of aetiology of acute respiratory failure could influence mortality, [30] investigators are strongly encouraged to have an active diagnostic strategy. Results of

the noninvasive diagnostic tests, bronchoalveolar lavage and chest CT-scan will be collected. [23]

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

Continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. The analysis will be performed on an intention-to-treat basis, including all patients who underwent randomisation. Deviations from the protocol will be described and analysed on a case-by-case basis after validation by a blind review committee.

No imputation for missing values will be done.

Analysis pertaining to the main criteria of evaluation

Mortality rates at day 28 after randomization will be compared between the 2 groups by means of a Chi^2 test. The analysis of this primary outcome will subsequently be completed by multivariate logistic regression after testing for interactions between treatment effect and strata.

The survival time will be described by means of Kaplan–Meier method and compared with a log-rank test at day 28. A Cox proportional-hazards model will be used to calculate hazard ratio with 95% confidence interval.

Logistic and Cox regression maximal models will include all the variables associated with mortality at day 28 with a p value <0.20 in the univariate analysis. The final model will be obtained by a backward-selection procedure and will include variables significantly associated with mortality at day 28 with a P value of less than 0.05.

Analysis pertaining to the secondary criteria of evaluation

Lengths of stay, number of ventilator-free days and number of oxygenation techniques-free days will be compared between the two treatment groups using the Student's t-Test (or Mann-Whitney test if necessary). Time to ICU death, time to hospital death or time to intubation will be described by means of Kaplan Meier method and compared between the two treatment groups with a logrank test. Efficacy and tolerance of oxygenation techniques will be compared between the 2 groups using Student's t-Test (or Mann-Whitney test) for quantitative variables and Chi^2 test for qualitative variables. Ventilator-free days at day 28 will be calculated as one point for each day between enrolment to day 28 that patients are both alive and free of mechanical ventilation.

Predetermined Subgroup Analysis

Randomization is stratified according to the type of immunosuppression in order to have the same number of patients with hematologic malignancy, leukopenia or neutropenia induced by chemotherapy in each group. A subgroup analysis will consequently be performed for the main and secondary criteria of evaluation in this subgroup of patients and in patients with other type of immunosuppression. Prior to adjustment, an interaction test will be carried out to detect heterogeneity of treatment effect according to the type of immunosuppression.

As benefits of HFOT may be influenced by baseline PaO_2/FiO_2, a subgroup analysis will be performed for the main and secondary criteria of evaluation in patients with a $PaO_2/FiO_2 \leq 200$ mm Hg at enrolment.

Data monitoring

An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centres on site to check adherence to the protocol and accuracy of the data recorded.

Patient and public involvement

Patients and public were not involved in the study

ETHICS AND DISSEMINATION

Consent or assent

Patients will be included after verification of the eligibility criteria and having provided an informed consent to the investigator according to the decision of the central ethics committee. For patients not able to provide informed consent, their next-of-kin will be contacted according to the same procedure. Patients will be informed as soon as possible by the investigator of their participation in the study and their consent to continue to participate in the study will be retrieved.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 25 years. The clean database file will be de-identified and kept for 25 years.

Declaration of interest

The FLORALI-IM study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2015 from an inter-regional hospital clinical research program ('Programme Hospitalier de Recherche Clinique Inter-Régional 2015'). The European research network REVA has endorsed the study project. The study is promoted by the University Hospital of Poitiers. The study promoter received a grant from AADAIRC and SOS oxygène. The firm Fisher & Paykel Healthcare provides high-flow oxygen therapy equipment and face masks for NIV to all the participating centres but has no other involvement in the study.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicize and explain the research to clinicians, commissioners and service users.

DISCUSSION

In immunocompromised patients, invasive ventilation is associated with particularly high mortality rates and application of NIV is currently recommended as a means of avoiding intubation.[4] Almost 20 years ago, two randomised controlled trials including a small sample of patients reported decreased intubation and mortality rates with NIV as compared to standard oxygen therapy.[6,7] By contrast, more recent studies including larger samples of patients found either similar outcomes or even an increased risk of mortality in patients treated with NIV compared to oxygen alone.[5,9]. In a large controlled trial including 376 immunocompromised patients, outcomes were similar between patients treated with NIV and those treated with oxygen therapy.[5] However, a high proportion of patients had mild respiratory failure, more than one-third of the patients in the control group received HFOT while those in the interventional group received short sessions of NIV, and all these factors together may have mitigated the difference between the 2 groups.[5] In a post-hoc analysis of a randomized controlled trial including 82 immunocompromised patients with severe acute hypoxemic respiratory failure, patients treated with HFOT alone had lower mortality than those treated with HFOT with NIV sessions.[9]

To explain the lack of effect or harmful effects of NIV, it could be argued that NIV was not carried out with optimal ventilator settings for patients of whom the majority met the clinical criteria for ARDS. Indeed, they had particularly large tidal volumes under NIV, which could be associated with an increased risk of mortality by potential worsening of pre-existing lung injury.[13–15,32,33] PEEP levels remained relatively low whereas the treatment represents a major adjustment in ARDS patients, and NIV was applied for a duration of only 8h in mean within the first 24 hours.[5,9] Another study has found that NIV performed with helmet may be more efficient than with face mask.[34] Interestingly, patients treated with helmet also received lower pressure-support levels and higher PEEP levels than those treated with facemask, thereby highlighting the potential impact of ventilatory settings on outcomes.[34] Consequently, we decided to apply a protective NIV protocol aimed at avoiding large tidal volumes, and applying prolonged sessions of NIV with high PEEP levels.

In a recent large randomized controlled trial including 776 immunocompromised patients, mortality rates at day 28 did not differ between patients treated with HFOT and those treated with standard oxygen.[27] However, 40% of the deceased patients in the HFOT group died without prior intubation and the high proportion of patients with do-not-intubate order may have mitigated the beneficial effects of HFOT.[27] By contrast,

several studies have reported promising results of HFOT alone versus standard oxygen or NIV in patients with *de novo* respiratory failure, even in immunocompromised patients.[9–12]

The FLORALI-IM trial has several strengths. First, this will be the first study comparing HFOT alone versus HFOT with NIV sessions in immunocompromised patients. Second, the study will include only severe patients with acute hypoxemic respiratory failure. Third, NIV will be optimized using low levels of pressure-support targeting a tidal volume between 6 and 8 ml/kg, PEEP levels at least 8 cm H_2O, and duration of NIV more than 12h a day during the first 48h.

In conclusion, the FLORALI-IM trial is an investigator-initiated randomised controlled trial empowered to test the hypothesis that HFOT alone may in comparison with HFOT and NIV decrease mortality rate at day 28 of immunocompromised patients admitted to ICU for acute respiratory failure. Innovative aspects include the 2 groups of treatment in this clinical setting and the optimised protocol to carry out NIV and HFOT.

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Table 1. Characteristics and outcomes of previous trials comparing noninvasive ventilation to oxygen therapy in immunocompromised patients. Outcomes of patients in the control arm are displayed in italics.

Authors	Year	Setting	N=	Arms	Intubation rate	In-ICU mortality rate
Antonelli *et al.*	2000	ICU, monocentre	*20*	*O_2*	*70%*	*50%*
			20	NIV	20%	20%
Hilbert *et al.*	2001	ICU, monocentre	*26*	*O_2*	*77%*	*69%*
			26	NIV	46%	38%
Lemiale *et al.*	2015	ICU, multicentre	*183*	*O_2*	*45%*	*25%*
			191	NIV	38%	21%
Squadrone *et al.*	2010	Ward, monocentre	*20*	*O_2*	*40%*	*75%*[1]
			20	CPAP	10%	15%[1]
Frat *et al.*[2]	2015	ICU, multicentre	*30*	*O_2*	*43%*	*20%*
			26	NIV	65%	42%
			26	HFOT	31%	15%

[1] Hospital mortality (ICU mortality was not indicated in the article); [2] post-hoc analysis of a randomised trial.

CPAP: continuous positive airway pressure; HFOT: high-flow nasal cannula oxygen therapy; O_2: oxygen therapy; NIV: noninvasive ventilation

FIGURE LEGENDS

Figure 1: Flow chart of the patients and study design.

Figure 2: Flow chart of timing collection of different variables.

Abbreviations:

FiO_2: Fraction of inspired oxygen

HFOT: High flow nasal cannula oxygen therapy

ICU: Intensive care unit

NIV: Noninvasive ventilation

PaO_2: Partial pressure of arterial oxygen

$PaCO_2$: Partial pressure of arterial carbon dioxide

SpO_2: Peripheral capillary oxygen saturation

Authors Contributions

RC, J-PF and AWT, in collaboration with all authors and the REVA Network designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with RC

All authors contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

The study was funded by the 'Programme Hospitalier de Recherche Clinique Inter-régional 2015' of the French Ministry of Health. The study promoter is the University Hospital of Poitiers, Poitiers, France.

The study promoter received financial grants from SOS Oxygène and AADAIRC.

Disclaimer

The firm Fisher & Paykel provides the high-flow oxygen therapy equipment and the noninvasive masks to all the participating centres but has no other involvement in the study.

Competing interests

RC reports travel expense coverage to attend scientific meetings from Fisher & Paykel and MSD.

JPF reports travel expense coverage to attend scientific meetings and personal fees from Fisher & Paykel and SOS Oxygène.

SE reports consulting fees from Aerogen, La diffusion technique française, Baxter, Bayer, lecture fees from Aerogen, Fisher & Paykel, unrestricted research grants / research support from from Fisher & Paykel, Hamilton medical, Aerogen, La diffusion technique française.

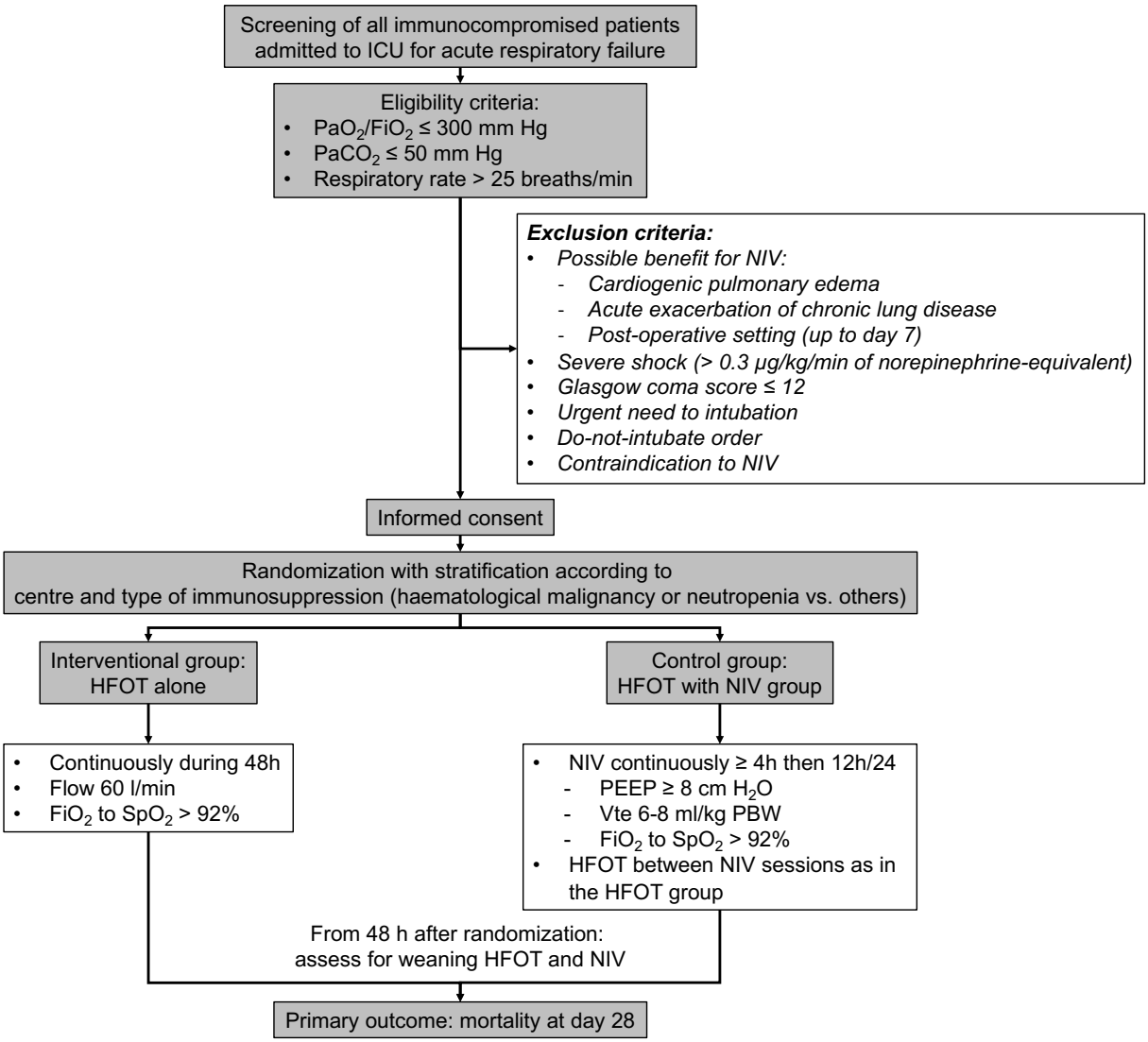
Chr G reports travel expense coverage to attend scientific meetings, personal fees and logistic support from Fisher & Paykel, Resmed and Lowenstein Medical.

AWT reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel, Covidien, Maquet-Getinge, General Electric Healthcare.

SJ reports personal fees for lectures from Hamilton Medical and Nihon Kohden.
GG reports payment for lectures from Getinge, Draeger Medical, Pfizer, Fisher&Paykel, and travel/accommodation/congress registration support from Biotest and Getinge.
FP, NT, MD, GP, Cha G, DC, JB, AG, JD, DM, GL, JPQ, AH, JD, DB, EV, SN, GC, DT, MA, Cl G, DB, TL, AK, SR and report no conflict of interest.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ouest III, Poitiers, France) with the registration number 2016-A00834-47 (23 March 2016).



HFOT: high flow nasal cannula oxygen therapy; ICU: intensive care unit; NIV: noninvasive ventilation; PBW: predicted body weight; PEEP: positive end-expiratory pressure; Vte: expired tidal volume

Actions	Inclusion =H0	H1	H6-H12	H24 ± 6	H48 ± 6	H72 ± 6	Intubation	ICU and hospital discharge	D28 D90 D180
Informed consent	X								
Inclusion /exclusion criteria	X								
Randomization and stratification (type of immunosuppression)	X								
Clinical characteristics									
Height, weight, body temperature	X								
Vital signs	X	X	X	X	X	X	X		
Tolerance (dyspnea and comfort evaluation)	X	X	X	X	X	X	X		
HFOT or NIV settings	X	X	X	X	X	X			
Supplementary analysis									
Arterial blood gases	X	X	X	X	X	X	X		
Chest X-ray	X						X		
SOFA score	X		X	X	X	X	X		
Daily duration of HFOT and NIV				X	X	X			
Status (alive/dead) and cause of death								X	X

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Page	Section/item	Item No	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
3		2b	All items from the World Health Organization Trial Registration Data Set
5	Protocol version	3	Date and version identifier
26	Funding	4	Sources and types of financial, material, and other support
1-4	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
4		5b	Name and contact information for the trial sponsor
4		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
NA		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)
	Introduction		
8	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
8		6b	Explanation for choice of comparators
9	Objectives	7	Specific objectives or hypotheses
9	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)

	Methods: Participants, interventions, and outcomes		
9	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
9-10	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)
10	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
11-12		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)
12		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
12	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
13	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)
12-13	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
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
14	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

14	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
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
7	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
14	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
14		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
16	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
15-16	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
16		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
15		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)
	Methods: Monitoring		
16	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

NA		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
16	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
16	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
5	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
17	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)
16	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
17	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
17	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
17	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
NA	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
17	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
26		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

App	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
NA	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

*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.

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High-flow nasal oxygen therapy alone or with noninvasive ventilation in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure: the randomised multicentre controlled FLORALI-IM protocol

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SJ reports personal fees for lectures from Hamilton Medical and Nihon Kohden.

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FP, NT, MD, GP, Cha G, DC, JB, AG, JD, DM, GL, JPQ, AH, JD, DB, EV, SN, GC, DT, MA, Cl G, DB, TL, AK, SR and report no conflict of interest.

Ethics approval

The first version of the study protocol has been approved by the central ethics committee (Ethics Committee Ouest III, Poitiers, France) with the registration number 2016-A00834-47 (23 March 2016).

Provenance and peer review

Not commissioned; externally peer reviewed.

ABSTRACT (249 words)

Introduction: Noninvasive ventilation (NIV) is recommended as first-line therapy in respiratory failure of critically ill immunocompromised patients as it can decrease intubation and mortality rates as compared to standard oxygen. However, its recommendation is only conditional. Indeed, the use of NIV in this setting has been challenged recently based on results of trials finding similar outcomes with or without NIV or even deleterious effects of NIV. To date, NIV has been compared to standard oxygen but not to high-flow nasal oxygen therapy (HFOT) in immunocompromised patients. Several studies have found lower mortality rates using HFOT alone than when using HFOT with NIV sessions in patients with de novo respiratory failure, and even in immunocompromised patients. We are hypothesizing that HFOT alone is more effective than HFOT with NIV sessions and reduces mortality of immunocompromised patients with acute hypoxemic respiratory failure.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing HFOT alone or with NIV in immunocompromised patients admitted to ICU for severe acute hypoxemic respiratory failure. Around 280 patients will be randomised with a 1:1 ratio in two groups. The primary outcome is the mortality rate at day 28 after inclusion. Secondary outcomes include the rate of intubation in each group, length of ICU and hospital stay, and mortality up to day 180.

Ethics and dissemination: The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT02978300

Keywords: immunosuppression, acute respiratory failure, noninvasive ventilation, high-flow nasal cannula oxygen therapy, clinical trial, mortality

Strengths and limitations of the study

- This trial is the first to compare high-flow nasal oxygen therapy (HFOT) alone versus HFOT with non-invasive ventilation (NIV) sessions for treatment of acute hypoxemic respiratory failure in immunocompromised patients admitted to ICU.
- The settings of the oxygenation techniques compared have been protocolised based on physiologic studies in order to optimise their efficiency (improvement in oxygenation, decrease in work of breathing, limitation of patient self-inflicted lung injury).
- The sample size of this trial has been designed to have the power to detect a difference in mortality rates of patients with severe acute hypoxemic respiratory failure.
- Limitation: The individual study assignments of the patients will not be masked. Given the nature of the two strategies under evaluation, a double-blind trial is not possible.

Word count: 3582

INTRODUCTION

Background and rationale

Acute hypoxemic respiratory failure is the leading cause of admission to intensive care units (ICU) in immunocompromised patients.[1] Intubation and subsequent invasive mechanical ventilation are needed in about two-thirds of cases and are associated with particularly high mortality reaching 50-70% of cases.[1–3] Therefore, it is crucial to assess the best strategy of oxygenation with the aim of avoiding the need for intubation in immunocompromised patients.

According to a large international cohort study, noninvasive ventilation (NIV) is used in up to 21% of cases in this setting.[4] It is worth noting that recent European/American clinical practice guidelines have recommended NIV as first-line therapy for management of acute hypoxemic respiratory failure in immunocompromised patients.[5] Indeed, by pooling all randomised controlled trials, NIV has been associated with decreased intubation and mortality rates as compared to standard oxygen (**Table 1**).[6–9] However, the largest randomised controlled trial comparing NIV versus standard oxygen found no difference in intubation or mortality rates and application of NIV was consequently only a conditional recommendation.[6]

All previous studies have compared NIV to standard oxygen and not versus high-flow nasal oxygen therapy (HFOT).[5] Recently, better outcomes have been reported with HFOT than with standard oxygen, and even as compared to HFOT with NIV in patients with acute hypoxemic respiratory failure.[10–12] However, the design of these studies (retrospective monocentre or post-hoc) excludes any definite conclusion on the best treatment option for immunocompromised critically ill.[10,11,13] Therefore, there is an urgent need for a dedicated trial designed to compare NIV to HFOT in immunocompromised critically ill patients taking into account the suggested deleterious effects of NIV.[10,11] Indeed, NIV may be associated with harmful effects in *de novo* respiratory failure,[14] especially in patients generating strong inspiratory efforts and subsequent large tidal volumes due to high transpulmonary pressures.[15,16] It could be argued that NIV protocol had not been protective enough, *i.e.* by applying low levels of pressure-support to avoid large tidal volumes that may worsen underlying lung injury,[17] by applying high levels of positive end-expiratory pressure (PEEP) to promote alveolar recruitment as is the case in patients invasively ventilated for acute respiratory

distress syndrome (ARDS),[18,19] and by applying prolonged sessions of NIV to avoid derecruitment during NIV breakoffs .[20,21] Indeed, while most of these patients meet the clinical criteria for ARDS,[22] optimisation of ventilator settings during NIV could lead to better outcomes, as is the case in patients under invasive mechanical ventilation.

Objectives

We are aiming to conduct a prospective multicentre randomised controlled trial comparing HFOT alone or with optimised NIV sessions in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure. Our hypothesis is that HFOT alone may reduce mortality rate at day 28 as compared to HFOT with NIV, despite application of NIV with protective ventilator settings.

Primary objective

To compare the mortality rate at day 28 after inclusion between HFOT alone and HFOT with NIV in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure.

Secondary objectives

- To compare the rates of intubation, and of mortality in ICU, in hospital, at day 90 and at day 180 after inclusion between the 2 strategies.
- To compare length of stay in ICU, in hospital, and number of ventilator-free days (invasive or noninvasive mechanical ventilation) within the 28 days following inclusion.
- To compare tolerance between the 2 strategies.

Trial design

The FLORALI-IM study is an investigator-initiated, prospective, multicentre, randomised, controlled, open trial comparing 2 strategies of oxygenation using HFOT alone or with NIV in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure. Patients will be randomly assigned to the HFOT alone group or the HFOT with NIV group with a 1:1 ratio.

METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The FLORALI-IM study is taking place in 29 ICUs in France and 1 ICU in Italy.

Eligibility criteria

Inclusion criteria

Adult immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure are considered eligible.

Acute hypoxemic respiratory failure is defined by respiratory rate ≥ 25 breaths/min, and PaO_2/FiO_2 ≤ 300 mm Hg while spontaneously breathing under standard oxygen with oxygen flow rate of at least 10 l/min, under HFOT, or under NIV. For patients under standard oxygen, FiO_2 is calculated according to the following formula: FiO_2 = 0.21 + 0.03 per supplemental litre of oxygen.[14]

Immunosuppression is defined by one of the following criteria: hematologic malignancy (active or remitting for less than 5 years), allogenic stem cell transplantation within the last 5 years, active solid cancer, leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l induced by chemotherapy, solid organ transplantation, acquired immunodeficiency syndrome, systemic steroids ≥ 0.5 mg/kg/day of prednisone equivalent for at least 3 weeks, immunosuppressive or immunomodulatory drugs.[23]

Exclusion criteria

Patients fulfilling one of the following criteria will not be included: $PaCO_2$ above 50 mm Hg, patients who could strongly benefit from NIV *i.e.* with underlying chronic lung disease, cardiogenic pulmonary oedema or postoperative patients; severe shock defined as vasopressor dose > 0.3 µg/kg/min of norepinephrine-equivalent to maintain systolic blood pressure > 90 mm Hg or with impaired consciousness with a Glasgow coma score ≤ 12; patients with urgent need for intubation *i.e.* respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, severe hypoxemia defined as SpO_2 lower than 90% despite maximal oxygen support; patients with do-not-intubate order at time of inclusion; or patients with contraindication to NIV according to the French consensus conference,[24] *i.e.* patient refusal, cardiorespiratory arrest, coma, non-drained pneumothorax, unresolved vomiting, upper airway obstruction, hematemesis, or severe facial trauma.

Intervention

Patients eligible for inclusion will be informed, asked for consent, then randomised within the first 6 hours after they meet inclusion criteria, and assigned to one of the 2 following groups: 1) The patients assigned to control group will receive HFOT with NIV sessions; 2) The patients assigned to interventional group will receive HFOT alone.
The purpose of this 6-hour time frame is to avoid the possibly harmful delayed initiation of oxygenation strategies. As NIV may be more effective in hematologic or neutropenic patients,[7] randomization will be stratified according to the existence of underlying hematologic malignancy, leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l induced by chemotherapy.

Interventional group: HFOT alone

Immediately after randomisation, patients assigned to the interventional group will be continuously treated by HFOT (Optiflow or AIRVO2, Fisher & Paykel, Auckland, New Zealand) with a flow of 60 l/min and FiO_2 adjusted to obtain adequate oxygenation (SpO_2 ≥ 92%) through a heated humidifier (MR 850, Fisher & Paykel, Auckland, New Zealand) set to the 'intubation' position. For patients experiencing HFOT intolerance due to high flow levels despite reinsurance, flow will be decreased to the maximal tolerated level.

Control group: HFOT with NIV

Immediately after randomisation, NIV will be initiated with a first session of at least 4h until clinical improvement (assessed by the attending physician) and then applied by sessions of at least 1h for a minimal duration of at least 12 hours a day. NIV will be carried out with a ventilator dedicated for NIV (ICU ventilator after activation of NIV mode or NIV bi-level ventilator)[25] in pressure-support (PS) ventilatory mode with a minimal PS level of 5 cm H_2O targeting a tidal volume of 6 ml/kg of predicted body weight and avoiding tidal volumes exceeding 8 ml/kg, a PEEP level of at least 8 cm H_2O, and FiO_2 adjusted to obtain adequate oxygenation (SpO_2 ≥ 92%). Between NIV sessions, HFOT will be delivered as in the interventional group. For patients experiencing NIV intolerance despite reinsurance, physicians will be encouraged to modify NIV settings (level of pressure-support and PEEP, minimizing leaks, adjustment of inspiratory trigger and cycling, interface switch) to improve NIV tolerance.

Duration of treatment

In the 2 groups, strategies of oxygenation will be applied for a minimal duration of 48h. After that, continuation of the treatment will be decided according to patient respiratory status **(Figure 1)**.

Criteria for weaning oxygenation strategies

As there is no consensual method of weaning from HFOT or NIV, we propose a standardised weaning protocol to mitigate differences between centres. From 48h after inclusion, weaning from both oxygenation strategies will be assessed twice a day during the investigator's round.

In the HFOT alone group, HFOT will be stopped and switched to standard oxygen when respiratory rate is < 25 breaths/min and SpO_2 ≥ 92% with FiO_2 ≤ 50% and flow ≤ 50 L/min.

In the NIV group, NIV will be stopped first when respiratory rate is < 25 breaths/min and SpO_2 ≥ 92% with FiO_2 ≤ 50%, and then HFOT will be stopped and switched to standard oxygen as in the HFOT alone group.

At any time after weaning of oxygenation techniques, if respiratory rate is ≥ 25 breaths/min or SpO_2 < 92% HFOT or HFOT with NIV sessions will be resumed according to randomisation group.

Prespecified intubation criteria

In order to avoid harmful effects of delayed intubation in patients treated with NIV[26,27] and HFOT,[28] intubation will be performed if at least one of the following criteria is fulfilled: neurological failure defined as agitation or altered consciousness defined as a Glasgow coma scale below 12 points, hemodynamic failure defined as the need for a dose of norepinephrine greater than 0.3 µg/kg/min of norepinephrine-equivalent to maintain systolic blood pressure greater than 90 mm Hg, persisting or worsening respiratory failure defined by the presence of at least 2 criteria among the following: respiratory rate > 40 /min, lack of improvement of high respiratory muscle workload, severe hypoxemia defined as a need for FiO_2 of 100% to maintain SpO_2 ≥ 92% or PaO_2/FiO_2 ≤ 100 mm Hg, and acidosis defined as pH < 7.35 units.

Outcomes

Primary outcome

The primary outcome is mortality at day 28 after randomization.

Secondary outcomes

Secondary outcome variables include the following:

1. Mortality in ICU, in hospital, at day 90 and at day 180,
2. Intubation at day 28 from randomization.
3. Length of stay in ICU and in hospital,
4. Number of ventilator-free days, and number of oxygenation techniques-free days within the 28 days following randomization,
5. Tolerance of oxygenation techniques.

Sample size

We determined that inclusion of 280 analysable patients would provide a power of 80% to highlight an absolute difference of 15% in rate of mortality at day 28 after randomization between the control group using HFOT with NIV (mortality rate estimated of 35%) and the intervention group using HFOT alone (mortality rate estimated of 20%). As NIV may be more effective according to type of immunosuppression, stratification will be performed in order to have the same number of patients with hematologic malignancy, leukopenia or neutropenia induced by chemotherapy in each group.

Estimated rates of mortality in the two groups

The estimated mortality rates in the two groups are based on the recent literature. Mortality rates at day 28 reported in patients treated with HFOT and NIV are particularly homogeneous: 37% in a retrospective monocentre study,[13] 38% in a post-hoc analysis of a randomized trial,[10] and 36% in our preliminary study.[11] A lower mortality rate (24%) has been reported in patients treated with NIV in a randomised trial.[6] However, this difference could be explained by the lower severity of respiratory failure at admission. According to our previous studies, we can estimate a mortality rate of 20% in the interventional group.[10,11] A recent trial reported a mortality rate of 36% in patients treated with HFOT alone.[29] However, a high proportion of patients died without prior intubation in the HFOT alone group (55 patients, 40%), *i.e.* with a do-not-intubate order, and the actual mortality rate was closer to 25% after exclusion of these patients.

Recruitment

Initial expected duration of patient inclusion is 2 years, starting in January 2017.

- End of 2015: grant award;
- 2016: approval by an independent ethics committee;
- 2017: inclusion of patients;
- 2019: end of inclusions, monitoring of participating centres and queries to investigators; overseeing by the steering committee at the REVA Network meetings; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;
- 2020-2021: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNEMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

A computer-generated randomization is performed with stratification according to centre and the type of immunosuppression (haematological malignancy or leukopenia < 1 G/l or neutropenia ≤ 0.5 G/l vs. the other types of immunosuppression) in a 1:1 ratio and by blocks, using a centralized web-based management system (Clinfile). After randomization, the strategy assigned to the patient (HFOT alone or with NIV) will be initiated immediately.

Data collection and management

Data will be collected on an electronic-Case Report Form by a trained investigator or research assistant at each centre (**Figure 2**). At time of inclusion, the following data will be collected: informed consent, demographic characteristics, Charlson score, [28] vital signs, current oxygenation settings (oxygen flow under standard oxygen, FiO_2 and gas flow under HFOT, and FiO_2, pressure-support levels and PEEP under NIV), tolerance to oxygenation devices using a visual analogic scale, arterial blood gases and analysis of chest X-ray. Similar data and an evaluation of dyspnoea using a 5-point Likert scale will be recorded at H1, between H6 and H12, at H24 ± 6h, H48 ± 6h and H72 ± 6h after randomization. Duration of the first NIV session and total duration of NIV within the first 24h, between H24 and H48 and between H48 and H72 will be

collected to ensure adherence to the protocol. The type of ventilator used for NIV and the NIV interface will be noted. For intubated patients, time and reason for intubation will be documented according to the above-mentioned criteria. Invasive ventilatory settings, arterial blood gases and chest X-ray will be recorded during the first 3 days following intubation. At day 28, vital status, need for intubation, total duration of invasive ventilation and of each oxygenation technique studied will be recorded. At ICU and hospital discharge, vital status and length of stay will be noted. At day 90 and day 180, vital status and Eastern Cooperative Oncology Group score will be recorded.[30]

As the absence of aetiology of acute respiratory failure could influence mortality,[31] investigators are strongly encouraged to have an active diagnostic strategy. Results of the noninvasive diagnostic tests, bronchoalveolar lavage and chest CT-scan will be collected. [32]

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

Continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges or mean and standard deviation), while indicating the number of missing data. Category variables will be presented in the form of absolute frequency and percentage in each modality. The analysis will be performed on an intention-to-treat basis, including all patients having undergone randomisation. Deviations from the protocol will be described and analysed on a case-by-case basis after validation by a blind review committee.

No imputation for missing values will be carried out.

Analysis pertaining to the main criteria of evaluation

Mortality rates at day 28 after randomization will be compared between the 2 groups by means of a Chi^2 test. Analysis of this primary outcome will subsequently be completed by multivariate logistic regression after testing for interactions between treatment effect and strata. Survival time will be described by means of Kaplan–Meier

method and compared with a log-rank test at day 28. A Cox proportional-hazards model will be used to calculate hazard ratio with 95% confidence interval.

Logistic and Cox regression maximal models will include all the variables associated with mortality at day 28 with a p value <0.20 in the univariate analysis. The final model will be obtained by a backward-selection procedure and will include variables significantly associated with mortality at day 28 with a P value of less than 0.05.

Analysis pertaining to the secondary criteria of evaluation

Length of stay, number of ventilator-free days and number of oxygenation technique-free days will be compared between the two treatment groups using the Student's t-Test (or Mann-Whitney test if necessary). Time to ICU death, time to hospital death or time to intubation will be described by means of the Kaplan Meier method and compared between the two treatment groups with a logrank test. Efficacy and tolerance of oxygenation techniques will be compared between the 2 groups using Student's t-Test (or Mann-Whitney test) for quantitative variables and Chi^2 test for qualitative variables. Ventilator-free days at day 28 will be calculated as one point for each day between inclusion to day 28 that patients are both alive and free of mechanical ventilation.

Per-protocol analysis

The proportion of patients treated according to the prespecified intervention goals will be calculated for each randomisation group. According to their sample size, their outcomes will be compared using the same methods as in the intention-to-treat analysis.

Predetermined Subgroup Analysis

Randomization is stratified according to type of immunosuppression in order to have the same number of patients with hematologic malignancy, leukopenia or neutropenia induced by chemotherapy in each group. A subgroup analysis will consequently be performed for the main and secondary criteria of evaluation in this subgroup of patients and in patients with another type of immunosuppression. Prior to adjustment, an interaction test will be carried out to detect heterogeneity of treatment effect according to type of immunosuppression.

As benefits of HFOT may be influenced by baseline PaO_2/FiO_2, a subgroup analysis will be performed for the main and secondary criteria of evaluation in patients with $PaO_2/FiO_2 \leq 200$ mm Hg at inclusion.

Subgroup analysis will be performed according to:

- The cause of respiratory failure as it may influence outcomes; [31]
- The type of NIV interface in the control group as it may influence outcomes; [33]
- The existence of protocol violations during the first 48 hours after inclusion.

Ancillary study

Data on nutrition practice in patients with acute respiratory failure is scarce.[34] In voluntary participating centres, we have planned to collect nutrition practice. Therefore, in an ancillary study, we will describe daily nutritional intake from inclusion to day 28 or intubation or ICU discharge or death, type of nutrition, amount of calories intake, existence of complications related to nutrition and the reason for maintaining patient fasting.

Data monitoring

An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centres on site to check adherence to the protocol and accuracy of the data recorded.

Patient and public involvement

Patients and public were not involved in the study

Study status

- Current status: the last patient was included on March 4th 2019;
- Expected date of complete data collection: mid-September 2019 (6-month follow-up of the last patient included);
- Expected date of the end of monitoring of participating centres: December 2019
- Expected starting date of data analysis: 1st trimester 2020

ETHICS AND DISSEMINATION

Consent or assent

Patients will be included after verification of the eligibility criteria and having provided an informed consent to the investigator according to the decision of the central ethics committee. For patients not able to provide informed consent, their next-of-kin will be contacted according to the same procedure. Patients will be informed as soon as possible by the investigator of their participation in the study and their consent to continue to participate in the study will be retrieved.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 25 years. The clean database file will be de-identified and kept for 25 years.

Declaration of interest

The FLORALI-IM study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2015 from an inter-regional hospital clinical research program ('Programme Hospitalier de Recherche Clinique Inter-Régional 2015'). The European research network REVA has endorsed the study project. The study is promoted by the University Hospital of Poitiers. The study promoter has received a grant from AADAIRC and SOS oxygène. Fisher & Paykel Healthcare provides high-flow oxygen therapy equipment and face masks for NIV to all the participating centres but has no other involvement in the study.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicize and explain the research to clinicians, commissioners and service users.

DISCUSSION

In immunocompromised patients, invasive ventilation is associated with particularly high mortality rates and application of NIV is currently recommended as a means of avoiding intubation.[5] Almost 20 years ago, two randomised controlled trials including a small sample of patients reported decreased intubation and mortality rates with NIV as compared to standard oxygen therapy.[7,8] By contrast, more recent studies including larger samples of patients have found either similar outcomes or even an increased risk of mortality in patients treated with NIV compared to oxygen alone.[6,10]. In a large controlled trial including 376 immunocompromised patients, outcomes were similar between patients treated with NIV and those treated with oxygen therapy.[6] However, a high proportion of patients had mild respiratory failure, more than one-third of the patients in the control group received HFOT while those in the interventional group received short sessions of NIV, and all these factors together may have mitigated the difference between the 2 groups.[6] In a post-hoc analysis of a randomized controlled trial including 82 immunocompromised patients with severe acute hypoxemic respiratory failure, patients treated with HFOT alone had lower mortality than those treated with HFOT with NIV sessions.[10]

To explain the lack of effect or harmful effects of NIV, it could be argued that NIV was not carried out with optimal ventilator settings for patients of whom the majority met the clinical criteria for ARDS. Indeed, they had particularly large tidal volumes under NIV, which could be associated with increased risk of mortality by potential worsening of pre-existing lung injury.[15–17,35,36] PEEP levels remained relatively low whereas the treatment represents a major adjustment in ARDS patients, and NIV was applied for a duration of only 8h in mean within the first 24 hours.[6,10] Another study has found that NIV performed with helmet may be more efficient than with face mask.[33] Interestingly, patients treated with helmet also received lower pressure-support levels and higher PEEP levels than those treated with facemask, thereby highlighting the potential impact of ventilatory settings on outcomes.[33] Consequently, we decided to apply a protective NIV protocol aimed at avoiding large tidal volumes, and applying prolonged sessions of NIV with high PEEP levels.

In a recent large randomized controlled trial including 776 immunocompromised patients, mortality rates at day 28 did not differ between patients treated with HFOT and those treated with standard oxygen.[29] However, 40% of the deceased patients in the HFOT group died without prior intubation and the high proportion of patients with

do-not-intubate order may have mitigated the beneficial effects of HFOT.[29] By contrast, several studies have reported promising results of HFOT alone versus standard oxygen or NIV in patients with *de novo* respiratory failure, even in immunocompromised patients.[10–12,14]

The FLORALI-IM trial has several strengths. First, it will be the first study comparing HFOT alone versus HFOT with NIV sessions in immunocompromised patients. Second, the study will include only severe patients with acute hypoxemic respiratory failure. Third, NIV will be optimized using low levels of pressure-support targeting a tidal volume between 6 and 8 ml/kg, PEEP levels of at least 8 cm H_2O, and duration of NIV more than 12h a day during the first 48h.

In conclusion, the FLORALI-IM trial is an investigator-initiated randomised controlled trial empowered to test the hypothesis that HFOT alone may in comparison with HFOT and NIV decrease mortality rate at day 28 of immunocompromised patients admitted to ICU for acute respiratory failure. Innovative aspects include the 2 groups of treatment in this clinical setting and the optimised protocol to carry out NIV and HFOT.

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Table 1. Characteristics and outcomes of previous trials comparing noninvasive ventilation to oxygen therapy in immunocompromised patients. Outcomes of patients in the control arm are displayed in italics.

Authors	Year	Setting	N=	Arms	Intubation rate	In-ICU mortality rate
Antonelli *et al.*	2000	ICU, monocentre	*20*	*O_2*	*70%*	*50%*
			20	NIV	20%	20%
Hilbert *et al.*	2001	ICU, monocentre	*26*	*O_2*	*77%*	*69%*
			26	NIV	46%	38%
Lemiale *et al.*	2015	ICU, multicentre	*183*	*O_2*	*45%*	*25%*
			191	NIV	38%	21%
Squadrone *et al.*	2010	Ward, monocentre	*20*	*O_2*	*40%*	*75%*[1]
			20	CPAP	10%	15%[1]
Frat *et al.*[2]	2015	ICU, multicentre	*30*	*O_2*	*43%*	*20%*
			26	NIV	65%	42%
			26	HFOT	31%	15%

[1] Hospital mortality (ICU mortality was not indicated in the article); [2] post-hoc analysis of a randomised trial.

CPAP: continuous positive airway pressure; HFOT: high-flow nasal cannula oxygen therapy; O_2: oxygen therapy; NIV: noninvasive ventilation

FIGURE LEGENDS

Figure 1: Flow chart of the patients and study design.

Figure 2: Flow chart of timing in collection of different variables.

Abbreviations:

FiO_2: Fraction of inspired oxygen

HFOT: High flow nasal cannula oxygen therapy

ICU: Intensive care unit

NIV: Noninvasive ventilation

PaO_2: Partial pressure of arterial oxygen

$PaCO_2$: Partial pressure of arterial carbon dioxide

SpO_2: Peripheral capillary oxygen saturation

Author Contributions

Remi Coudroy, Jean-Pierre Frat and Arnaud W Thille, in collaboration with Stephan Ehrmann, Frédéric Pène, Nicolas Terzi, Maxens Decavèle, Gwenaël Prat, Charlotte Garret, Damien Contou, Jeremy Bourenne ,Arnaud Gacouin, Christophe Girault, Jean Dellamonica, Dominique Malacrino, Guylaine Labro, Jean-Pierre Quenot, Alexandre Herbland, Sébastien Jochmans, Jérôme Devaquet, Dalila Benzekri, Emmanuel Vivier, Saad Nseir, Gwenhaël Colin, Didier Thevenin, Giacomo Grasselli, Mona Assefi, Claude Guérin, David Bougon, Thierry Lherm, Achille Kouatchet, Stéphanie Ragot and the REVA Network designed the study and wrote the manuscript together. Stephanie Ragot provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with Remi Coudroy.

Remi Coudroy, Jean-Pierre Frat, Stephan Ehrmann, Frédéric Pène, Nicolas Terzi, Maxens Decavèle, Gwenaël Prat, Charlotte Garret, Damien Contou, Jeremy Bourenne ,Arnaud Gacouin, Christophe Girault, Jean Dellamonica, Dominique Malacrino, Guylaine Labro, Jean-Pierre Quenot, Alexandre Herbland, Sébastien Jochmans, Jérôme Devaquet, Dalila Benzekri, Emmanuel Vivier, Saad Nseir, Gwenhaël Colin, Didier Thevenin, Giacomo Grasselli, Mona Assefi, Claude Guérin, David Bougon, Thierry Lherm, Achille Kouatchet, Stéphanie Ragot, and Arnaud W Thille contributed in drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. Remi Coudroy, Jean-Pierre Frat, Stephan Ehrmann, Frédéric Pène, Nicolas Terzi, Maxens Decavèle, Gwenaël Prat, Charlotte Garret, Damien Contou, Jeremy Bourenne ,Arnaud Gacouin, Christophe Girault, Jean Dellamonica, Dominique Malacrino, Guylaine Labro, Jean-Pierre Quenot, Alexandre Herbland, Sébastien Jochmans, Jérôme Devaquet, Dalila Benzekri, Emmanuel Vivier, Saad Nseir, Gwenhaël Colin, Didier Thevenin, Giacomo Grasselli, Mona Assefi, Claude Guérin, David Bougon, Thierry Lherm, Achille Kouatchet, Stéphanie Ragot, and Arnaud W Thille give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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The study promoter received financial grants from SOS Oxygène and AADAIRC.

Disclaimer

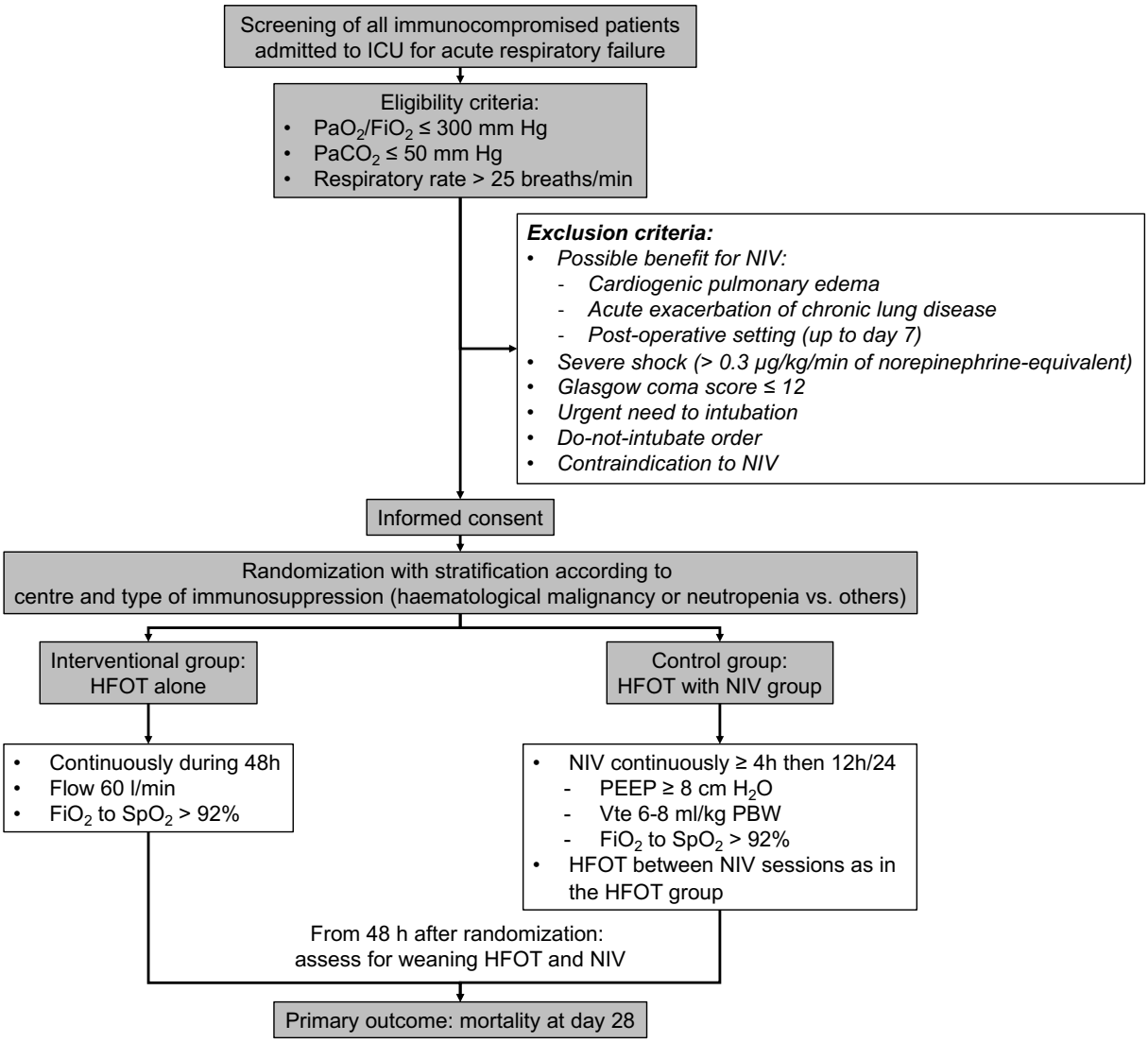
The firm Fisher & Paykel provides the high-flow oxygen therapy equipment and the noninvasive masks to all the participating centres but has no other involvement in the study.

Competing interests

RC reports travel expense coverage to attend scientific meetings from Fisher & Paykel and MSD.
JPF reports travel expense coverage to attend scientific meetings and personal fees from Fisher & Paykel and SOS Oxygène.
SE reports consulting fees from Aerogen, La diffusion technique française, Baxter, Bayer, lecture fees from Aerogen, Fisher & Paykel, unrestricted research grants / research support from from Fisher & Paykel, Hamilton medical, Aerogen, La diffusion technique française.
Chr G reports travel expense coverage to attend scientific meetings, personal fees and logistic support from Fisher & Paykel, Resmed and Lowenstein Medical.
AWT reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel, Covidien, Maquet-Getinge, General Electric Healthcare.
SJ reports personal fees for lectures from Hamilton Medical and Nihon Kohden.
GG reports payment for lectures from Getinge, Draeger Medical, Pfizer, Fisher&Paykel, and travel/accommodation/congress registration support from Biotest and Getinge.
FP, NT, MD, GP, Cha G, DC, JB, AG, JD, DM, GL, JPQ, AH, JD, DB, EV, SN, GC, DT, MA, CI G, DB, TL, AK, SR and report no conflict of interest.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ouest III, Poitiers, France) with the registration number 2016-A00834-47 (23 March 2016).



HFOT: high flow nasal cannula oxygen therapy; ICU: intensive care unit; NIV: noninvasive ventilation; PBW: predicted body weight; PEEP: positive end-expiratory pressure; Vte: expired tidal volume

Actions	Inclusion =H0	H1	H6-H12	H24 ± 6	H48 ± 6	H72 ± 6	Intubation	ICU and hospital discharge	D28 D90 D180
Informed consent	X								
Inclusion /exclusion criteria	X								
Randomization and stratification (type of immunosuppression)	X								
Clinical characteristics									
Height, weight, body temperature	X								
Vital signs	X	X	X	X	X	X	X		
Tolerance (dyspnea and comfort evaluation)	X	X	X	X	X	X	X		
HFOT or NIV settings	X	X	X	X	X	X			
Supplementary analysis									
Arterial blood gases	X	X	X	X	X	X	X		
Chest X-ray	X						X		
SOFA score	X		X	X	X	X	X		
Daily duration of HFOT and NIV				X	X	X			
Status (alive/dead) and cause of death								X	X

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

Page	Section/item	Item No	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
3		2b	All items from the World Health Organization Trial Registration Data Set
5	Protocol version	3	Date and version identifier
26	Funding	4	Sources and types of financial, material, and other support
1-4	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
4		5b	Name and contact information for the trial sponsor
4		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
NA		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)
	Introduction		
8	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
8		6b	Explanation for choice of comparators
9	Objectives	7	Specific objectives or hypotheses
9	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)

	Methods: Participants, interventions, and outcomes		
9	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
9-10	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)
10	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
11-12		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)
12		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
12	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
13	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)
12-13	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
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
14	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

14	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
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
7	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
14	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
14		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
16	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
15-16	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
16		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
15		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)
	Methods: Monitoring		
16	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

NA		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
16	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
16	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
5	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
17	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)
16	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
17	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
17	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
17	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
NA	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
17	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
26		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

App	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
NA	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

*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.