Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS
CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

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SIGNATURE page for a research PROTOCOL

Research code number:

Title: “Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia”

Version n°. 5 dated: 12/11/2020

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia
Acronym/reference	COVIDICUS
Coordinating investigator	Pr Jean-François TIMSIT
Scientific Director	Pr Lila BOUADMA
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	The main manifestation of COVID-19 is acute hypoxemic respiratory failure (AHRF). In patients with AHRF, the need for invasive mechanical ventilation is associated with high mortality. Two hypotheses will be tested in this study. The first hypothesis is the benefit of high dose corticosteroid therapy on severe COVID-19 infection admitted in ICU in terms of survival. The second hypothesis is that, in the subset of patients free of mechanical ventilation at admission, either Continuous Positive Airway Pressure (CPAP) or High-Flow Nasal Oxygen (HFNO) allows to reduce intubation rate safely during COVID-19 related acute hypoxemic respiratory failure.
Main objective and primary endpoint	The main objective is to assess the impact of high-dose dexamethasone on overall mortality at day-60 after randomization in patients admitted in ICU for severe COVID-19 infection. In non mechanical ventilation (MV) patients, the additional objective is to assess whether oxygen support based on either HFNO or CPAP modality in COVID-19 related AHRF reduces the need for mechanical ventilation at day-28.
Secondary objectives and endpoints	For the study of the effect of high-dose corticosteroids, secondary objectives include: 1. To compare the evolution of the viral load in the respiratory tract 2. To compare the occurrence of healthcare-associated infections 3. To compare the exposition to mechanical ventilation 4. To compare the evolution of SOFA score 5. To compare the exposition to renal replacement therapy 6. To compare the lengths of ICU and hospital-stay For the study of the effect of oxygen support modalities, secondary objectives are, to compare each of oxygen support group to the control group in terms of: 1. To compare the overall survival 2. To compare the exposition to mechanical ventilation 3. To compare occurrence of severe hypoxemia during tracheal intubation 4. To compare occurrence of cardiac arrest following tracheal intubation 5. To compare the occurrence of healthcare-associated infections 6. To compare the length of ICU and hospital-stay

Objective and endpoint Ancillary studies	An ancillary study CACAO (Covidicus air contamination) will be performed in 4 centers aiming at assessing the environmental contamination by SARS-CoV-2 according to the oxygen support modality. Additional funding will be searched for these analyses (submitted for ANR call). An ancillary study will be performed for evaluating the long-term evolution of patients admitted in ICU for severe COVID-19 infection, using data from the SNDS. A metanalysis on individual data will be performed using patients enrolled in the 3 PHRC flash exploring the activity of corticosteroids.
Design of the study	The design will be stratified on patient severity; - In non-mechanically ventilated patients, a 2x2 factorial design will be used to assess the two interventions, separately. This will result in 6 treatment arms, additionally to the standard of care: 1- Standard oxygen and placebo of Dexamethasone 2- Standard oxygen, and Dexamethasone 3- CPAP and placebo of Dexamethasone 4- CPAPand Dexamethasone 5- HFNO and placebo of Dexamethasone 6- HFNO, and Dexamethasone - In mechanically ventilated patients, only 2 randomized groups will be constituted: 1- Placebo of high-dose Dexamethasone 2- High dose Dexamethasone
Population of study participants	Adult patient with COVID-19 acute hypoxemic respiratory failure (AHRF)
Inclusion criteria	1. Age ≥ 18 years 2. Admitted to ICU within 48 hours 3. Confirmed or highly suspected COVID-19 infection 4. Acute hypoxemic respiratory failure (PaO2 <70 mmHg or SpO2<90% on room air or tachypnea>30/min or labored breathing or respiratory distress; need for oxygen flow >=6L/min) 5. Any treatment intended to treat the SARS-CoV-2 infection if accessible, in the absence of contraindications (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity).

Exclusion criteria	1. Moribund status 2. Pregnancy or breastfeeding 3. Long term corticotherapy at a dose of 0.5mg/kg/j or higher 4. Active and untreated bacterial, fungal or parasitic infection 5. Not written informed consent from the patient or a legal representative if appropriate. If absence a legal representative the patient may be included in emergency procedure 6. Hypersensitivity to dexamethasone or to any of the excipients 7. Not Affiliation to the French social security
Investigational medicinal product(s)	- High dose Dexamethasone IV (14mg D1-D5 then 4mg D6-D10) - HFNO - CPAP
Comparator treatment	- Placebo of high-dose Dexamethasone - Standard oxygen
Expected benefits for the participants and for society	Optimal care according to the current knowledge that will be updated according to new results for all the patients that will be enrolled (see below). Expected benefit in term of need of intubation, organ failures free days and survival.
Risks and burdens added by the study	The use of high flow oxygenation is associated with a theoretical increased risk in the aerosolized particles. The rooms will be maintained in negative or null pressure and health care workers will be equipped with FFP2 face masks and specific clothes according to guidelines. All patients will receive Dexamethasone at the daily dose of 6 mg, as recommended by the Haut Conseil de Santé Publique in France on July, 23,2020. Dexamethasone may theoretically prolong the viral shedding of COVID-19 and a systematic monitoring of rt PCR is planned. All patients will receive an antiviral therapy (as part of routine care) that is active in vitro on coronaviruses, unless contraindications. Dexamethasone may increase the risk of superinfections. This risk will be prevented by early diagnostic procedure use according to current guidelines. Dexamethasone may also increase the risk of hyperglycemia with the need of insulin. Close monitoring of glycemia will therefore be performed to detect those events. The risk level of the study D
Practical implementation	During this baseline visit, the intensivist investigator in charge of the patient will provide full information of patients or their relative or support person. All consecutive patients with a Confirmed or highly suspected COVID-19 infection will be considered for eligibility. They will be included by the investigating physician if they meet all the inclusion criteria and none of the exclusion criteria. The patient will be randomized in one of treatment groups according to the procedure, in addition to the standard of care: - For study effect of high-dose corticosteroids o In the experimental group: dexamethasone 14mg o In the control group: Placebo of 14mg Dexamethasone - For study effect of oxygen support modality o HFNO

	o CPAP o Standard oxygen therapy Patients will be evaluated daily while hospitalized in the ICU until D60.
Number of participants included	550 (including 330 MV patients)
Number of centres	19 sites in France
Duration of the study	- inclusion period: 12 months - participation period (treatment + follow-up):75 days - total duration: 14,5 months
Number of enrolments expected per site and per month	2,4 patients per site and per month
Statistical analysis	All primary analyses of the high-dose corticosteroids and oxygen support, will be performed under the intention-to-treat (ITT principle), irrespective of the actual treatment of each enrolled patient who will be each analysed in the group that has been attributed by randomization. Estimation of high-dose Dexamethasone effect will be based on the direct comparison of the two randomization arms in the ITT population. Estimation of the effect of the oxygenation, support systems, will be considered separately: HFNO versus standard oxygen, CPAP versus standard oxygen, with control for multiple comparisons based on Bonferroni adjustment. Estimation of treatment by period interaction will be performed, given the modification of the standard of care in September, 2020. Last, estimation of the dexamethasone effect will be performed on the “as treated population”, distinguishing the actual dose levels (0, 6, and 20 mg), based on instrumental variable methods. Interim analyses will use Bayesian monitoring after every 50 patients in order to avoid inflation of type I error
Funding sources	National PHRC 2020 Ministry of Health
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Two hypotheses will be tested in this study.
The first hypothesis is the benefit of corticosteroid therapy on severe COVID-19 infection admitted in ICU in terms of survival.
The second hypothesis is that, in the subset of patients free of mechanical ventilation at admission, either CPAP or HFNO allows to reduce intubation rate safely during COVID-19 related acute hypoxemic respiratory failure.

2.2 Description of knowledge relating to the condition in question

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Currently there is no approved therapeutic agent or supportive treatment for coronavirus infection. We design a study to evaluate in patients infected with SARS-CoV-2 the impact on patients' outcomes of one therapeutic agent in addition to standard of care of in date of July, 2020 (Dexamethasone, 6 mg) and antiviral treatment: High-dose dexamethasone [Randomization (R)-DXM] and one oxygen supportive treatment [R-O2], i.e. High-Flow Nasal Oxygen (HFNO) or Continuous Positive Airway Pressure (CPAP).

The main manifestation of COVID-19 is acute hypoxemic respiratory failure (AHRF). In patients with AHRF, the need for invasive mechanical ventilation is associated with high mortality. HFNO is a non-invasive, high concentration oxygen delivery interface that has been increasingly used in critically ill adults over the last number of years. During HFNO, heated and humidified oxygen is delivered to the nose at flow rates as high as 50-60 L/minute, allowing clinicians to better match the inspiratory demands of patients with AHRF. These high flow rates also generate low levels of positive pressure in the upper airways, and the fraction of inspired oxygen (FiO2) can be adjusted by changing the fraction of oxygen in the driving gas. The high flow rates may also decrease physiological dead space by flushing expired carbon dioxide from the upper airway, a process that potentially explains the observed decrease in the work of breathing (1). HFNO has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask in patients with AHRF (2). In a study conducted in patients with AHRF, HFNO achieved better survival as compared to standard oxygen and non-invasive ventilation (NIV) (3). However, its high gas flow raises concerns about aerosolization of infectious particles and spread of

infection. Although clear data are lacking for SARS-CoV-2, experimental confirmation of viral aerosol generation was demonstrated in a patient with SARS coronavirus.

CPAP is a simple to use and affordable technique for non-invasive ventilatory support. In patients with AHRF, applying a positive pressure to the airway opening has been shown to mitigate the reduction in functional residual capacity and to improve respiratory mechanics and gas exchange (4), with early physiologic improvement (5). The Boussignac CPAP device (Vygon, Ecouen, France) is easy to use, compatible with all face masks and does not need any ventilator to work. Pressure is generated by a standard gas flow passing through micro-capillaries (located all around the CPAP device) increasing its speed and generating turbulence therefore creating a "virtual valve". This technique offers multiple advantages for respiratory support and can be adapted with the insertion of a heated and mixture exchanger for use in COVID-19 patients (6).

To our knowledge, the effect of CPAP or HFNO on major outcomes have not been assessed in adults with COVID-19 related AHRF. We chose not to assess NIV, i.e., bi-level assistance delivered by ventilators because this technique requires adequate training and a mechanical ventilator, which may be challenging in the context of an epidemics. In addition, recent reports suggest that this approach may be associated with excessive tidal volumes during AHRF (7), the latter being potentially involved in patient-self-inflicted lung injury (8). Recent studies do not suggest any benefit of NIV during de novo AHRF (3) and the 2017 European Respiratory Society/American Thoracic Society NIV clinical practice guideline made no recommendation regarding the use of NIV for acute de novo respiratory failure (9). This impact study of oxygen support on patient outcomes will be combined and completed by an ancillary study CACAO to assess whether the use of HFNO, or CPAP, as compared to standard oxygen therapy increases the risk of environmental contamination of air or surfaces during the care of patients with Covid-19 (ANR call).

The place of steroids is of paramount importance in patients suffering from viral pneumonia related to COVID-19. Indeed, a worsening of the lung injury is described around Day 8 and (10,11) paradoxically at the same time that a decrease of the viral load. The lung damage at this phase could be related to immunopathological lesions, resulting from an overexuberant pro-inflammatory host response, rather than uncontrolled viral replication, as suggested by the description of Huang and al., suggesting that a cytokine proinflammatory storm was associated with disease severity. A cohort study from Wuhan (12) showed a benefit of the use of steroids in patients with severe COVID-19 infections. The hazard of mortality associated with corticosteroid use was hazard ratio 0.38; 95%CI, 0.20-0.72; P = .003. Despite this potential benefit, the use of corticosteroids have been associated with extended duration of MERS-COV shedding.

Our hypotheses are that the use of HFNO or CPAP might reduce the need for mechanical ventilation and that steroids can reduce mortality of severe COVID-19 patients. We will use dexamethasone as successfully used in acute respiratory distress syndrome (ARDS) (13).

Integrating clinical trials of experimental therapeutics as part of the response during COVID-19 pandemics is urgently required to try to save the most severe forms and determining efficacy of potential therapies. The purpose of this randomized trial is to provide substantial evidence on the efficacy, or lack of efficacy and safety of steroids and HFNO or CPAP given the expected large number of cases.

2.3 Summary of relevant pre-clinical experiments and clinical trials

According to the data discussed below, there is a rationale for both interventions:

- The inflammasome activation associated with COVID-19 is now experimentally demonstrated (14). Clinical data clearly demonstrated that the pro-inflammatory parameters are associated with poor prognosis in severe COVID-19 pneumonia (15). Finally, recent study showed that in non-COVID-19 ARDS, dexamethasone decrease significantly the D28 and day 60 mortality. All these data argued for a potential benefit of corticosteroids, mainly Dexamethasone in severe COVID-19 pneumonia.
- A specific system of oxygen delivery to decrease the need of intubation requirement. In *COVID-19* infections admitted in ICU, the risk of mortality associated with ARDS and intubation is 55-90%. Preliminary data suggest that HFNO trends to reduce the need for invasive ventilation in immune-compromized patients (16). CPAP has been associated with a decrease of the need of invasive mechanical ventilation in acute respiratory failures associated with *Pneumocystis carinnii* pneumonia. Although causality is not demonstrated, any attempt to reduce the need for intubation may therefore reduce the risk of death.
- Recovery study: Preliminary data was published 16 June 2020 by University of Oxford concerning use of Dexamethasone to reduce death in hospitalised patients with severe respiratory complications of COVID-19.

  In March 2020, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK. On 8 June 2020, recruitment to the dexamethasone arm was halted since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit. A total of 2,104 patients were randomized to receive dexamethasone 6 mg once per day (either per os or intravenously) for 10

days in addition to standard of care, compared to 4,321 patients randomized to usual care.

Among the patients who received the usual care alone, 28-day mortality was expectedly the highest in those who required ventilation (41%), intermediate in those who required oxygen supply (25%), and the lowest among those who did not require any oxygen supply (13%). Based on subset analyses, the effect of dexamethasone appeared to depend on the population, with a 35% reduced death rate in ventilated patients (rate ratio, 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003), a one fifth reduction in those receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021), while there were no benefit among patients who did not require any oxygen supply (rate ratio, 1.22 [0.86 to 1.75]; p=0.14).

2.4 Description of the population to be studied and justification for the choice of participants

The population enrolled are detailed in the Eligibility criteria in section 6.

As stated above, published data argued for a potential benefit of corticosteroids, mainly Dexamethasone in severe COVID-19 pneumonia. Therefore, this study focuses on the population of COVID-19 pneumonia with acute respiratory failure. Given the potential increase in the viral shedding described with other coronavirus, the Dexamethasone will be always associated with a molecule with *in vitro* antiviral activity against SARS-CoV-2.

In the subset of no mechanically ventilated patients, the prognosis depends on the severity of pneumonia, resulting in more than 50% of the cases with a further need of mechanical ventilation. This justifies our attempt to additionally assess in this subset the benefit of oxygenation strategies, unless patients had chronic obstructive pulmonary disease or hypercapnia that may justify NIV.

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2.5 Identification and description of the investigational medication or medications

There are two interventions to be simultaneously studied and compared in addition to the standard of care:

1) For all patients, the intervention consists in the IV administration of dexamethasone 14 mg / 3,5 ml (D1-D5), then 4 mg / 1 ml D6-D10. The comparator arm will receive NaCL 0,9% as placebo of dexamethasone, 3,5 ml (D1-D5), then 1 ml D6-D10; all patients whatever the group will receive a therapy effective *in vitro* against SARS-CoV-2.

2) In the subset of patients without (i) invasive mechanical ventilation, (ii) anatomical factors precluding the use of nasal cannula, (iii) hypercapnia indicating NIV (paCO2 ≥ 50 mmHg) OR (iv) intolerance to one of the 3 modes of oxygenation studied at admission, two oxygen support interventions will be further considered, either HFNO or CPAP, randomly allocated, and started within the hour after randomization. The comparator arm will receive standard oxygen therapy. Note that to avoid any increased risk of contamination for the health care teams in charge of the patient, such oxygenation supports will be performed in rooms in negative or null pressure. Healthcare workers will be equipped systematically with FFP2 face mask and specific materials as described (17) (see section 8.1.1).

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

See Section 8 for further information about the administration of product.

2.7 Summary of the known and foreseeable benefits and risks for the research participants

The COVID-19 epidemic is currently expanding in France and throughout the world.
Approximately 15-20% of hospitalized infected patients are admitted in the ICU due to a respiratory failure. About two third of the ICU patients will required invasive mechanical ventilation with estimated death rate of 50-90%. A growing literature suggest that this worsening might be due to an increased inflammatory state of the lung targeted by COVID-19. This trial will allow (1) to demonstrate the potential benefit of high-dose dexamethasone in COVID-19 acute respiratory failure and (2) to identify the best modality for oxygen support, including for the security of healthcare workers, as HFNO has been associated with a higher aerosolization of respiratory pathogen (ancillary study CACAO), as well as to improve the management of the lung disease, aside antiviral therapy and standard of care. This will lead to direct benefits both to the included patients and the society in the fight against COVID-19 epidemics.

3 OBJECTIVES

3.1 Primary objective

For the study of the effect of corticosteroids: The main objective is to assess the impact of high-dose dexamethasone on overall mortality at day-60 after randomization in patients admitted in ICU for severe COVID-19 infection.

For the study of the effect of oxygen support modality: The main objective is to assess whether oxygen support based on either HFNO or CPAP modality in COVID-19 related acute hypoxemic respiratory failure reduces the need for mechanical ventilation at day-28.

3.2 Secondary objectives

For the study of the effect of high-dose corticosteroids, secondary objectives include:

1. To compare the evolution of the viral load in the respiratory tract
2. To compare the occurrence of healthcare-associated infections
3. To compare the exposition to mechanical ventilation
4. To compare the evolution of SOFA score
5. To compare the exposition to renal replacement therapy
6. To compare the lengths of ICU and hospital-stay

For the study of the effect of oxygen support modalities, secondary objectives are, to compare each of oxygen support group to the control group in terms of:

1. To compare the overall survival
2. To compare the exposition to mechanical ventilation
3. To compare occurrence of severe hypoxemia during tracheal intubation
4. To compare occurrence of cardiac arrest following tracheal intubation
5. To compare the occurrence of healthcare-associated infections
6. To compare the length of ICU and hospital-stay

3.3 Objective of ancillary studies

3.3.1 CACAO (Covidicus air contamination)

An ancillary study CACAO will be performed in 4 centers aiming at assessing the environmental contamination by SARS-CoV-2 according to the oxygen support modality.
Additional funding will be searched for these analyses (submitted for ANR call).

3.3.2 Long term evolution

An ancillary study will be performed for evaluating the long-term evolution of patients admitted in ICU for severe COVID-19 infection, using data from the SNDS.

3.3.3 Comparison study of thrombo-inflammation parameters

COVID19 is associated with a critical thrombo-inflammatory state that can be rapidly deleterious, leading to organ injury, including lung, kidney and brain. Therefore, the main known cellular actors involved in thrombo-inflammation and their related soluble parameters

are good candidate biomarkers that could be associated with poor prognosis and their study could also help us to better understand the pathophysiology of this disease.
We hypothesize that studying all these parameters sequentially in ICU patients will allow us to identify relevant parameters associated with poor prognosis.

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

For the study of the effect of high-dose corticosteroids, the primary endpoint is the time-to-death from all causes within the first 60 days after randomization.
For the study of the effect of oxygen support modalities, the primary endpoint is the time to need for mechanical ventilation (MV), as defined by any of the 3 criteria for intubation defined below, within the first 28 days after randomization. The use of those criteria rather than actual mechanical ventilation was justified to decrease information bias due to (i) the open design, (ii) possibility of delayed MV due to logistic constrains, and (ii) do not resuscitate orders (DNR).
The **pre-specified criteria for intubation** have been used previously (3):

1) signs of persisting or worsening respiratory failure, defined by at least two of the following criteria: a respiratory rate above 35 cycles/min, lack of improvement of signs of respiratory-muscle fatigue, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO_2 below 90% despite FiO_2 ≥80% for more than 5 min without technical dysfunction, or intolerance to NIV; or one of the following

2) hemodynamic instability defined by a systolic blood pressure below 90 mmHg, mean blood pressure below 65 mmHg or requirement for vasopressor,

3) deterioration of neurologic status with a Glasgow coma scale below 12 points.

4.1.2 Secondary endpoints

For the study of the effect of high-dose corticosteroids, secondary endpoints include:

1. The cycle threshold for SARS-CoV-2 PCR at baseline, day 7+/-1 and day 10+/-1 in samples of the same origin (preferably subglottic i.e. bronchoalveolar lavage or tracheal aspiration, otherwise nasopharyngeal swab)
2. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and D28
3. Number of days alive without mechanical ventilation at day 28

4. Changes in SOFA score from day 1 to day 3, day 7, day 10, day 21, day 28 or discharge-day from ICU as appropriate
5. Number of days alive without renal replacement therapy at day 28
6. Lengths of ICU-stay and hospital-stay

For the study of the effect of oxygen support modality, secondary endpoints are:

1. Overall survival within 60 days after randomization
2. Number of days alive without invasive mechanical ventilation at day 28
3. Proportion of patients with severe hypoxemia, which is defined as an oxygen saturation of less than 80% during the same interval during the interval between induction and 2 minutes after tracheal intubation
4. Proportion of patients with cardiac arrest within 1 hour after intubation
5. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and day 28
6. Lengths of ICU-stay and hospital-stay

4.1.3 Endpoints for the ancillary studies

The endpoint for the ancillary study CACAO (Covidicus Air ContAminatiOn) is the concentration of SARS-CoV-2 in the patient's room ambient air and surfaces.

The endpoints for the ancillary study on the long-term evolution are the consumption of care in the outpatient setting, as well as hospital episodes and possible entry in the register of Affections de Longue Durée, and vital status.

For the ancillary study of thrombo-inflamation parameters, in all patients, we will compare thrombo-inflammation parameters at D1 D7 D outcome as mentioned below:

- Blood cell count and coagulation parameters (PT, APTT, fibrinogen, FV FII, fibrin monomers D-dimers, FVIII:C, anti-Xa activity)
- Platelet activation markers (P-selectin, TLT-1, platelet-leucocytes aggregates)
- Lymphocyte monocyte and neutrophil activation phenotype and mediator release, netosis capacity (CXCL10, MCP-1, IL6, IL8, TNF alpha, IL-1beta, NETs).
- Functional assays (cytokine secretion by both lymphoid and myeloid cells, neutrophil priming and degranulation)

4.2 Description of research methodology

4.2.1 Design of the study

This will be a multicenter randomized controlled trial stratified on the patient severity at inclusion (Figure 1).

All consecutive patients with COVID-19 infection admitted in ICU, receiving the best standard of care including low-dose dexamethasone (see below) and any therapy for the treatment of their COVID-19 infection (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity) and who met the eligibility criteria will be proposed to participate.

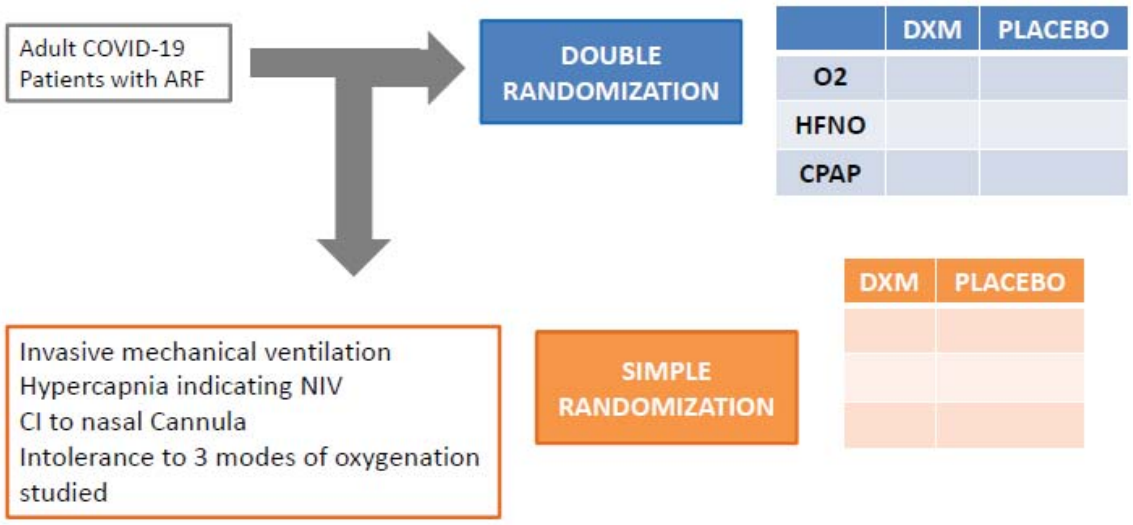


Figure 1: Design of the protocol: Stratification of the randomization according to the patient severity; DXM: dexamethasone

The design will be stratified on patient severity;

- **In patients without (i) invasive mechanical ventilation, (ii) anatomical factors precluding the use of nasal cannula, (iii) hypercapnia indicating NIV (paCO2 ≥ 50 mmHg) OR (iv) intolerance to one of the 3 modes one of oxygenation studied at admission**, a 2x2 factorial design will be used to assess the two interventions, separately. This will result in 6 treatment arms

    1- Standard oxygen and placebo of high-dose dexamethasone
    2- Standard oxygen, and high-dose dexamethasone
    3- CPAP and placebo of high-dose dexamethasone
    4- CPAP, and high-dose dexamethasone
    5- HFNO and placebo of high-dose dexamethasone
    6- HFNO and high-dose dexamethasone

- **In patients with (i) invasive mechanical ventilation, (ii) anatomical factors precluding the use of nasal cannula, (iii) hypercapnia indicating NIV (paCO2 ≥**

50 mmHg) OR (iv) intolerance to one of the 3 modes one of oxygenation studied at admission, only 2 randomized groups will be constituted:

1- Placebo of high-dose dexamethasone
2- high-dose dexamethasone

Dexamethasone and placebo will be administered IV (14mg/3,5ml D1-D5 then /1ml D6-D10) Randomization will be stratified on center.

The conception of a dexamethasone placebo is not possible due to the emergency to begin the trial. Sponsor will provide pre randomized boxes including all necessary masked vials of dexamethasone or normal saline.

All patients will receive the best **standard of care** available at the time. Based on the *Haut Conseil de Santé Publique* (July, 23, 2020), dexamethasone will be administered at a daily dosage of 6 mg for a maximum of 10 days, after evaluation of the individual benefit/risk ratio in patients under 70 years of age requiring oxygen and resuscitation. This results in a pragmatic trial comparing dexamethasone 6mg +14mg of vs dexamethasone 6mg + placebo. Thus, the protocol focuses on the effect of high-dose dexamethasone compared to low-dose..

There will be a continuous Bayesian monitoring to allow early stopping for efficacy or safety (See section 13 for more details). An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.

For the High Flow Oxygen and standard oxygen groups, a trial of NIV will be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation.

For MV patients, weaning decisions will follow strict standardized criteria, identical in all randomization groups, according to applicable recommendations. These standardized weaning criteria will be collected every day for each randomized patient and are:

- No further need for sedative agents,
- Good level of consciousness with little or no sedation,
- No further need for significant use of vasopressors or inotropes,
- Fraction of inspired oxygen (FiO_2) ≤ 50% with oxygen saturation (SaO_2) ≥ 88%,

- Positive End Expiratory Pressure (PEEP) ≤ 8 cmH2O with SaO2 ≥ 88%.

Follow-up of participants will be the same for all participants. Clinical data for efficacy will be assessed daily in the ICU, and on days 7, 10, 14, 21, 28, 60 for patients who will be transferred to other hospital-wards at these dates. Safety data will be collected every day during therapy, and every week until day 28 after the end of treatment. A biocollection will be constituted with all BAL samples collected as part of care and blood samples at day 1, 7, 10, 14, 28.

In addition, ancillary study CACAO (Covidicus Air ContAminatiOn) will be performed in 4 centers with collection of air of the patient's room for the analysis of the SARS-CoV-2 eventual dissemination depending on oxygen support modality. Additional funding will be searched for these analyses (submitted for ANR call).

In addition, although the request for access to SNDS data is subject to separate formalities in a separate protocol (with a request for an opinion from CEREES and then a request for authorisation from the CNIL), it should nevertheless be specified here that the collection of the NIR will be carried out within the framework of this research protocol. In concrete terms, the participant's NIR will be collected from his or her medical file and recorded on a contact sheet specifically dedicated to its collection.

4.2.2 Number of participating sites

This is a multicenter trial with 19 participating centres.
Participating centers and investigators are detailed in the addenda "investigators list" separated of the protocol.

4.2.3 Identification of participants

The participants in this research will be identified as follows:
Site number. (3 digits) - Sequential enrolment number for the site including the strata number (4 digits, beginning with 1001 or 2001, respectively) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

4.2.4 Randomisation

After signing the informed consent (or according to the emergency inclusion), and checking the eligibility criteria, including the severity strata, patients will be randomized across the arms (as detailed above in section 5.2.1).

Randomization will be balanced (1:1:1 in non-MV patients, 1:1 in MV patients), centralized, and stratified on centre. Computer-generated randomization lists will be generated, using permutation blocks of varying sizes that will be kept confidential to the investigators. The randomization lists will be generated by a statistician from Saint Louis hospital (sbim). All these points will insure the allocation concealment of the randomization process.
A centralized 24/24, password-protected Internet service (CleanWeb® solution) expressly designed for the study and developed under the responsibility of the URC Paris Nord, will be used. Information will be recorded in the electronic system in order to prevent the investigator and medical team from predicting the group allocated to patients. To include and randomize a patient in the study, investigators will access the website using an individual password, and fill out a short medical record form. After each randomization, a treatment number is allocated to the patient and a confirmation email of randomization will be sent automatically to the investigator concerned and the URC Paris Nord.

4.2.5 Blinding methods and measures put in place to protect blinding

The conception of a placebo is not possible due to the emergency to begin the trial for Dexamethasone, or due to the nature of intervention for the oxygen support modalities. Pre randomized boxes containing masked vials dexamethasone or normal saline will be available in each center. These precautions and the use of primary endpoints (mortality within day 60, or specific criteria for MV) will minimize the risk of biases due to the open nature of the study (see section 4.2.1).

Statistical analyses will be conducted blinded to treatment assignment, with treatment arms denoted by letters instead of explicit labelling; note that the control arm of oxygenation support will be identified for analysis purposes (given only comparison of each intervention to that control arm is to be performed). All investigators will be unaware of aggregate outcomes during the study.

4.2.6 Unblinding procedures, if applicable

Unblinding will be requested for any reason considered essential by the investigating physician by calling upon:

- **In all cases** at the poison control centre at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48**

5 IMPLEMENTATION OF THE STUDY

5.1 Baseline visit

5.1.1 Obtaining inform consent

Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

For patients who are not able to sign the informed consent form, the consent of a relative or support person will be required, if they are present. Emergency inclusions will be allowed in this research protocol in accordance to the French Public Health Code, article L1122-1-2.

The relative or support person and the concerned person will be informed as soon as possible and a new consent will be required for the pursuit of this research. The relative or support person and the concerned person may also oppose to the use of his data in the research. See chapter 15.1 for more details.

A patient card will be completed and given to the patient, or kept in the medical file and will be given to him as soon as possible.

A free and written informed consent form must be signed by each individual participating in the trial prior to any act carried out by the research protocol.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
1. The patient 2. A relative or support person	• the principal investigator or collaborating physician declared and trained in the study	1. Baseline visit 2. As soon as possible if the patient is included under the emergency inclusion procedure	1. Baseline visit 2. As soon as possible if the patient is included under the emergency inclusion procedure

5.1.2 Required clinical, biological and radiological exams

During this visit, the intensivist investigator in charge of the patient will provide full information of patients or their relative or support person (see 5.1.1 about obtaining consent). All consecutive patients with a Confirmed or highly suspected COVID-19 infection will be considered for eligibility. They will be included by the investigating physician if they meet all the inclusion criteria and none of the exclusion criteria. For eligible patients not included in the study, the reason for non-inclusion will be compiled.

Inclusion and non-inclusion criteria will be assessed and collected in the CRF.
This visit will include:

- Detailed interview of the patient or his/her relatives on his/her demographic data, medical history and current medications
- Complete physical exam, including vital parameters and respiratory rate
- Blood sampling for standard biology
- Data for SOFA scoring
- SARS-CoV-2 PCR (preferably subglottic sample i.e. bronchoalveolar lavage or tracheal aspiration, otherwise nasopharyngeal swab)
- Blood β-HCG test for women of child-bearing age

The patient will be randomized in one of treatment groups according to the procedure described in chapter 4.2.4:

- For study effect of corticosteroids
    - In the experimental group: high-dose dexamethasone
    - In the control group: placebo of high-dose dexamethasone
- For study effect of oxygen support modality
    - HFNO
    - CPAP
    - Standard oxygen therapy

To limit the risk of loss to follow-up, the contact details of patients, his/her surrogates and their primary care physician will be collected at inclusion on a report form. This form will be not conserved after termination of the study.
Treatment will then be initiated according to the protocol exposed in chapter 7.
<u>The following data will be collected on inclusion by the investigator in charge of the patient</u>:

- Inclusion and non-inclusion criteria
- Standard demographic information: patient's initials, gender, date of birth and the birth place
- Social Security number (NIR)
- Significant comorbidities and baseline characteristics including treatments administered
- Date of admission to hospital and date and time of admission to ICU
- Previous location before admission in the ICU: emergency room / home / medical or surgical ward / another ICU
- Reason for ICU admission: respiratory
- Presence of the following comorbid conditions (Y/N): chronic respiratory insufficiency requiring long-term oxygen therapy, heart failure (New York Heart

Association class III-IV), chronic treatment for arterial hypertension, insulin-dependent diabetes mellitus, chronic renal failure, solid organ transplant, immunosuppression, cirrhosis

- SOFA scores at admission
- Physical exam (vital parameters, respiratory rate)
- Number of days under mechanical ventilation prior randomization if applicable
- Number of days under high flow nasal oxygen therapy prior randomization if applicable

For the ancillary study CACAO:

Environmental samples, including air and surfaces from the COVID-19 patients' room, will be collected at 6 occasions over the 24 first hours using a BioSampler or VIVAS device (for air) and Dacron swabs pre-moistened for surfaces.

The samples will be centralised to virology laboratory for Virological analyses to performed in order to detect and quantify the presence of the SARS-CoV-2, and evaluate its infectivity by viral culture. Specific analytical methods will be developed.

The contamination of the patients' room will be studied using mixed effect statistical modeling of the data.

For the ancillary study of thrombo-inflammation parameters: blood specific samples

- 2 citrate tube blood 3.5ml
- 1 EDTA tube blood 7 mL +
- 1 dry tube blood 5 ml
- 1 heparinate tube blood 7 ml

5.2 Follow-up visits

Patients will be evaluated daily while hospitalized in the ICU.

These daily evaluations will include assessment of adverse events (intubation requirement after inclusion, deaths, nosocomial infections).

Patients will receive the treatment according to the protocol presented in chapter 8.

In addition, the following visits will be performed during patient's follow up and the following data will be collected by the investigator in charge of the patient:

Visit 2 on day 3 ± 1:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode

- Data for SOFA scoring and type of organ or system failure
- Blood sampling
- Adverse events
- Concomitant treatments
- Hospitalization ward

Visit 3 on day 7 ± 1:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode
- Data for SOFA scoring and type of organ or system failure
- Blood sampling
- SARS-CoV-2 PCR (same sample type as day 1; preferably subglottic sample i.e. bronchoalveolar lavage or tracheal aspiration, otherwise nasopharyngeal swab)
- Adverse events
- Concomitant treatments
- Hospitalization ward

For the ancillary study of thrombo-inflamation parameters: blood specific samples

- 2 citrate tube blood 3.5ml
- 1 EDTA tube blood 7 mL +
- 1 dry tube blood 5 ml
- 1 heparinate tube blood 7 ml

Visit 4 on day 10 ± 1:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode
- Data for SOFA scoring and type of organ or system failure
- Blood sampling
- Adverse events
- Concomitant treatments
- Hospitalization ward

Visit 5 on day 14 ± 1:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode
- Data for SOFA scoring and type of organ or system failure

- Blood sampling
- Adverse events
- Concomitant treatments
- Hospitalization ward

Visit 6 on day 21 ± 2:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode
- Data for SOFA scoring and type of organ or system failure
- Blood sampling
- Adverse events
- Concomitant treatments
- Hospitalization ward

Visit 7 on day 28 ± 2:

- Vital status
- Physical exam (vital parameters, respiratory rate)
- Ventilation mode
- Data for SOFA scoring and type of organ or system failure
- Blood sampling
- Adverse events
- Concomitant treatments
- Hospitalization ward

5.3 Last study visit

The last follow up visit will be performed at month 60 days ± 2 weeks. This visit will include the evaluation of the vital status and the quality of life (EQ-5D-5L questionnaire). This follow-up visit can be done by telephone or during a consultation at the hospital if the patient is hospital discharge.

5.4 Expected length of participation and description of the chronology and duration of the study.

The maximal duration of participation of each patient will be 60 days.

Duration of enrolment period	12 months
The length of participation for participants, of which	75 days

- Maximum period between selection and inclusion	NA
- Treatment period	10 days
- Follow up period	60 days +/– 2 weeks
Total study duration	14 ,5months

5.5 Table or diagram summarising the chronology of the study

Actions	Baseline visit	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit at ICU discharge / hospital discharge	End of research
	D1 +/- 1 day	D3 +/- 1 day	D7 +/- 1 day	D10 +/- 1 day	D14 +/- 1 days	D21 +/- 2 days	D28 +/- 2 days		D60 +/- 2weeks
Clinical Data									
Inclusion and non-inclusion criteria	▲								
Informed consent	▲								
Informed consent pursuit if necessary	▲	▲	▲	▲	▲	▲	▲		
Demographics & Medical History	X								
Complete physical exam, including vital parameters, vital status	**Continuously**								
SOFA Score	▲	▲	▲	▲	▲	▲	▲	▲	
Consultation at hospital or Phone questionnaire (EQ-5D-5L questionnaire)									▲
Adverse events	**Continuously**								
Randomisation : R1									
Treatment : - Experimental group E1: Dexamethasone treatment – - Control group C1: placebo of dexamethasone	▲	▲	▲	▲					
Randomisation : R2									
Treatment : - Experimental group E2A: HFNO - Experimental group E2B : CPAP - Control group C2: standard oxygen therapy	▲	▲	▲	▲	▲	▲	▲		
Radiological Data									
Chest X Ray	**At least every 48h during ICU stay, and forHospital**								
Biological Data									
Blood β-HCG test for women of child-bearing age	X								
Standard biology	X	X	X	X	X	X	X	X	
SARS-CoV-2 PCR (preferably subglottic sample i.e. bronchoalveolar lavage plugged telescopic catheter, or tracheal aspiration, otherwise nasopharyngeal swab)	X		X						
Blood sampling for Bio collection	▲	▲	▲		▲		▲	▲	
Environment air collection	▲								

▲: realized for the research X: realized as part of the care

5.6 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Procedures	Standard Oxygen Therapy Blood β-HCG test for women of child-bearing age	HFNO CPAP
Treatments	Dexamethasone, 6 mg, according to the French *Haut Conseil de Santé Publique* (July, 23, 2020) Drug with an antiviral activity (i.e lopinavir/ritonavir, remdesivir, hydroxychloroquine, Favipiravir or any new drug approved during the time of the study)	Dexamethasone, 14 mg Placebo (Nacl)
Blood samples		Blood sampling for biocollection at baseline, D3, D7, D14, D28 or ICU discharge
Respiratory samples	Respiratory samples as bronchoalveolar lavage, plugged telescopic catheter or tracheal aspiration, or nasopharyngeal swab if others are not feasible	
Environment air collection samples		Environment air samples at D1
Imaging	Chest X Ray, computed tomography	

5.7 Biological samples collection

Samples (serum and respiratory samples as bronchoalveolar lavage, plugged telescopic catheter, tracheal aspiration, or nasopharyngeal swab) taken as part of the study will be stored in a biological sample collection.

During the study the sample collection(s) will be stored at the Centre de Ressources Biologiques (CRB) de l'Hôpital Bichat-Claude Bernard under the supervision of Dr Sarah Tubiana for duration of 15 years.

SARS-CoV-2 is a new virus responsible of covid-19 disease, and development of a biobank from patients with this condition may be very useful for further research.

The samples may be used with the explicit agreement of the subject on the consent form for further analyses not included in the protocol and which could be beneficial for the pathology based on evolution in scientific knowledge.

The collection will be declared to the ANSM in the context of biomedical research.
At the end of the research, the samples will be preserved and will be declared to the minister responsible for research [and to the director of the regional health authority with local jurisdiction] (Article L. 1243-3 of the CSP (French Public Health Code)).

Type of sample	Quantity	Storage location	Collection Supervisor	Purpose of the collection	Storage duration
BAL (bronchoalveolar lavage)	2 vials	CRB Bichat	Dr Sarah TUBIANA	To characterize biological endotypes of COVID-19	Until Exhaustion samples
EDTA tube blood	2 vials	CRB Bichat	Dr Sarah TUBIANA	To characterize biomarkers	Until Exhaustion samples
Serum Bank	30 ml	CRB Bichat	Dr Sarah TUBIANA	To characterize biomarkers	Until Exhaustion samples
Serum Bank For Bichat and Strasbourg patients	12 ml	CRB Bichat	Dr Sarah TUBIANA	To characterize biomarkers	Until Exhaustion samples
Blood samples For Bichat and Strasbourg patients	78 ml	Hematology Laboratory	Pr Nadine Ajzenberg	Ancillary study of thrombo-inflamation parameters	Analysis during study

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Patients fulfilling all the following criteria will be eligible:

1. Age ≥ 18 years
2. Admitted to ICU within 48 hours
3. Confirmed or highly suspected COVID-19 infection
4. Acute hypoxemic respiratory failure (PaO2 <70 mmHg or SpO2<90% on room air or tachypnea>30/min or labored breathing or respiratory distress; need for oxygen flow >=6L/min)
5. Any treatment intended to treat the SARS-CoV-2 infection if accessible, in the absence of contraindications (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, oseltamivir, hydroxychloroquine and any other new drug with potential activity).

6.2 Non-inclusion criteria

Will not be eligible patients meeting one of the following criteria:

1. Moribund status
2. Pregnancy or breastfeeding

3. Long term corticotherapy at a dose of 0.5mg/kg/j or higher
4. Active and untreated bacterial, fungal or parasitic infection
5. Not written informed consent from the patient or a legal representative if appropriate. If absence a legal representative the patient may be included in emergency procedure
6. Hypersensitivity to dexamethasone or to any of the excipients
7. Not Affiliation to the French social security

6.3 Recruitment procedure

The current epidemics of SARS-CoV-2 is currently growing. A very high number of COVID-19 cases are currently hospitalized in the intensive care, and keeps increasing. In all centers, over the first week end of March 2020, 20 patients were admitted to the intensive care.

	Number of participants
Total number of participants to be included	550
Number of centres	19
Enrolment period (months)	12
Number of participants/centre	28,9
Number of participants/centre/month	2,4

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)

- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 2 months following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead
- If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 11.3

6.4.4 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

In all cases in which a study is discontinued, the care options must be specified for participants currently enrolled in the study. Notably, it must be specified if the participants included in the study must be monitored until the end of their participation, as set forth in the protocol.

If the study is prematurely discontinued for safety reasons (considered as urgent safety measure (USM)), the decision, justification and taken measures (with recommendations from the Data Safety Monitoring Board if applicable) will be provided without delay by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).
The sponsor submits within a period of 15 days a request for substantial modification notifying these USM (for authorization by ANSM and for opinion by the CPP).

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product(s)

7.1.1 Universal strategy of protection of healthcare workers for caring ICU patients confirmed with SARS-CoV-2 used in R-DXM and R-O2) (adapted from Bouadma L et al Intensive care med 2020)

Dress precautions before entering the room where suspected or confirmed SARS-CoV-2 infected patients are admitted for oxygen therapy

Place an instruction sheet to staff on how to don and doff PPE without contamination on

All staff must wear a designated scrub.

Airborne precautions using a FFP2 mask or equivalent; wear a mobcap to facilitate the removal of FFP2

Contact and droplet precautions in addition to using standard precautions: clean, non-sterile, gown with long –sleeved with fabric reinforcement (arms, front side) and gloves.

Eye protection with reusable goggles or facial protection (face shield) (soaked in bleach for 15 minutes).

Personal items are not allowed into the room.

In case of a sterile procedure the same precautions should be taken however using sterile gown and gloves.

Environment/equipment (no equipment should be shared)

If possible, patients are placed into negative pressure isolation rooms with anteroom and door closed at all time. Alarm supervision station and at best video camera equipment to monitor the patient

If negative pressure isolation rooms are not available, one may use mobile air decontamination units in the patient's room

Alcohol-based handrub and disinfectants, gloves, gowns, and masks should be readily available

Careful and frequent cleaning of surfaces with disposable clothes and bleach, or effective disinfectant

7.1.2 Investigational medicinal product in study of the effect of corticoids

Presentation:

Pre randomized, labelled, numbered according to the treatment list, Box of 10 DEXAMETHASONE 20 mg or NaCl 0,9%, solution for injection in ampoule of 5mL.

Each allocated box contains complete treatment from D1 to D10 for one patient.

Storage:

Treatments have to be stored below 25°C in a secured local.

Posology for clinical trial:

All patients from the experimental group will receive by IV route at the following dose: 14mg daily from day 1 to day 5 then 4mg daily from day 6 to day 10

7.1.3 Investigational medicinal product: study of the effect of oxygen support modality

7.1.3.1 In all groups

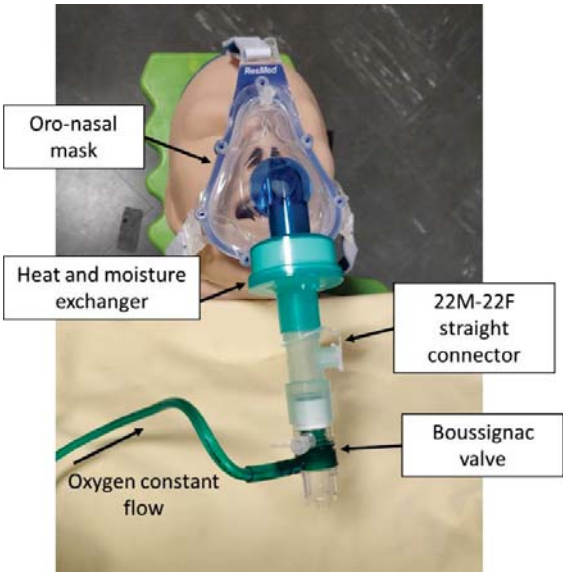
Within the hour after the validation of selection criteria, patients will be assigned to the allocated strategy (conventional oxygen or CPAP of HFNO) after having signed informed consent. In all groups, the oxygen flow will be adjusted to maintain an oxygen saturation level of 92% or more, as measured by means of pulse oximetry (SpO_2). Nursing staff at the site will administer the respiratory support under the responsibility of the investigator. Any omission of study treatment will be recorded in the Case Report Form (CRF) to monitor treatment compliance.

7.1.3.2 Standard oxygen treatment

Patients assigned to the standard treatment group will receive oxygen delivered through a nonrebreather face mask until endotracheal intubation, death, or fulfillment of oxygen delivery cessation criteria (an SpO_2 above 92% without oxygen and a respiratory rate below 25 cycles/min).

7.1.3.3 CPAP treatment

Patients assigned to the CPAP plus oxygen group will receive periods of CPAP in addition to the standard treatment. All study centers will use a Boussignac device (Vygon) connected to an oro-nasal mask composed of a transparent mask and a soft inflatable cushion, with a heat and moisture exchanger exchanger (“Filter Boussignac CPAP”). In order to protect the environment and the medical staff from any contamination from the patient’s airway, the principle of the “Filter Boussignac CPAP” is to add a heat and moisture exchanger, which acts as a “microbiological barrier” between the oro-nasal mask and the Boussignac valve. The connection requires a 22M-22F connector (Figure).



Any NIV mask can be used except for masks equipped with an intentional leak system, which must be proscribed in this situation to avoid contamination of healthcare workers.
The detailed procedure for the use of the Filter Boussignac CPAP is available at: **http://www.reamondor.aphp.fr/covid19**
CPAP will be started at 15L/min oxygen (which correspond to an average pressure of 8 cmH_2O. The level will be decreased to 10L/min or increased to 20L/min as needed based on the clinical response and tolerance. For at least the first 6 to 12 hours, CPAP will be given continuously and then discontinuously (for at least 6 hours/day) based on patient tolerance (5). CPAP will be continued until endotracheal intubation, death, or fulfillment of the following cessation criteria: SpO_2 above 92% and respiratory rate below 25 cycles/min with FiO_2 of 30% or less and a CPAP level of 5 cmH_2O. The criteria for oxygen delivery cessation will be the same as in the standard therapy group.

7.1.3.4 HFNO treatment

In the high-flow–nasal cannula group, oxygen will be delivered through a heated humidifier (Airvo-2, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, with a gas flow rate of 30 liters per minute and adjusted based on the clinical response. FiO_2 will be adjusted for the target SpO_2. HFNO will be continued until endotracheal intubation, death, or fulfillment of the following cessation criteria: SpO_2 above 92% and respiratory rate below 25 cycles/min with a FiO_2 of 30% or less and a gas flow of 30 liters per minute. The criteria for oxygen delivery cessation will be the same as in the standard therapy group.

7.2 Description of Additional medicinal product(s) (treatments required to conduct the study)

Patients will be allowed to receive non experimental medication required by their medical condition, particularly antiviral therapy.

7.3 Description of traceability elements accompanying the investigational medicinal product(s)

Sponsor will provide local pharmacies with experimental treatments.
Automatic allocation system obligates to store all boxes in a single place. According to local organization, it will be in local pharmacy or in ICU.

7.4 Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

Open label steroids (hydrocortisone as a 50-mg intravenous bolus every 6 hours, and fludrocortisone given as a 50-µg tablet through a nasogastric tube once daily, for 7 days, without tapering) will be authorized in case of septic shock defined as follows:

- the presence of a clinically or microbiologically documented infection,
- a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 for at least two organs for at least 6 hours,
- and receipt of vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥0.25 µg per kilogram of body weight per minute or ≥1 mg per hour), increasing for at least 6 hours to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg (18).

In both groups, the administration of low-dose dexamethasone (at 6 mg/day) will be part of the standard of care, including the continuation of any administration of dexamethasone to patients who have already been administrated dexamethasone before arriving in ICU.
Such an administration is indeed that recommended by the French *Haut Conseil de Santé Publique* in patients aged less than 70 years.

7.5 Methods for monitoring compliance with the treatment

The compliance to allocated treatment will be evaluated daily in a specific CRF by the investigator in charge of the patient.

Ten removable labels are present on each box to permit traceability of each administration on “administration monitoring form for nurse”.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

For the study of the effect of high-dose corticosteroids

The primary efficacy outcome variable is the time-to-death from all causes at Day 60 after randomization.

Secondary efficacy endpoints include:

1. The cycle threshold for SARS-CoV-2 PCR at baseline, day 7 and end-of therapy in samples of the same origin (preferably subglottic i.e. bronchoalveolar lavage protected telescopic catheter or tracheal aspiration, otherwise nasopharyngeal swab)
2. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and D28
3. Number of days alive without mechanical ventilation between randomization and day 28
4. Changes in SOFA score from day 1 to day 3, day 7, day 10, day 14, day 21, day 28 or discharge-day from ICU as appropriate
5. Number of days alive without renal replacement therapy between randomization and day 28
6. Length of ICU-stay and hospital-stay

For the study of the effect of oxygen support modality

The primary efficacy outcome variable is the cumulative incidence of mechanical ventilation within 28 days after randomization. We will take into account death as a potential competing risk to mechanical ventilation.

Secondary efficacy endpoints are:

1. Overall mortality at day 28 and day 60
2. Number of days alive without invasive mechanical ventilation between randomization and day 28
3. Proportion of patients with severe hypoxemia, which is defined as an oxygen saturation of less than 80% during the same interval during the interval between induction and 2 minutes after tracheal intubation
4. Proportion of patients with cardiac arrest within 1 hour after intubation

5. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and day 28
6. Lengths of ICU-stay and hospital-stay

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

For the study of the effect of corticosteroids

Primary Efficacy Outcome Variable

Parameter: overall mortality

Method: vital status assessment

Timetable: day 60

Secondary Efficacy Outcome Variables

1. Parameter: The cycle threshold for SARS-CoV-2 PCR
   Method: SARS-CoV-2 PCR on samples of the same origin (preferably subglottic i.e. bronchoalveolar lavage, plugged telescopic catheter or tracheal aspiration, otherwise nasopharyngeal swab)
   Timetable: at baseline, day 7 and end-of therapy
2. Parameter: Proportion of patients with at least one episode of any healthcare associated infection between randomization and D28
   Method: medical history
   Timetable: registration of the number of patients with at least one episode of any healthcare associated infection between randomization and D28
3. Parameter: Number of days alive without mechanical ventilation between randomization and day 28
   Method: medical history
   Timetable: registration of the number of days on which the patient received invasive or noninvasive mechanical ventilation between randomization and day 28
4. Parameter: Changes in SOFA score
   Method: The SOFA score, a scoring system to determine the extent of 6 organ systems dysfunctions has the advantage to be very sensitive. The scale of the SOFA score ranges from 0 to 24, with higher scores indicating a greater severity of organ failure. Sub-scores of SOFA range from 0 to 4 for each of the 6 organ systems (respiratory, cardiovascular, hepatic, coagulation, renal and neurological), with an aggregate sum score of 0 to 24.
   Timetable: D1, D3, D7, D10, D14, D21, D28 or ICU-discharge day

5. Parameter: Number of days alive without renal replacement therapy between randomization and day 28
   Method: medical history
   Timetable: registration of the number of days on which the patient received renal replacement therapy between randomization and day 28
6. Parameter: Length of ICU-stay and hospital-stay
   Method: medical history
   Timetable: date of ICU and hospital discharge

For the study of the effect of oxygen support modality

Primary Efficacy Outcome Variable

Parameter: mechanical ventilation

Method: ventilation mode assessment

Timetable: daily until day-28 or ICU discharge

Secondary Efficacy Outcome Variables

1. Parameter: Overall mortality at day 28 and day 60
   Method: vital status (obtained by telephone if the patient is discharged from hospital or lost to follow-up)
   Timetable: day 28, day 60
2. Parameter: Number of days alive without invasive mechanical ventilation between randomization and day 28
   Method: medical history
   Timetable: registration of the number of days on which the patient received invasive or non-invasive mechanical ventilation between randomization and day 28
3. Parameter: Proportion of patients with severe hypoxemia
   Method: medical history
   Timetable: registration of the number of patients with severe hypoxemia, defined as an oxygen saturation of less than 80% during the same interval during the interval between induction and 2 minutes after tracheal intubation
4. Parameter: Proportion of patients with cardiac arrest within 1 hour after intubation
   Method: medical history
   Timetable: registration of the number of patients with cardiac arrest within 1 hour after intubation
5. Parameter: Proportion of patients with at least one episode of any healthcare-associated infection between randomization and day 28
   Method: medical history

Timetable: registration of the number of patients with at least one episode of any healthcare-associated infection between randomization and day 28

6. Parameter: Length of ICU-stay and hospital-stay
   Method: medical history
   Timetable: date of ICU and hospital discharge

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

The steering committee includes:

The coordinating investigator: Pr Jean-François Timsit

The scientific director: Pr Lila Bouadma

The methodologists: Pr Sylvie Chevret, Dr Charles Burdet,

The representative of the sponsor: Naima Beldjoudi (URC Paris Nord) and Fadila Amerali (DRCI)

The missions of the steering committee are to organize the research, to coordinate the information and to monitor the conduct of research.

The steering committee meets every 6 months.

9.2 Scientific Committee

List the members of scientific committee:

- Pr Jean-François Timsit, Medical Reanimation, AP-HP BICHAT

- Pr Lila Bouadma (ICU, Bichat), Pr Julien Poissy (ICU, CHU Lille), Pr Armand Mekontso Dessap (ICU, Henri Mondor), Pr Ferhat Mezziani (ICU, CHU Strasbourg), Pr Yves Cohen (ICU, Avicenne), Pr Sylvie Chevret (URC Saint-Louis), Dr Benoît Visseaux (Virology Lab, Bichat), Dr Charles Burdet (DEBRC, Bichat).

The missions of the scientific committee are to define the objectives of the research, to propose changes of the protocol during research, to determine the methodology.

The scientific committee decides during the research what to do in unexpected situations.

The scientific committee will meet before first inclusion, at each interim analysis in same time DSMB committee.

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Description of Safety endpoints assessment parameters

For both studies (effect of high-dose corticosteroids and effect of oxygen support modality) the secondary safety outcome variables are:

- Proportion of patients with at least one episode of any healthcare-associated infection between randomization and day 28
- Changes in SOFA score from day 1 to day 3, day 7, day 10, day 14, day 21, day 28 or discharge-day from ICU as appropriate.

The evaluation of tolerance to treatments used in this study is not the main goal of this research project. However, adverse events will be collected in the CRF and the SAE will be reported to the sponsor.

10.2 Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints

For both studies (effect of high-dose corticosteroids and effect of oxygen support modality)

1. Parameter: Healthcare associated infection
   Method: clinical history, temperature, chest X-ray, bronchoalveolar lavage, tracheal aspiration, or nasopharyngeal samples
   Timetable: every day in the ICU
2. Parameter: overall mortality
   Method: vital status assessment
   Timetable: day28

In addition to these safety assessments, a data safety monitoring board will be constituted for this research.

3. Parameter: Changes in SOFA score
   Method: The SOFA score, a scoring system to determine the extent of 6 organ systems dysfunctions has the advantage to be very sensitive. The scale of the SOFA score ranges from 0 to 24, with higher scores indicating a greater severity of organ failure. Sub scores of SOFA range from 0 to 4 for each of the 6 organ systems (respiratory, cardiovascular, hepatic, coagulation, renal and neurological), with an aggregate score of 0 to 24.
   Timetable: day 1 to day 3, day 7, day 10, day 14, day 21, day 28 or ICU-discharge day

10.3 Recording and reporting adverse events

10.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalisation or prolongs existing hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorised.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.

For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.

Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction;

b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor, as well as potential follow-up reports;

c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety

Examples:

- a serious adverse event likely to be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed study on animal subjects (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted with the same investigational medicinal product in another country, for safety reasons
- an unexpected serious adverse reaction related to a non-investigational medicinal product required to conduct the trial, (e.g.: "challenge agents", rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants

e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

10.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF)

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:

- either by using general terms:
  - *Mild: tolerated by the patient, does not interfere with daily activities*
  - *Moderate: sufficiently uncomfortable to affect daily activities*
  - *Severe: prevents daily activities*
- or by using a rating scale for adverse events appended to the protocol : Common Terminology Criteria for Adverse Events(CTCAE) (V5.0 : November 27, 2017) [National Cancer Institute]

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product(s), or interventions/procedures added by the study.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

**Or study procedures

10.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay (and at the latest within 24 hours) on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death

2- is life-threatening to the participant enrolled in the study

3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.3.2.2 Specific features of the protocol

10.3.2.2.1 Other events that require the investigator to notify without delay the sponsor

- ***In utero* exposure**

The investigator must notify the sponsor without delay (and at the latest within 24 hours) on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

10.3.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms.

- *Normal and natural course of the condition*:
  - *Worsening of the respiratory condition under investigation*
  - *Ventilator-acquired bacterial pneumonia*
  - *Documented fungal infections*
  - *HSV/CMV PCR positivity after inclusion*
  - *Bloodstream infections*
  - *Hyperglycemia > 13 mM/ ml not resolving with insulin therapy*
  - *ICU acquired neuropathy*

The severe COVID-19 pneumonia admitted in ICU resulted in mechanical ventilation in 60-80% of the cases. ARDS occurred in more than ¾ of the intubated patients. Acute renal failure occurred in ARDS patients usually 3-5 days after ARDS onset. Hyperbilirubinemia (> 10 N) is common in the severe forms of ARDS with acute renal failure.

Ventilator associated pneumonia occurred in 20-30% of ARDS patients. Data on first patients with ARDS due to COVID-19 found nosocomial infections most of time occurring during the third and fourth week of evolution.

The primary objective of the study is to assess the impact of Dexamethasone on overall mortality at day-60 after randomization in patients admitted in ICU for severe COVID-19 infection.

The interventions added by the study being: injection of Dexamethasone IV, **deaths (only related to disease progression and not to the investigational medicinal product and/or procedures specific to the study) do not need to be notified to the sponsor without delay but will be recorded in the case report forms.**

The retrieval of deaths data will be sent by email to the members of the Data Safety Monitoring Board and to the safety Department (DRCI) at the address expertisecsi.drc@aphp.fr by the Clinical Research Unit before any meeting of DSMB and at least every 50 patients included.
It will be the same for nosocomial infections and the need for intubations (with delay between inclusion and intubation).

If there is any discrepancy between the groups or the mortality rate is higher than expected affecting participant safety and which requires the sponsor to take urgent safety measures, the ANSM (French Health Products Safety Agency) will be informed about the emerging safety issue without delay.

- Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up

  The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV). This frequently events are:

  - *Documented fungal infections*
  - *HSV/CMV PCR positivity after inclusion*
  - *Bloodstream infections*
  - *Hyperglycemia > 13 mM/ ml not resolving with insulin therapy*
  - *ICU acquired neuropathy*

10.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant signs the consent form
- throughout the whole follow-up period required for the trial (until D60 ± 2 weeks)
- after the end of the clinical trial if the SAE is likely to be due to the investigational medicinal product (IMP) or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital

abnormalities). In that case, the investigator does not have to systematically and indefinitely collect all SAEs possibly related to the IMP, but must notify all possible SAEs related to the IMP of which he has knowledge.

10.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.
Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.
Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department **by email (eig-vigilance.drc@aphp.fr).** It should be noted that it is possible to send SAE reports to the Safety Department **by fax to +33 (0)1 44 84 17 99** only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

10.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and procedures and any other treatments,

  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions

  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.

  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):

- refer to the SmPC for DEXAMETHASONE specialty enclosed in appendix 19.3 to this protocol

❖ The serious adverse events potentially related to the procedures or examinations specific to the study are:

- High-Flow Nasal Oxygen (HFNO) : ulceration of the nostril, nosebleeds and a theoretical risk of gastric distension
- Continuous Positive Airway Pressure (CPAP) : intolerance to the nasal mask, dry nose and mouth and / or rhinitis and rhinorrhoea
- Standard oxygen: ulceration of the nostril, nose bleeds, nasal / oral dryness.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:

- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.

Furthermore, ANSM requests that all suspected <u>expected</u> serious adverse reactions <u>if they are fatal or life-threatening</u> will be sent by the sponsor to the ANSM as SUSAR.

However, it is expected that the volume of these SARs is high.

<u>Then, the sponsor will send weekly to the ANSM a listing of all these SARs.</u>

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.3.3.3 Annual safety report

Not applicable as total research duration (6 months) less than 1 year.

10.3.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established for this trial. Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and sponsor. The DSMB members will be separate and independent of study personnel participating in this trial.

The DSMB will consist of independent members with appropriate expertise to contribute to the interpretation of the data from this trial. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The interim trial results will be monitored by the DSMB, and if at any stage evidence emerges that any one treatment arm is definitely inferior then it will be centrally decided that that arm will be discontinued. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB will review grouped data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability to continue, modify, or terminate this trial.

The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
- List the members of the DSMB:
    - Pr CARIOU Alain, Medical Reanimation, AP-HP Cochin
    - Pr BOYER Alexandre, Medical Reanimation, CHU Bordeaux
    - Dr Patricia PAVESE, Infectiology, CHU Grenoble
    - Pr Bruno GIRAUDEAU, Clinical Investigation Center, CHRU Tours

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

For the data collection in electronic format, the statistical software CleanWeb for data entry will be used. The software will fulfil the regulatory requirements and security norms.

11.3 Right to access data and source documents

11.3.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.
During this research, the Social Security Number (NIR) is collected.

The social security number is collected in order to enable subsequent matching with health insurance data (via the DCIR, inter-regime consumption datamart), hospital data (via the PMSI) and causes of death (via the CEPIDC).

The DCIR database contains all the individualised health care claims reimbursed by the French health insurance. These claims data include, in particular, drugs dispensed coded according to the Anatomical Therapeutic Chemical (ATC) classification, ambulatory medical acts coded according to the French medical classification of clinical acts (CCAM) and biological acts coded according to the French classification of biological acts (NABM).

The PMSI database provides detailed medical information on all admissions to public and private hospitals in France, including ICD-10 codes for discharge diagnoses, medical acts coded according to the French medical classification for clinical acts.

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

The bioinformatician will program the data entry software, as well as the consistency checks of the data (delay, limit values, conditional elements, and score calculations).

The proposed software will be validated by the Principal investigator as well as by the study team (methodologist, project manager, statistician, and data manager). The validated application will be available online and could be used for data entry.
The research team members could use the software functionalities for validation and consistency checks of data

The data manager, under the supervision of the reference statistician, will produce a document, the Data Validation Plan (DVP). There, validation rules for the consistencies checks of the data complementary to those initially programmed by the bioinformatician will be described.
By means of one of the statistical software, the data manager will program the controls, and will request clarification of the entries (queries) to the research team (ARCs).

When validation of the data circuit between ARC and data manager will finish, the later will write a Data-management report (controls done, new variables added, unsolved problems). At the end of this stage, a Database Freeze form will be validated and signed by the Principal investigator. The data manager will transfer the data to the statistician for analyses. In exceptional cases, it might be necessary to be back to the database. A « refrozen process » will be done identical to the one described before for the Database Freeze.

Statistical analysis will be performed under the responsibility of Pr Sylvie Chevret.
The data retention period in active database and in archiving will be 2 years after the publication of the research, as indicated in the information notice. This represents, according to the project, a total conservation of the data for 2 years until 2024. The details of this period:
- 14 months and 2 weeks for the study duration: 12 months of inclusion period and 2 months and 2 weeks of follow-up per patient

- 6 months of processing of the database (data-management and statistics) for preparation of the publication of the research. This duration is also justified by several types of complex biological analysis to be carried out at the end of the study.
- 24 months of storage after publication

11.4.2 Data entry

Data will be entered electronically via a web browser.
The research team will list individuals with software rights and their specific profiles. A profile assigns the software rights and specific roles to users. The data entry will be ensured by persons with specific profiles (data entry, data writing, data consistency checks…).

11.5 Data *ownership*

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 General considerations

Flow-charts will describe the flow of patients during the study, from inclusion until final participation, by randomization arms.

All analyses will be performed under the intention-to-treat (ITT principle), irrespective of the actual treatment of each enrolled patient who will be each analyzed in the group that has been attributed by randomization.

Summary statistics will be used, either frequencies and percentages for categorical variables, or median and interquartile range (IQR) for continuous or discrete variables. Number of missing values will be reported. No statistical tests will be performed between randomization groups in terms of base line characteristics.

Estimation of high-dose dexamethasone effect will be based on the direct comparison of the two randomization arms in the intention-to-treat (ITT) population. We will estimate the effect of high-dose dexamethasone, whatever the dose (20 mg), in comparison to the standard of care+Placebo arm (6 mg). We will secondly assess the treatment by period interaction (using the amendment date of September, 2020, as the threshold for protocol modification related to the standard of care).

Secondly, the estimated effect of the dose of actually administered dose of dexamethasone (either 0, 6, or 20 mg) will be based on the “as-treated” population, using the instrumental variable approach, as detailed below.

Estimation of the effect of the oxygenation, support systems, will be considered separately: HFNO versus standard oxygen, CPAP versus standard oxygen, with control for multiple comparisons based on Bonferroni adjustment (see sample size computation below). Exploratory analyses of the comparative benefit of CPAP versus HFNO will use Bayesian inference (see below), given it allows to quantify the distribution of the difference in outcomes across the two groups, conditionally on the recorded data in the trial.

Interim analyses of efficacy and safety data will use Bayesian monitoring in order to avoid inflation of type I error (see section 12.2.4 for details).

All statistical analyses will be performed using R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 3.6 or later, or SAS software v 9.1.

12.2 Planned statistical methods, including the timetable for any planned interim analyses

12.2.1 Analysis of the primary endpoints

The primary endpoints of the study are time-to-failure endpoints, that will be analyzed using survival methods assuming noninformative right-censoring of the data; this is obviously true for the cumulative incidence of all deaths, whatever the cause, used in the evaluation of corticosteroids; this is also assumed to be true in non-mechanically ventilated patients, due to the fact that no death prior to criteria for MV will be expected. In both cases, no lost to follow up that could be related to the disease will be expected within the first 28 or 60 days after study enrollment. Thus, only administrative censoring at the time of analysis (see below interim analyses) or at day 28 or day 60 (for patients still alive free of failure at that time) will be expected.

Under such assumptions, survival curves will be estimated in each randomization arm according to the Kaplan-Meier method, then compared by the Log-Rank test. Cox models stratified on the patient severity at inclusion (MV or not) will quantify the effect size by hazard ratio with 95% confidence intervals. Subset by treatment interactions will be tested by the Gail and Simon interaction statistics.

Beside the ITT analyses, analysis of the corticosteroids effect, will use an instrumental variable (IV) method in the "as-treated population[1]. The IV approach will be used to assess the magnitude of the as-received treatment effect in contrast to the ITT approach, which focuses on the as-assigned treatment effect, whatever the administered treatment. The use of two models under the IV approach, one relating treatment received to outcome (the AT model), and the other relating randomized intervention assignment to the treatment received, has led many researchers to refer to the IV method as a two-stage estimation procedure. The most common IV in medicine is randomization within a randomized controlled trial that has treatment contamination[2]: IV analysis can bridge the gap between the more policy focused question posed by intention to treat analyses and the patient focused question of biological efficacy This is particularly well-suited to our setting, where "contamination" refers to the administration of dexamethasone, possibly considering the dose actually administered. Note that the use of predictive covariates in the model relating the randomized intervention to treatment received will increase the precision of the predicted treatment probability that replaces observed treatment received in the IV model for the outcome. Including predictors of outcome in the model for outcome of course reduces the residual error.

12.2.2 Analysis of the secondary endpoints

In accordance to the secondary criteria for Dexamethasone versus standard of care,

1. The evolution of the viral load in the respiratory tract will modelled and compared by linear mixed models.
2. The proportions of healthcare-associated infection at day-28 and day-60 will be compared between groups by an exact Fisher test.
3. The number of days alive without mechanical ventilation will be compared between groups by a Wilcoxon rank sum test.
4. The evolution of SOFA-score will modelled and compared by linear mixed models.
5. The number of days alive without renal replacement therapy will be compared between groups by a Wilcoxon rank sum test.
6. The length of ICU and hospital-stay will be compared between groups by a Wilcoxon rank sum test.

[1] Sommer A, Zeger S. On estimating efficacy from clinical trials. Statistics in Medicine 1991;10:45– 52. [PubMed: 2006355]

[2] Sussman JB. An IV for the RCT: using instrumental variables to adjust for treatment contamination in randomised controlled trials. BMJ. 2010; 340: c2073.

Secondary analyses comparing (i) HFNO and standard oxygen therapy and (ii) CPAP and standard oxygen therapy

1. The number of days alive without mechanical ventilation will be compared by a Wilcoxon rank sum test.
2. The proportion of healthcare-associated infection at day-28 and day-60 will be compared by an exact Fisher test.
7. The length of ICU and hospital-stay will be compared by a Wilcoxon rank sum test

12.2.3 Calculation hypotheses for the number of participants required and the result

Computation of sample sizes has been done for each intervention, independently. Based on those computation, it was computed that the trial needs to recruit 550 subjects including 330 patients who were not mechanically-ventilated at inclusion.

1) **Effect of high-dose dexamethasone**

According to the literature, the reported cumulative incidence of death at Day-60 is about 60%.

A two-sided log-rank test with an **overall sample size of 550 subjects** (275 in each group) achieves 80.1% power at a 0.050 significance level to detect a hazard ratio of 0.75 when the proportion surviving in the control group is 0.40 (that is, the survival rate in the Dexamethasone group is expected to be 0.50). The study lasts for 150 days of which subject accrual (entry) occurs in the first 90 days. The accrual pattern across time periods is uniform (all periods equal). No subjects drop out of the control group. No subjects drop out of the treatment group. No patient is assumed to switch from the control group to the other group.

2) **In the population of non-severe non-mechanically-ventilated Covid-19 infected patients**

Based on data from the literature, the cumulative incidence of intubation at day 28 is estimated to be 80% in the standard of care group.

Computation was done for each of the two comparisons, using an adjusted type I error rate of 0.025 given the multiple comparisons.

A two-sided log-rank test with an overall sample size of 220 subjects (110 in the control group and 233 in the treatment group) achieves 80.0% power at a 0.025 significance level to detect a hazard ratio of 0.65 when the proportion surviving in the control group is 0.20 (that is, a 28-day cumulative incidence of need for VM of 80% in the control arm versus 65% in the experimental arm). The study lasts for 120 days of which subject accrual (entry) occurs in the first 60 days. The accrual pattern across time periods is uniform (all periods equal). No

subjects drop out of the control group. No subjects drop out of the treatment group. No switches are expected.
Therefore, a total of 110 patients in each of the 3 arms will be required, that is a total of 330 non mechanically ventilated patients at randomization to be included in the trial.

12.2.4 Interim Analyses

For ethical reasons, clinical trial data will be analyzed repeatedly at any time prior to the formal completion of the trial, as recommended for decades (19), with results presented to the data monitoring committee of the trial. Moreover, when comparing multiple commercially available and perhaps U.S. Food and Drug Administration (FDA)- or European Medicines Agency (EMEA)-approved products or treatment strategies against one another via comparative effectiveness research (CER) trial, Bayesian analyses appear particularly well suited (20–22). Indeed, Bayesian approaches to the monitoring of group sequential designs have two main advantages compared with classical group sequential designs (23,24): first, they facilitate the implementation of interim success and futility criteria that are tailored to the subsequent decision making based on explicit probabilistic statements (that may offer strong benefit for their ability to calculate the probability that each treatment is the best or worst) (25), and second, they allow inclusion of prior information on the treatment differences and on the control group, actualized over the trial.
Interim monitoring for success will begin after 50 patients have been enrolled and will be repeated after every additional 50 patients are enrolled. Interim analyses will be stratified on the patient base line severity group, based on the primary outcome measure and main secondary endpoints of each stratum:

- Severe group: survival time, SOFA score
- Moderate group: time to MV criterion, survival

The analyses will therefore rely on computing the posterior distribution of the hazard ratio (main endpoints) or between the experimental and control arms for time-to-event co-primary outcomes and the posterior distributions of event rates in each arm for binary co-primary outcomes. From the latter, the posterior distribution of the difference in event rate will be derived. These posterior distributions will be graphically displayed, and summarized by their medians and 95% credibility intervals (the Bayesian counterparts of confidence intervals).

Noninformative priors will be used, that is the prior distribution for the log hazard ratio will be a Gaussian distribution with mean 0 and variance 10^6. Following Harrel and Lindsell, posterior probabilities will be reported as follows[3]:

P1=P(HR < 1 | data)	Any benefit
P2=P(HR < 0.75 | data)	High-dose DXM benefit
P3=P(HR < 0.65 | data)	Oxygen support benefit
P4=P(HR >1.05 | data)	More than trivial harm
P5=P(0.8 <HR <1.2 | data)	Similarity between oxygenation supports

For this study, action triggers will be:
Stop with evidence for efficacy if P1>0.95
Stop with evidence for moderate or greater efficacy if P2 or P3>0.8
Stop with evidence for inefficacy if P4>0.8
Stop with evidence for harm if P5>0.75

Last, once at least 100 patients have been enrolled, and thereafter after every additional 50 patients, we will also assess the presence of any period-by-treatment interaction, by estimating the ratio of the estimated effect in both periods, in a Bayesian setting[4]. Posterior probabilities of such a ratio will be estimated using Markov chain Monte Carlo (MCMC) methods.

The DSMB could be asked to recommend early termination based on results of the safety/efficacy interim analyses.

12.2.5 Anticipated level of statistical significance

Final anticipated level of statistical significance is of 0.05.

12.2.6 Method for taking into account missing, unused or invalid data

Missing data for the primary endpoint (vital status or ventilation mode), and other endpoints related to the ICU stay are not expected. Indeed, the complete follow up of each enrolled patient is assured by the study's design since the observation period is defined from day 1

[3] https://hbiostat.org/proj/covid19/bayesplan.html
[4] Millen BA, Dmitrienko A, Song G. Bayesian assessment of the influence and interaction conditions in multipopulation tailoring clinical trials. J Biopharm Stat. 2014;24(1):94-109.

(randomization) until day 28, ICU discharge, or death, whichever occurs first. For the other endpoints, missing data will be handled by multiple imputation techniques

Missing data will be described on the overall population and by treatment group, and method of handling them according to their frequencies and nature will be used. Sensitivity analysis will confirm reliability of conclusions upon various hypotheses on missing values.

12.2.7 Management of modifications made to the analysis plan for the initial strategy

All major modifications to the planned analysis will be submitted to approval of the scientific committee.

12.2.8 Choice of individuals to be included in the analyses

All primary analyses will follow the Intention-to-treat method. All randomized patients will be analyzed in their allocated group, irrespective of intervention eventually received or lost to follow-up. Deviations from the protocol will be registered as well as the raisons for deviation.

Estimation of administered corticosteroid effect will use the as-treated population, where each patient will be considered in the group (either 0, 6, or 20, mg) of administered dexamethasone.

12.3 Metanalysis of individual data of the patients enrolled in the 3 phrc flash

According to the DGOS suggestion, we planned a meta-analysis of individual data according to the proposal abstracted below:

Steroids in ICU Adults with COVID19

An Individual Patient Data Meta-Analysis

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REMAP-CAP COVID-19 : Pr Djillali Annane, Service de Réanimation, Hôpital Raymond Poincaré, Université Versailles Saint Quentin, Garches, 92380, France

CAPE-COVID19 : Pr Pierre-François Dequin, Service de Réanimation, Centre Hospitalier Universitaire de Tours, 37 044 Tours, France

Statisticians

Pr Sylvie Chevret, Service de Biostatistique et Informatique Médicale, Hôpital St Louis, Université Paris Diderot, ECSTRRA Team, CRESS UMR 1153 Paris, 75010, France

Pr Bruno Giraudeau, Service de Biostatistique, Centre Hospitalier Universitaire de Tours, 37 044 Tours, France

12.3.1 Introduction

Three clinical trials at the time are scheduled to be perform in ICU patients with COVID19, aiming at evaluating the benefit of corticosteroids in those patients [1,2,3].

The primary objective of this study is to estimate with maximal precision the effects of corticosteroids on 28-day mortality in ICU patients with COVID19, by leveraging (i) the possibility of combining individual patient data from different trials and (ii) the availability of informative baseline data on trial patients. Therefore, we will conduct a study using individual patient data (IPD) from the three trials on low-dose corticosteroids for ICU patients with COVID 19 syndrome. In addition, in order to better personalize the treatment, the second objective of this study is to assess treatment effects according to the drug used, either dexamethasone or hydrocortisone, to modalities of drug administration (bolus versus continuous infusion for hydrocortisone; fixed 7-day treatment duration versus variable duration), to disease severity (ARDS only versus multiple organ dysfunction), and age (< versus > 60-year-old)

12.3.2 Methods

12.3.2.1 Study Design

The present study is an individual participant data (IPD) meta-analysis of randomised controlled trials designed to test the hypothesis that short term association of corticosteroids reduces mortality in ICU adults with COVID19. The present meta-analysis will be performed according to the PRISMA-IPD statements (26).
The intention to treat population will be used for all analyses, i**ncluding all patients according** to randomised treatment arm regardless of actual treatment.

12.3.2.2 Population

We considered ICU adults with acute hypoxemic respiratory failure (AHRF) COVID19 as defined in individual trials. A summary of the inclusion and exclusion criteria for each individual trial is provided in Table 1.

Table 1: Comparison of eligibility criteria of the trials

	REMAP-CAP COVID-19	COVIDICUS	CAPE-COVID19
Main inclusion criteria	1. Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission 2. symptoms or signs or both that are consistent with lower respiratory tract infection 3. AND 4. Radiological evidence of new onset infiltrate of infective origin 5. Up to 48 hours after ICU admission, receiving organ support with one or more of: • Non-invasive or invasive ventilatory support; • vasopressor or inotropes or both 6. Proven/ suspected COVID-19 infection	1. Age ≥ 18 years 2. Admitted to ICU within 48 hours 3. Confirmed or highly suspected COVID-19 infection 4. Acute hypoxemic respiratory failure (PaO2 <70 mmHg or SpO2<90% on room air or tachypnea>30/min or labored breathing or respiratory distress; need for oxygen flow >=6L/min) 5. Any treatment intended to treat the SARS-CoV-2 infection. 6. Written informed consent from the patient or a legal representative if appropriate	1. ≥ 18 years 2. Admission to the ICU 3. Lab confirmation of SARS-CoV-2 infection 4. Focal shadowing/infiltrate on chest X-ray or CT-scan 5. At least one of the following: • Mechanical ventilation (PEEP ≥ 5 cm H2O) • High-flow oxygen therapy with a FiO2 ≥ 50% and a P/F < 300 • Non--rebreathing mask oxygen therapy with an estimated P/F ratio < 300 (tables) • Pneumonia Severity Index (PSI) > 130 6. Study drug infusion initiated no longer than 24 hours post first severity criterion 7. Patient receiving an anti-viral therapy 8. Informed consent
		1. Moribund status 2. Pregnancy or breastfeeding 3. Long term corticotherapy at a dose of 0.5mg/kg/j or higher 4. Active and untreated bacterial, fungal or parasitic infection	1. Cystic fibrosis 2. Co-infection with flu (rapid PCR-test) 3. Active tuberculosis or fungal infection 4. Active viral hepatitis or active infection with herpes viruses 5. Patient needing anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason. 6. Patient already enrolled in another trial with ventilator-free days as endpoint 7. Pregnant or breastfeeding woman 8. Patient on judicial protection

12.3.2.3 Interventions

The experimental interventions considered for this analysis corticosteroids, with three possible drug regimens: (a) Dexamethasone IV (14mg D1-D5 then 4mg D6-D10), (b) low dose hydrocortisone (200mg of intravenous (bolus q6 or continuous infusion) hydrocortisone daily for 7 days or variable duration), or (c) placebo or usual care.

12.3.2.4 Outcomes

We considered 28-day mortality as the primary outcome. The secondary outcomes will be mortality at 90 days and at discharge, cumulative incidence of a SOFA score <8, of vasopressor, of organ free days (vasopressor free days, mechanical ventilation free days, renal replacement free days et ICU free days), and of mechanical ventilation withdrawal, as well as length of stay in ICU and in hospital. We also analysed the rate of superinfection, as defined by any new infection occurring ≥48 hours after randomization, acquired ICU muscle weakness.

12.3.2.5 Statistical Analysis

Common variables from all three datasets will be gathered and combined to conduct the analysis. All analyses will be performed on an intent-to-treat basis. Baseline patient characteristics will be presented by study and treatment group. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) will be reported as descriptors of central tendency, as appropriate. For categorical variables, the number of observations in each category and corresponding proportions are reported. Patient characteristics across groups will be contrasted using nonparametric Kruskal-Wallis tests for continuous variables and chi-square or Fisher exact tests for categorical variables.

We will consider of primary interest the comparison between either hydrocortisone or dexamethasone and either standard of care or placebo. Pre-specified secondary analyses included all possible pairwise comparisons, namely hydrocortisone versus control, dexamethasone versus control, and hydrocortisone versus dexamethasone.

For direct comparisons, we will conduct a conventional meta-analysis to synthesize the results, using random-effects models and fixed-effects models as sensitivity analyses. We will estimate the average treatment effect adjusting for study, age, baseline CRP, Simplified Acute Physiology Score (SAPS2) and SOFA score at baseline, and initial need for mechanical ventilation. Many of these covariates are highly associated with mortality, rendering substantial the potential for increased efficiency. For each outcome of interest, the

average treatment effect will be described using a hazard ratio (HR) estimate along with a corresponding 95% CI and p-value. The presence of qualitative interactions between treatment effect and baseline characteristics will be investigated using the Gail and Simon interaction test.

Secondly, we will combine direct and indirect comparisons via a network meta-analysis using the hierarchical model of Lu and Ades (27) with a Bayesian approach. In a Bayesian framework, estimates are based on the posterior distribution of the endpoint and are called credible intervals (Cis). Usually, the 95% CI corresponding to the interval that has a posterior probability of 95% that the endpoint lies within it. Unlike the frequentist approach, the Bayesian approach does not allow the calculation of the p value. Conclusions are drawn from whether or not 1 (which corresponds to a no-difference relative risk) or 0 (which corresponds to no mean differences) belongs to the credible interval. We will use Markov Chain Monte Carlo to implement the model.

All tests will be two-sided and conducted at significance level 0.05. All analyses will be performed in the R statistical environment running on a Mac OS X platform.

12.3.2.6 References

1. REMAP-CAP COVID-19 (NCT02735707)
2. CAPE-COVID19
3. COVIDICUS
4. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. Cochrane Database Syst Rev 2015;:CD002243. doi:10.1002/14651858.CD002243.pub3

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.

The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

13.1.2 Scope of centre monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: **HIGH** level.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.

A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study. The consent is obtained when the patient arrive in ICU before the randomisation.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent or consent from any other person in the cases set forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code) as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

For patients who are unable to give consent and patients under guardianship/legal protection, in accordance with Article L.1122-2 CSP, the consent of a relative or support person will be required, if they are present.

But if the relative or support person is not present or no existing, the emergency inclusions will be allowed in accordance to the French Public Health Code, article L1122-1-3, because, in this research protocol, the condition of the patient upon arrival in the ICU requires the protocol's treatment strategy.

And the relative or support person will be informed as soon as possible and a new consent will be required for the pursuit of this research. The relative or support person and the concerned person may also oppose to the use of his data in the research.

And the concerned person will be informed as soon as possible and a new consent will be required for the pursuit of this research. The patient may also oppose to the use of his data in the research

Special circumstances: If the person is physically unable to give his or her written consent, consent may be witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative. These persons must be fully independent of the investigator and of the sponsor.

14.2 *Prohibition from participating in another clinical study or exclusion period set after the study*

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study. They will be allowed to participate to non-interventional research (cat 3) at any time during the trial.

14.3 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.4 Legal obligations

14.4.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.4.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.4.3 Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.4.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Request for authorisation by the CNIL (French Data Protection Agency)

This research is not governed by the CNIL “Reference Method” (MR-001) becauseinclusion due to an emergency situation without collection of consent at the time of inclusion and collect of social security numbers/NIRs.

The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.
A informed consent is given to patients before their inclusion in the study, which details the procedures taken by the sponsor about the regulation GDPR.
The processing of data collected in this study is in accordance with the patients' rights conferred by this law. (See informed consent)

14.4.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.4.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.4.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :

- the successive versions of the protocol (identified by the version number and its date), and any appendices
- the ANSM authorisations and CPP (Research Ethics Committee) decisions
- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2020 (Ministère de la Santé)

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

The following terms will be used for any publication relative to this research:
AP-HP, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

The following sentence will be used for any publication relative to this research in the acknowledgments:

"The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Innovation Delegation)"

16.3 Mention of the financial backer in the acknowledgements of the text

The following sentence will be used for any publication relative to this research in the financial acknowledgement: The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2020 (Ministère de la Santé)

This study has been registered on the website http://clinicaltrials.gov/ under number NCT 04344730

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18 LIST OF ADDENDA

18.1 Serious Adverse Events notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **COVIDICUS**

⚠ **Recherche prioritaire sur COVID-19**

Code de la Recherche : APHP 200388

Risque : D

Date de notification : |__|__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Date de prise de connaissance de l'EIG par l'investigateur : |__|__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Titre complet de la recherche :

"Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia"

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale – initiale
nom prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance :
|__|__|__|__|__|__|
mm aaaa

Age : |__|__|__|ans

Date de signature du consentement : |__|__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Date de randomisation : |__|__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :

.....
.....
.....
.....
.....
.....
.....

Pour les patients non-ventilés :
☐ Groupe DXM-O2 ☐ Groupe DXM-CPAP ☐ Groupe DXM-HFNO
☐ Groupe Placebo-O2 ☐ Groupe Placebo -CPAP ☐ Groupe Placebo -HFNO
Pour les patients déjà ventilés :
☐ Groupe DXM ☐ Groupe Placebo
N° randomisation (si nécessaire) : N° traitement (si nécessaire) :

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Administration de la DEXAMETHASONE de J1 à J5	…IV…	14 mg/j	|__|__|__|__|_2_|_0_|__|__|	☐	|__|__|__|__|_2_|_0_|__|__|
Administration de la DEXAMETHASONE de J6 à J10	…IV…	4 mg/j	|__|__|__|__|_2_|_0_|__|__|	☐	|__|__|__|__|_2_|_0_|__|__|
Administration du Placebo : NaCl 0,9% ……	…IV…	……	|__|__|__|__|_2_|_0_|__|__|	☐	|__|__|__|__|_2_|_0_|__|__|

5. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Mise en place du système d'oxygénation : HFNO, CPAP, Oxygénation conventionnelle.	|__|__|__|__|_2_|_0_|__|__|	☐	☐
……	|__|__|__|__|_2_|_0_|__|__|	☐	☐

COVIDICUSErreur ! Source du renvoi introuvable.

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|

n°centre – n° ordre de sélection – initiale – initiale
nom prénom

6. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable
(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)

⇨ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire

……

<u>Organe(s) concerné(s)</u> :

……

<u>Date de survenue des premiers symptômes</u> : |__|__|__|__|_2_|_0_|__|__|

Préciser lesquels :

……

<u>Date d'apparition</u> de l'EIG :

|__|__|__|__|_2_|_0_|__|__|

jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

<u>Délai</u> entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :

|__||__| / |__||__| |__||__|

jj hh min

<u>Critères de gravité</u> :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__|__|__|_2_|_0_|__|__|

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME

☐ arrêt définitif du ME

☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|

☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : ……

L'évènement a-t-il conduit à une levée d'insu ?

☐ Non ☐ Oui Date : |__|__|__|__|_2_|_0_|__|__| ☐ Non applicable

L'évènement fait-il suite à :

- une erreur médicamenteuse ? ☐ Non ☐ Oui Date : |__|__|__|__|_2_|_0_|__|__|
- un surdosage ? ☐ Non ☐ Oui Date : |__|__|__|__|_2_|_0_|__|__|
- un mésusage ? ☐ Non ☐ Oui Date : |__|__|__|__|_2_|_0_|__|__|
- autre (préciser) : …… ☐ Non ☐ Oui Date : |__|__|__|__|_2_|_0_|__|__|

au |__|__|__|__|_2_|_0_|__|__| ☐ *en cours*

☐ Décès

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

☐ Autre(s) critère(s) médicalement significatif(s), préciser :

……

……

Degré de sévérité :

☐ Léger ☐ Modéré ☐ Sévère

COVIDICUS Erreur ! Source du renvoi introuvable.

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale - initiale
nom prénom

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__|__|__|__|_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__|__|__|__|_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....
.....
.....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....
.....
.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

<u>Lié à la recherche</u> :

☐ **Oui :** ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**

Lequel : …DEXAMETHASONE / PLACEBO ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**

La/lequel(le) : ……HFNO…… ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

La/lequel(le) : ……CPAP…… ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

La/lequel(le) : Oxygénation conventionnelle. ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : Infection à COVID-19**

☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**

☐ **à une maladie intercurrente, laquelle : ……**

☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

18.2 Pregnancy notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

1. Identification de la recherche

Acronyme : COVIDICUS

Recherche prioritaire sur COVID-19

Code de la recherche : APHP 200388

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Date de prise de connaissance de la grossesse par l'investigateur : |__|__|__|__|__|2_|0_|__|__|
jj mm aaaa

Titre complet de la Recherche :

"Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia"

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

Date de naissance : |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|

Groupe de randomisation :
Pour les patients déjà ventilés :
☐ Groupe DXM ☐ Groupe Placebo
Pour les patients non-ventilés :
☐ Groupe DXM-O2 ☐ Groupe DXM-CPAP ☐ Groupe DXM-HFNO
☐ Groupe Placebo-O2 ☐ Groupe Placebo -CPAP ☐ Groupe Placebo -HFNO

Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

Date de naissance : |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|

Groupe de randomisation :
Pour les patients déjà ventilés :
☐ Groupe DXM ☐ Groupe Placebo
Pour les patients non-ventilés :
☐ Groupe DXM-O2 ☐ Groupe DXM-CPAP ☐ Groupe DXM-HFNO
☐ Groupe Placebo-O2 ☐ Groupe Placebo -CPAP ☐ Groupe Placebo -HFNO

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux : **Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence)	Date de première administration	Date de dernière administration	Voie	Posologie / 24h

ou Dénomination Commune Internationale	Ou non administré	Ou en cours	d'administration(1)	
Administration de la DEXAMETHASONE de J1 à J5	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IV**	**14 mg/j**
Administration de la DEXAMETHASONE de J6 à J10	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IV**	**4 mg/j**
Administration du Placebo : NaCl 0,9%	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IV**	

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
Mise en place du système d'oxygénation : HFNO, CPAP, Oxygénation conventionnelle	|__|__||__|__| |_2_|_0_|__|__|		

Acronyme : *Erreur ! Source du renvoi introuvable. Erreur ! Source du renvoi introuvable.* ***COVIDICU***

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale – initiale
nom prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0185

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

Souffrance fœtale : ☐ Non ☐ Oui, précisez :

Mort-né : ☐ Non ☐ Oui, précisez :

Placenta normal : ☐ Oui ☐ Non, précisez :

Liquide amniotique : ☐ Clair ☐ Autre, précisez :

Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune		
10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)		
Sexe : ☐ Masculin ☐ Féminin Poids : |__|__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____		
Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :		
Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :		
Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable		
Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

18.3 SmPC or Investigator's Brochure

Refer to the SmPC for the Dexamethasone should be consulted:

http://document-rcp.vidal.fr/2c/48fb7289565b43f5a03d5377dfd13d2c.pdf

18.4 EQ-5D-5L questionnaire

EQ-5D-5L
Questionnaire sur la santé
Version française pour la France
(French version for France)

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

MOBILITÉ

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes légers pour me déplacer à pied ❑
J'ai des problèmes modérés pour me déplacer à pied ❑
J'ai des problèmes sévères pour me déplacer à pied ❑
Je suis incapable de me déplacer à pied ❑

AUTONOMIE DE LA PERSONNE

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

ACTIVITES COURANTES *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes légers pour accomplir mes activités courantes ❑
J'ai des problèmes modérés pour accomplir mes activités courantes ❑
J'ai des problèmes sévères pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

DOULEURS / GÊNE

Je n'ai ni douleur ni gêne ❑
J'ai des douleurs ou une gêne légère(s) ❑
J'ai des douleurs ou une gêne modérée(s) ❑
J'ai des douleurs ou une gêne sévère(s) ❑

J’ai des douleurs ou une gêne extrême(s) ❑

ANXIÉTÉ / DÉPRESSION

Je ne suis ni anxieux(se), ni déprimé(e) ❑

Je suis légèrement anxieux(se) ou déprimé(e) ❑

Je suis modérément anxieux(se) ou déprimé(e) ❑

Je suis sévèrement anxieux(se) ou déprimé(e) ❑

Je suis extrêmement anxieux(se) ou déprimé(e) ❑

18.5 MRC Score

Score neuromusculaire MRC (*Medical Research Council*)

Fonctions évaluées (6 à droite et 6 à gauche)	Score attribué à chaque groupe musculaire
Abduction du bras	0 = absence de contraction visible
Flexion de l'avant-bras	1 = contraction visible sans mouvement du membre
Extension du poignet	2 = mouvement insuffisant pour vaincre la pesanteur
Flexion de cuisse	3 = mouvement permettant de vaincre la pesanteur
Extension de la jambe	4 = mouvement contre la pesanteur et contre résistance
Flexion dorsale du pied	5 = force musculaire normale

Chaque membre est coté de 0 à 15. Le score total va de 0 (tétraplégie complète) à 60 (force musculaire normale).

Statistical Analysis Plan

TRIAL FULL TITLE	Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia
EUDRACT NUMBER	2020-001457-43
SAP VERSION	1
ISRCTN NUMBER	
SAP VERSION DATE	August, 2021
TRIAL STATISTICIAN	Pr Sylvie Chevret
TRIAL CHIEF INVESTIGATOR	Pr Jean-François TIMSIT
SAP AUTHOR	Pr Sylvie Chevret

SAP Signatures

Chief Investigator

Name:

Signature: _____

Date: _____

Statistician

Name: Chevret

Signature: _____

Date: Augus., . ., ...

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1 Abbreviations and Definitions

The list of the abbreviations and acronyms used in the Statistical Analysis Plan (SAP) with definitions is reported below. All terms appear in alphabetical order.

AE	Adverse Event
AHRF	Acute hypoxemic respiratory failure
ARDS	Acute respiratory distress syndrome
CER	comparative effectiveness research
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DNR	Do not resuscitate orders
DXM	Dexamethasone
FiO2	Inspired oxygen fraction
HFNO	High-Flow Nasal Oxygen
ICU	Intensive Care Unit
IQR	Inter Quartile Range
IMP	Investigational Medical Product
MCMC	Markov chain Monte Carlo
MV	Mechanical ventilation
NIV	Non Invasive ventilation
paO2	Partial oxygen pressure
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOFA	Sepsis-related Organ Failure Assessment
SpO2	Oxygen saturation of hemoglobin
URC	Unit of Clinical Research
VAP	ventilation-acquired pneumonia

2 Introduction

2.1 Summary

The main manifestation of COVID-19 is acute hypoxemic respiratory failure (AHRF). In patients with AHRF, the need for invasive mechanical ventilation (MV) is associated with high mortality. The place of steroids is of paramount importance in patients suffering from viral pneumonia related to COVID-19. The lung damage at this phase could be related to immunopathological lesions, resulting from an overexuberant pro-inflammatory host response, rather than uncontrolled viral replication, as suggested by the description of Huang and al., suggesting that a cytokine proinflammatory storm was associated with disease severity.

Our hypotheses were that the use of High-Flow Nasal Oxygen (HFNO) or Continuous Positive Airway Pressure (CPAP) might reduce the need for mechanical ventilation and that steroids can reduce mortality of severe COVID-19 patients. We used dexamethasone as successfully used in acute respiratory distress syndrome (ARDS).

Two hypotheses were thus specifically tested in this study.

The first hypothesis was the benefit of high dose corticosteroid therapy on severe COVID-19 infection admitted in ICU in terms of survival.

The second hypothesis was that, in the subset of patients free of mechanical ventilation at admission, either CPAP or HFNO allows to reduce intubation rate safely during COVID-19 related acute hypoxemic respiratory failure.

2.2 Purpose of the analyses

The analyses will assess the efficacy and safety of high dose dexamethasone in comparison with the standard of care (scheduled to receive low dose of dexamethasone) and will be included in the clinical study report

3 Study Objectives and Endpoints

3.1 Study Objectives

3.1.1 Primary objective

For the study of the effect of corticosteroids: To assess the impact of high-dose dexamethasone on overall mortality at day-60 after randomization in patients admitted in Intensive Care Unit (ICU) for severe COVID-19 infection.

For the study of the effect of oxygen support modality: To assess whether oxygen support based on either HFNO or CPAP modality in COVID-19 related acute hypoxemic respiratory failure reduces the need for MV at day-28.

3.1.2 Secondary objectives

For the study of the effect of high-dose corticosteroids, secondary objectives included:

1. To compare the evolution of the viral load in the respiratory tract
2. To compare the occurrence of healthcare-associated infections
3. To compare the exposition to mechanical ventilation
4. To compare the evolution of SOFA score
5. To compare the exposition to renal replacement therapy
6. To compare the lengths of ICU and hospital-stay

For the study of the effect of oxygen support modalities, secondary objectives were, to compare each of oxygen support group to the control group in terms of:

1. To compare the overall survival
2. To compare the exposition to mechanical ventilation
3. To compare occurrence of severe hypoxemia during tracheal intubation
4. To compare occurrence of cardiac arrest following tracheal intubation
5. To compare the occurrence of healthcare-associated infections
6. To compare the length of ICU and hospital-stay

3.2 Endpoints

3.2.1 Primary endpoint

For the study of the effect of high-dose corticosteroids, the primary endpoint is the time-to-death from all causes within the first 60 days after randomization.

For the study of the effect of oxygen support modalities, the primary endpoint is the time to need for MV, as defined by any of the 3 criteria for intubation defined below, within the first 28 days after randomization. The use of those criteria rather than actual mechanical ventilation was justified to decrease information bias due to (i) the open design, (ii) possibility of delayed MV due to logistic constrains, and (ii) do not resuscitate orders (DNR).

The **pre-specified criteria for intubation** have been used previously (3):

1) signs of persisting or worsening respiratory failure, defined by at least two of the following criteria: a respiratory rate above 35 cycles/min, lack of improvement of signs of respiratory-muscle fatigue, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO_2 below 90% despite FiO_2 $\geq$80% for more than 5 min without technical dysfunction, or intolerance to non-invasive ventilation (NIV); or one of the following

2) hemodynamic instability defined by a systolic blood pressure below 90 mmHg, mean blood pressure below 65 mmHg or requirement for vasopressor,

3) deterioration of neurologic status with a Glasgow coma scale below 12 points.

3.2.2 Secondary endpoints

For the study of the effect of high-dose corticosteroids, secondary endpoints include:

1. Cycle threshold for SARS-CoV-2 PCR at baseline, day 7+/-1 and day 10+/-1 in samples of the same origin (preferably subglottic i.e. bronchoalveolar lavage or tracheal aspiration, otherwise nasopharyngeal swab)
2. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and D28
3. Number of days alive without mechanical ventilation at day 28
4. Changes in SOFA score from day 1 to day 3, day 7, day 10, day 21, day 28 or discharge-day from ICU as appropriate
5. Number of days alive without renal replacement therapy at day 28
6. Lengths of ICU-stay and hospital-stay

For the study of the effect of oxygen support modality, secondary endpoints are:

1. Overall survival within 60 days after randomization
2. Number of days alive without invasive mechanical ventilation at day 28
3. Proportion of patients with severe hypoxemia, which is defined as an oxygen saturation of less than 80% during the same interval during the interval between induction and 2 minutes after tracheal intubation
4. Proportion of patients with cardiac arrest within 1 hour after intubation
5. Proportion of patients with at least one episode of any healthcare-associated infection between randomization and day 28
6. Lengths of ICU-stay and hospital-stay

4 Study Methods

4.1 General Study Design and Plan

- **Study configuration and experimental design**

This is a multicentre randomized controlled trial stratified on the patient severity at inclusion (Figure 1). All consecutive patients with COVID-19 infection admitted in ICU, receiving the best standard of care including low-dose dexamethasone (see below) and any therapy for the treatment of their COVID-19 infection (either as a compassionate use or in the context of a clinical trial, i.e., remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity) and who met the eligibility criteria could participate.

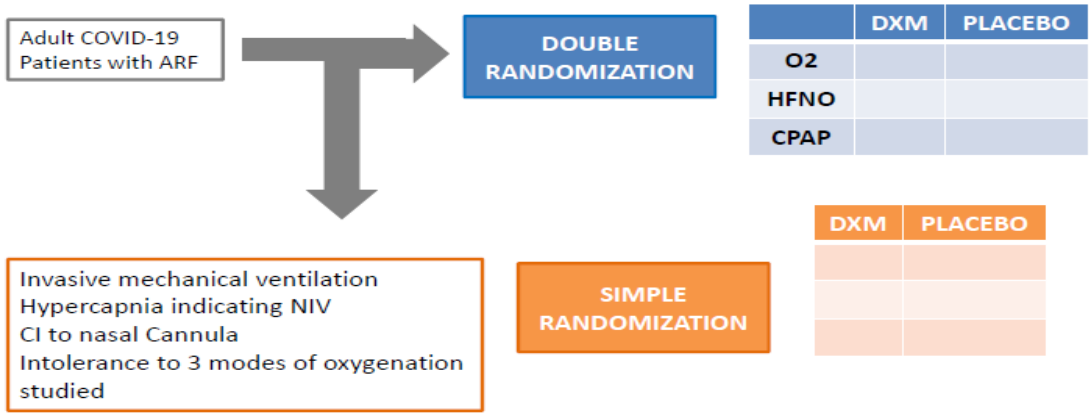

Figure 1: Design of the protocol: Stratification of the randomization according to patient severity; DXM: dexamethasone

The design was stratified on patient severity;

- **In patients without (i) invasive mechanical ventilation, (ii) anatomical factors precluding the use of nasal cannula, (iii) hypercapnia indicating NIV (paCO2 ≥ 50 mmHg) OR (iv) intolerance to one of the 3 modes one of oxygenation studied at admission**, a 2x2 factorial design was used to assess the two interventions, separately.

This resulted in 6 treatment arms

1- Standard oxygen and placebo of high-dose dexamethasone
2- Standard oxygen, and high-dose dexamethasone
3- CPAP and placebo of high-dose dexamethasone
4- CPAP, and high-dose dexamethasone
5- HFNO and placebo of high-dose dexamethasone
6- HFNO and high-dose dexamethasone

- **In patients with (i) invasive mechanical ventilation, (ii) anatomical factors precluding the use of nasal cannula, (iii) hypercapnia indicating NIV (paCO2 ≥ 50 mmHg) OR (iv) intolerance to one of the 3 modes one of oxygenation studied at admission**, only 2 randomized groups were constituted:
  1- Placebo of high-dose dexamethasone
  2- high-dose dexamethasone

- **Type of control**

All patients received the best standard of care available at the time. Based on the Haut Conseil de Santé Publique (July, 23, 2020), dexamethasone was administered at a daily dosage of 6 mg for a maximum of 10 days, after evaluation of the individual benefit/risk ratio in patients under 70 years of age requiring oxygen and resuscitation. This resulted in a pragmatic trial comparing dexamethasone 6mg+14mg of vs dexamethasone 6mg + placebo. Thus, the trial focused on the effect of high-dose dexamethasone compared to low-dose.

- **Level and method of blinding**

The conception of a placebo was not possible due to the emergency to begin the trial for Dexamethasone, or due to the nature of intervention for the oxygen support modalities. Pre randomized boxes containing masked vials dexamethasone or normal saline were available in each centre. These precautions and the use of primary endpoints (mortality within day 60, or specific criteria for MV) minimized the risk of biases due to the open nature of the study.
Statistical analyses will be conducted blinded to treatment assignment, with treatment arms denoted by letters instead of explicit labelling; note that the control arm of oxygenation support will be identified for analysis purposes (given only comparison of each intervention to that control arm is to be performed).
All investigators were unaware of aggregate outcomes during the study.

- **Method of treatment assignment**

Randomized clinical trial (see below, section 4.3.) A centralized 24/24, password-protected Internet service (CleanWeb® solution) expressly designed for the study and developed under the responsibility of the URC Paris Nord, was used. Information was recorded in the electronic system in order to prevent the investigator and medical team from predicting the group allocated to patients. To include and randomize a patient in

the study, investigators accessed the website using an individual password, and filled out a short medical record form. After each randomization, a treatment number was allocated to the patient and a confirmation email of randomization sent automatically to the investigator concerned and the URC Paris Nord.

- **At what point in time subjects are randomised relative to treatments**

After signing the informed consent (or according to the emergency inclusion), and checking the eligibility criteria, including the severity strata, patients were randomized across the arms.

- **Sequence and duration of all study periods**

The maximal duration of participation of each patient will be 60 days.

Duration of enrolment period	12 months
The length of participation for participants, of which	75 days
– Maximum period between selection and inclusion	none
– Treatment period	10 days
– Follow up period	60 days +/– 2 weeks
Total study duration	14 ,5months

4.2 Inclusion-Exclusion Criteria and General Study Population

4.2.1 Inclusion criteria

1. Age ≥ 18 years
2. Admitted to ICU within 48 hours
3. Confirmed or highly suspected COVID-19 infection
4. Acute hypoxemic respiratory failure (PaO2 <70 mmHg or SpO2<90% on room air or tachypnea>30/min or labored breathing or respiratory distress; need for oxygen flow ≥ 6L/min)
5. Any treatment intended to treat the SARS-CoV-2 infection if accessible, in the absence of contraindications (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, oseltamivir, hydroxychloroquine and any other new drug with potential activity).

4.2.2 Exclusion criteria

1. Moribund status
2. Pregnancy or breastfeeding
3. Long term corticotherapy at a dose of 0.5mg/kg/j or higher
4. Active and untreated bacterial, fungal or parasitic infection
5. Not written informed consent from the patient or a legal representative if appropriate. If absence a legal representative the patient may be included in emergency procedure
6. Hypersensitivity to dexamethasone or to any of the excipients
7. Not Affiliation to the French social security

4.3 Randomisation and Blinding

Randomization was balanced (1:1:1 in non-MV patients, 1:1 in MV patients), centralized, and stratified on centre.

Computer-generated randomization lists were generated, using permutation blocks of varying sizes that were kept confidential to the investigators. The randomization lists were generated by a statistician from Saint Louis hospital. All these points insured the allocation concealment of the randomization process.

4.4 Study Variables

Actions	Baseline visit	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit at ICU discharge / hospital discharge	End of research
	D1 +/- 1	D3 +/- 1	D7 +/- 1	D10+/-1	D14+/-1	D21+/-2	D28 +/- 2		D60 +/-2wks
Clinical Data									
Inclusion and non-inclusion criteria	▲								
Informed consent	▲								
Informed consent pursuit if necessary	▲	▲	▲	▲	▲	▲	▲		
Demographics & Medical History	X								
Complete physical exam, including vital parameters, vital status	**Continuously**								
SOFA Score	▲	▲	▲	▲	▲	▲	▲	▲	
Consultation at hospital or Phone questionnaire (EQ-5D-5L questionnaire)									▲
Adverse events	**Continuously**								
Randomisation : R1									
Treatment : - Experimental group E1: Dexamethasone treatment – - Control group C1: placebo of dexamethasone	▲	▲	▲	▲					
Randomisation : R2									
Treatment : - Experimental group E2A: HFNO - Experimental group E2B : CPAP - Control group C2: standard oxygen therapy	▲	▲	▲	▲	▲	▲	▲		
Radiological Data									
Chest X Ray	**At least every 48h during ICU stay, and forHospital**								
Biological Data									
Blood β-HCG test for women of child-bearing age	X								
Standard biology	X	X	X	X	X	X	X	X	
SARS-CoV-2 PCR (preferably subglottic sample i.e. bronchoalveolar lavage plugged telescopic catheter, or tracheal aspiration, otherwise nasopharyngeal swab)	X		X						
Blood sampling for Bio collection	▲	▲	▲		▲		▲	▲	
Environment air collection	▲								

▲: realized for the research X: realized as part of the care

5 Sample Size

Computation of sample sizes has been done for each intervention, independently. Based on those computation, it was computed that the trial needs to recruit 550 subjects including 330 patients who were not mechanically-ventilated at inclusion.

5.1 Effect of high-dose dexamethasone

According to the literature, the reported cumulative incidence of death at Day-60 was about 60%. A two-sided log-rank test with an overall sample size of 550 subjects (275 in each group) achieves 80.1% power at a 0.050 significance level to detect a hazard ratio of 0.75 when the proportion surviving in the control group is 0.40 (that is, the survival rate in the Dexamethasone group is expected to be 0.50). The study lasts for 150 days of which subject accrual (entry) occurs in the first 90 days. The accrual pattern across time periods is uniform (all periods equal). No subjects drop out of the control group. No subjects drop out of the treatment group. No patient is assumed to switch from the control group to the other group.

5.2 In the population of non-severe non-mechanically-ventilated Covid-19 infected patients

Based on data from the literature, the cumulative incidence of intubation at day 28 is estimated to be 80% in the standard of care group. Computation was done for each of the two comparisons, using an adjusted type I error rate of 0.025 given the multiple comparisons (i.e., Bonferonni adjustments of the nominal significance level). A two-sided log-rank test with an overall sample size of 220 subjects (110 in the control group and 233 in the treatment group) achieves 80.0% power at a 0.025 significance level to detect a hazard ratio of 0.65 when the proportion surviving in the control group is 0.20 (that is, a 28-day cumulative incidence of need for VM of 80% in the control arm versus 65% in the experimental arm). The study lasts for 120 days of which subject accrual (entry) occurs in the first 60 days. The accrual pattern across time periods is uniform (all periods equal). No subjects drop out of the control group. No subjects drop out of the treatment group. No switches are expected.

Therefore, a total of 110 patients in each of the 3 arms will be required, that is a total of 330 non-MV patients at randomization to be included in the trial.

6 General Considerations

6.1 Timing of Analyses

- Interim monitoring for success will begin after 50 patients have been enrolled and will be repeated after every additional 50 patients are enrolled
- The final analysis will be performed 60 days after the inclusion of the last patient unless the data monitoring is not closed
- The final analysis will be performed on data transferred from CleanWeb®, having been documented as meeting the cleaning and approval requirements of SOP and after the finalisation and approval of this SAP document.

6.2 Analysis Populations

6.2.1 Full Analysis Population

All primary analyses will follow the Intention-to-treat method. All randomized patients will be analyzed in their allocated group, irrespective of intervention eventually received or lost to follow-up. Deviations from the protocol will be registered as well as the raisons for deviation.

6.2.2 As Treated Population

Estimation of administered corticosteroid effect will use the as-treated population, where each patient will be considered in the group (either 0, 6, or 20, mg) of administered dexamethasone.

6.2.3 Safety Population

Safety population was defined as the intention-to-treat population, whatever the treatment actually received.

6.3 Covariates and Subgroups

Randomization was stratified on centre, but it will be omitted inn the analysis because it introduces too many categories.

Analysis will be stratified on patient stratum (either mechanically ventilated or not).

No a priori hypothesis of subgroup differences was assumed. Therefore, all subgroup analyses are post-hoc and exploratory.

Subgroup analyses should focus on the evidence for a difference in treatment effects: the interaction effect, using subgroup-specific summary statistics displayed on a forest plot.

6.4 Missing Data

Missing data for the primary endpoint (vital status or ventilation mode), and other endpoints related to the ICU stay are not expected. Indeed, the complete follow up of each enrolled patient is assured by the study's design since the observation period is defined from day 1 (randomization) until day 28, ICU discharge, or death, whichever occurs first. For the other endpoints, missing data will be handled by multiple imputation techniques

Missing data will be described on the overall population and by treatment group, and method of handling them according to their frequencies and nature will be used. Sensitivity analysis will confirm reliability of conclusions upon various hypotheses on missing values.

6.5 Interim Analyses and Data Monitoring

6.5.1 Purpose of Interim Analyses

For ethical reasons, clinical trial data will be analyzed repeatedly at any time prior to the formal completion of the trial, as recommended for decades (Jennison 1990), with results presented to the data monitoring committee of the trial. Moreover, when comparing multiple commercially available and perhaps U.S. Food and Drug

Administration (FDA)- or European Medicines Agency (EMEA)-approved products or treatment strategies against one another via comparative effectiveness research (CER) trial, Bayesian analyses appear particularly well suited (Connor 2013; Gasponer 2014; Ryan 2019). Indeed, Bayesian approaches to the monitoring of group sequential designs have two main advantages compared with classical group sequential designs (Berry 2004; Spiegelhalter 1994): first, they facilitate the implementation of interim success and futility criteria that are tailored to the subsequent decision making based on explicit probabilistic statements (that may offer strong benefit for their ability to calculate the probability that each treatment is the best or worst) (Jacob 2016), and second, they allow inclusion of prior information on the treatment differences and on the control group, actualized over the trial.

6.5.2 Planned Schedule of Interim Analyses

Interim monitoring for success will begin after 50 patients have been enrolled and will be repeated after every additional 50 patients are enrolled. Interim analyses will be stratified on the patient base line severity group, based on the primary outcome measure and main secondary endpoints of each stratum:

- Severe group: survival time, SOFA score
- Moderate group: time to MV criterion, survival

6.5.3 Scope of Adaptations

The analyses will therefore rely on computing the posterior distribution of the hazard ratio (main endpoints) or between the experimental and control arms for time-to-event co-primary outcomes and the posterior distributions of event rates in each arm for binary co-primary outcomes. From the latter, the posterior distribution of the difference in event rate will be derived. These posterior distributions will be graphically displayed, and summarized by their medians and 95% credibility intervals (the Bayesian counterparts of confidence intervals). Noninformative priors will be used, that is the prior distribution for the log hazard ratio will be a Gaussian distribution with mean 0 and variance 10^6. Following Harrel and Lindsell, posterior probabilities will be reported as follows (`https://hbiostat.org/proj/covid19/bayesplan.html`)

P1=P(HR < 1 | data)	Any benefit
P2=P(HR < 0.75 | data)	High-dose DXM benefit
P3=P(HR < 0.65 | data)	Oxygen support benefit
P4=P(HR >1.05 | data)	More than trivial harm
P5=P(0.8 <HR <1.2 | data)	Similarity between oxygenation supports

6.5.4 Stopping Rules

For this study, action triggers will be:

- Stop with evidence for efficacy if P1>0.95
- Stop with evidence for moderate or greater efficacy if P2 or P3>0.8

- Stop with evidence for inefficacy if P4>0.8
- Stop with evidence for harm if P5>0.75

Last, once at least 100 patients have been enrolled, and thereafter after every additional 50 patients, we will also assess the presence of any period-by-treatment interaction, by estimating the ratio of the estimated effect in both periods, in a Bayesian setting (Millen 2014). Posterior probabilities of such a ratio will be estimated using Markov chain Monte Carlo (MCMC) methods.

The DSMB could be asked to recommend early termination based on results of the safety/efficacy interim analyses.

6.5.5 Analysis Methods to Minimise Bias

The most effective design technique for avoiding selection bias and allowing causal inference is randomization, centrally performed to ensure allocation concealment. Moreover, to ensure such concealment, the size of the permutation blocks used in the generation of lists was varying.

To ensure the absence of attrition bias, the primary analysis will be made according to the intention-to-treat principle.

To ensure non-informative right censoring, a reference date for the analysis that achieved so-called administrative censoring will be used for the analysis of time-to-failure data for all outcomes that could not be fixed like 60-day mortality.

To avoid inflating the type I error rate, baseline characteristics (at randomization) of the randomized groups will be compared roughly, without formal statistical testing (Pocok 2002).

6.5.6 Adjustment of Confidence Intervals and p-values

Final level of statistical significance is of 0.05.

6.5.7 Practical Measures to Minimise Bias

Interim analyses were performed by the statistician blindly to the allocation groups that were displayed by letters (A, B, C, etc).

Reporting of interim analyses had to only be sent to the members of the DSMB.

S Chevret will perform any interim analysis

Members of the DSMB will see any data or analyses at the interim and make decisions

No information will be publically available following an interim analysis except that communicated by the members of the DSMB

No interim information will be provided to the sponsor and investigators

No one will be unblinded at any point in the trial unless the members of the DSMB asked for

S Chevret will perform any final analyses and remain blinded until decision of unblindness for the final report by the members of the DSMB.

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6.5.8 Documentation of Interim Analyses

Snapshots of the data at each interim analysis were preserved, as all documentation of analysis plans, programming code and reporting provided at each interim.

6.6 Multi-centre Studies

Post-hoc test for qualitative or quantitative treatment-by-centre interactions were performed on the primary outcomes based on Gail and Simon's statistics (1985).

6.7 Multiple Testing

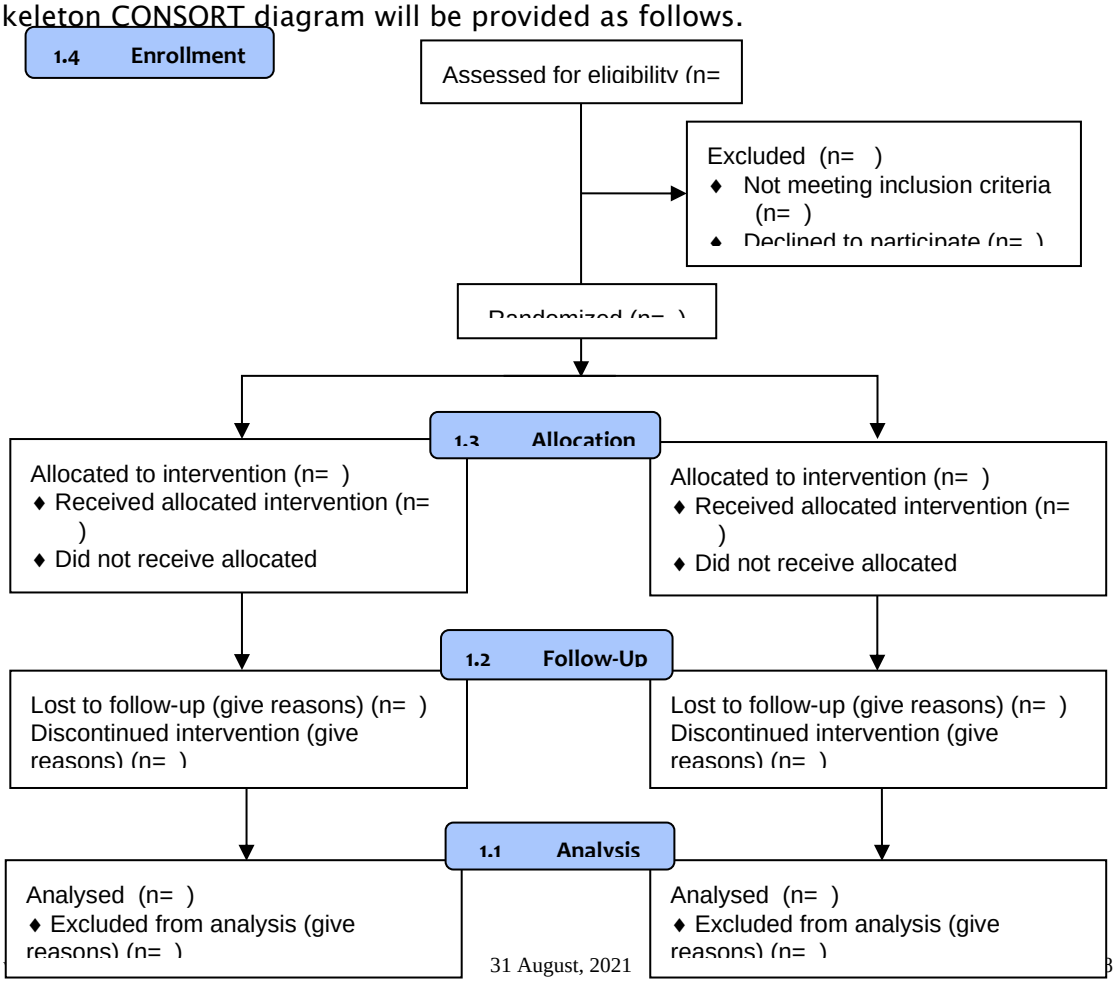
In non-mechanically ventilated patients, Bonferroni adjustments of the nominal significance level, was considered in the sample size computation.

7 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), median, interquartile range (IQR). The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

7.1 Subject Disposition

A skeleton CONSORT diagram will be provided as follows.



7.2 Protocol Deviations

No protocol deviation will be considered in the analysis.

7.3 Demographic and Baseline Variables

Age, Sex, weight, body mass index (BMI), segregated into normal (BMI,), overweight (xx-xx), moderate obese (xx-xx) and severe obese (>xx), were summarized,

Patient status at inclusion was recorded, including body temperature (°Celsius), consciousness, neurological deficit, and use of vasopressors and ventilation support.

Blood gazes as well as respiratory rate were also summarized, together with the SOFA score and sub-scores.

Viral data, including PCR and type of samples, were also reported as well as biological data (blood cells counts, glycemia, creatinine, prothrombin time, CP, D-Dimers, ferritin, PCT and troponin).

7.4 Concurrent Illnesses and Medical Conditions

Comorbidities were described, namely diabetes, high blood pressure, cardiac failure, chronic obstructive pulmonary disease, tobacco use, asthma, renal failure, cirrhosis, neurological failure, malignancy, hemopathy, transplantation, auto-immunity.

Prior and Concurrent Medications including base line COVID-19 treatments, were summarized.

8 Efficacy Analyses

Data will be summarized by treatment group. N, Median, and hazard ratios (HR) with 95 percent confidence intervals will summarize right-censored efficacy variables, whereas number and percent will summarize binary or categorical efficacy variables. All analyses of the continuous efficacy variables (e.g., number of days free of mechanical ventilation) will be performed based on nonparametric Wilcoxon rank sum test. Treatment groups will be tested at the 2-sided 5% significance level.

Right-censored endpoints will be summarized by survival functions estimated from the Kaplan-Meier estimator, while treatment effect based on hazard ratio (Cox, 1972). In case of competing risks, estimation of cumulative incidence will be reported in each randomized group, then compared by the Gray test (1988).

All assumptions for Cox regression models will be assessed. All analyses of categorical efficacy measures will be performed using logistic regression with treatment group and adjustments for study center.

8.1 Primary Efficacy Analysis

The primary endpoints of the study are time-to-failure endpoints, that will be analyzed using survival methods assuming noninformative right-censoring of the data; this is obviously true for the cumulative incidence of all deaths, whatever the cause, used in the evaluation of corticosteroids; this is also assumed to be true in non-mechanically ventilated patients, due to the fact that no death prior to criteria for MV will be expected. In both cases, no lost to follow up that could be related to the disease will be

expected within the first 28 or 60 days after study enrollment. Thus, only administrative censoring at the time of analysis (see below interim analyses) or at day 28 or day 60 (for patients still alive free of failure at that time) will be expected.
Under such assumptions, survival curves will be estimated in each randomization arm according to the Kaplan-Meier method, then compared by the Log-Rank test. Cox models stratified on the patient severity at inclusion (MV or not) will quantify the effect size by hazard ratio with 95% confidence intervals. Subset by treatment interactions will be tested by the Gail and Simon (1985) interaction statistics.

Beside the ITT analyses, analysis of the corticosteroids effect, will use an instrumental variable (IV) method in the "as-treated population (Sommer 1991). The IV approach will be used to assess the magnitude of the as-received treatment effect in contrast to the ITT approach, which focuses on the as-assigned treatment effect, whatever the administered treatment. The use of two models under the IV approach, one relating treatment received to outcome (the AT model), and the other relating randomized intervention assignment to the treatment received, has led many researchers to refer to the IV method as a two-stage estimation procedure. The most common IV in medicine is randomization within a randomized controlled trial that has treatment contamination (Sussman 2010): IV analysis can bridge the gap between the more policy focused question posed by intention to treat analyses and the patient focused question of biological efficacy.
This is particularly well-suited to our setting, where "contamination" refers to the administration of dexamethasone, possibly considering the dose actually administered.
Note that the use of predictive covariates in the model relating the randomized intervention to treatment received will increase the precision of the predicted treatment probability that replaces observed treatment received in the IV model for the outcome. Including predictors of outcome in the model for outcome of course reduces the residual error.

8.2 Secondary Efficacy Analyses

In accordance to the secondary criteria for Dexamethasone versus standard of care,

1. The evolution of the viral load in the respiratory tract will modelled and compared by linear mixed models.
2. The proportions of healthcare-associated infection at day-28 and day-60 will be compared between groups by an exact Fisher test.
3. The number of days alive without mechanical ventilation will be compared between groups by a Wilcoxon rank sum test.
4. The evolution of SOFA-score will modelled and compared by linear mixed models.
5. The number of days alive without renal replacement therapy will be compared between groups by a Wilcoxon rank sum test.
6. The length of ICU and hospital-stay will be compared between groups by a Wilcoxon rank sum test.

Secondary analyses comparing (i) HFNO and standard oxygen therapy and (ii) CPAP and standard oxygen therapy

1. The number of days alive without mechanical ventilation will be compared by a Wilcoxon rank sum test.
2. The proportion of healthcare-associated infection at day-28 and day-60 will be compared by an exact Fisher test.
3. The length of ICU and hospital-stay will be compared by a Wilcoxon rank sum test

9 Safety Analyses

All safety analyses will be based on the intention-to-treat population.

Complications, namely ventilation-acquired pneumonia (VAP) was estimated through cumulative incidence function, taking into account death free of VAP as competing-risks outcomes. We similarly estimated the cumulative incidence of bacteremia, and neuropathy.

9.1 Adverse Events

The proportion of patients who experience at least one serious adverse event will be analyzed as a categorical variable (with patients classified as either having experienced at least one serious adverse event, or not) using a χ-squared or Fisher's exact test (as appropriate). If appropriate, a more complex model of serious adverse event occurrences will be constructed utilizing adverse events as count variables. Possible models for this analysis include Poisson regression and negative binomial regression. An analysis of subgroups of serious adverse events will be performed separately, but in an identical manner to the overall adverse events analyses.

9.2 Clinical Laboratory Evaluations

Laboratory tests will be summarized using spaghetti plots, that is, scatter plot of the baseline value on the horizontal axis versus the subsequent values, as considered above, with different plotting symbols used to distinguish different treatment groups.

10 Figures

Where possible, all figures and tables relating to a given outcome should be grouped together.

11 Reporting Conventions

P-values $\geq$0.001 will be reported to 3 decimal places unless $\geq$0.01 when reported with 2 decimal places instead; p-values less than 0.0001 will be reported as "<0.0001".

The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 4 significant figures.

12 Technical Details

All reports will report software package or packages used, including the version number of the software; the operating system of the computer (e.g. Macintosh, Windows etc.).

The population to be used in a table or figure will be explicitly set at the start of a block of code that computes the output, ideally by looking up the population from the table of tables

Any outputs will have

- The date and time included
- The name of the code file that produced the analysis

At the start of any code file there will be a set of comments that give

- the date and time of writing
- references to inputs and outputs
- reference to any parent code file that runs the child code file

13 Summary of Changes to the Protocol

If the statistical analysis plan proposes changes to the statistical approach described in the protocol then summarize those changes in this section. Analyses are usually faithful to those specified in the protocol, but occasionally different, or supplemental, analyses are needed. Explain the reason for such changes. You may choose to identify those analyses that are not from the protocol in the relevant sections above. However, documenting the changes here greatly aids clarity.

Other important, non-statistical changes to the protocol should also be noted in this section, for example the introduction of an additional treatment group.

14 References

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CPP Ile de France XI
Comité de Protection des Personnes

St-Germain-en-Laye, le 11 novembre 2020

APHP
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Titre de l'essai :	**Dexamethasone et stratégies d'oxygénation des patients hospitalisés en réanimation atteints de pneumonies à Covid-19**
Promoteur :	**APHP**
Investigateur :	**Pr Jean-François TIMSIT**
Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

Demande d'avis valant autorisation sur une recherche de catégorie 1	**X**
Demande d'avis valant autorisation sur une recherche de catégorie 2	
Demande d'avis valant autorisation sur une recherche de catégorie 3	
Demande d'avis consultatif sur un changement substantiel de finalité dans l'utilisation d'une collection d'éléments biologiques humains (art. L. 1211-2 du CSP)	
Demande d'avis consultatif sur un projet de déclaration de constitution d'une collection d'échantillons biologiques humains (art. L. 1243-3 du CSP)	

Modification Substantielle N°3	
Documents examinés Numéro et date de version	
Courrier de demande d'avis	22/10/2020
Tableau comparatif des modifications	Joint
Protocole	Version 5 du 08/10/2020
CV des nouveaux investigateurs	Joints
La liste des investigateurs	Version 4 du 22/10/2020

Le CPP Ile de France XI a examiné dans sa séance du 5 NOVEMBRE 2020, la modification substantielle n°3 au projet de recherche référencé ci-dessus.

Ont participé à la délibération :

I – PREMIER COLLEGE

Caty BITOUN	Médecin
Gérard LOEB	Médecin
Axel LEVIER	Ingénieur
Kolia MILOJEVIC	Biostatisticien
Sabine de la PORTE	Chercheur

Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

Ariane QUEFFELEC	Médecin
Delphine REGNAULT	Biostatisticienne

II - DEUXIEME COLLEGE

Michèle CATZ	Psychologue
Christine GHESTEM	Association des familles du Vésinet
Odile LACHAUD	Représentant UDAF 78
Jean-François LAIGNEAU	Avocat
Olivier LANTRES	Avocat
Léon LOISEAU	Philosophe
Nicole TAVERNY	Association des familles du Vésinet

Aucun membre délibérant du comité n'est affecté par un conflit d'intérêt.

Pour le 1er point de cette modification substantielle, le CPP a décidé d'un AVIS DEFAVORABLE

Cette modification substantielle porte sur le changement du critère d'inclusion.

Justification : l'inclusion dans le protocole les personnes qui ne sont pas affiliées à un régime de sécurité sociale n'est pas acceptable au regard de la loi.

Pour rappel *: Pour les RIPH 1°(ou 2°), la dérogation accordée par le CPP doit se fonder au moins sur l'une des conditions suivantes :*
-1°l'importance du bénéfice escompté pour les personnes est de nature à justifier le risque prévisible encouru ;
- 2°les recherches se justifient au regard du bénéfice escompté pour d'autres personnes se trouvant dans la même situation juridique. Dans ce cas, le risque prévisible et les contraintes que comporte la recherche doivent présenter un caractère minime.

Aucune des conditions n'est remplie. En particulier la double randomisation et la nature de l'essai ne permettent pas de garantir un bénéfice.

De plus, dans un avis daté du 2 novembre, le Haut Conseil de la Santé Publique (HCSP) détaille ses recommandations concernant les indications et modalités d'utilisation des corticoïdes chez les patients hospitalisés pour infection Covid-19. Ces recommandations sont de nature à faciliter l'accès au traitement de ces personnes.

L'autre point reçoit un AVIS FAVORABLE : actualisation de la liste des investigateurs.

L'attestation de BPC pour les docteurs GERI et DUPUIS a été reçue par mail le 4 11 2020.

Sabine de la PORTE, Présidente de séance

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION D'ESSAI CLINIQUE DE MEDICAMENT A USAGE HUMAIN

Date : 10.04.2020

Identifiants de l'essai clinique			
Titre	Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia - COVIDICUS		
Promoteur	APHP		
Réf à rappeler	MEDAECNAT-2020-04-00007	N° EudraCT	**2020-001457-43**

Expéditeur
ANSM / Direction Produit INFHEP / Equipe Virologie – Thérapie génique

Destinataire (demandeur : nom / société / tél.)	
Fadila Amerali APHP 01 44 84 17 17	
Mél	fadila.amerali@aphp.fr

CPP destinataire	IDF11 - Ile-de-France XI	**Mél**	cppidf11@chi-poissy-st-germain.fr

Vu le code de la santé publique et notamment l'article L. 1123-8, et les dispositions réglementaires prises pour son application, et vu le dossier de demande d'autorisation d'essai clinique adressé à l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) ;

Vu les compléments versés par le promoteur en date du 09 avril 2020 et notamment le protocole de l'essai cité en objet modifié (version 1.2 datée du 09.04.20), suite à la demande de l'ANSM ;

L'autorisation mentionnée à l'article L. 1123-8 du code de la santé publique est accordée pour l'essai clinique cité en objet.

Dr Dominique MARTIN

Directeur général

Je vous demande de transmettre toute demande de modifications concernant ce dossier par courriel adressé à la boite : **ams-essaiscliniques@ansm.sante.fr** . Lors de l'envoi de ces dossiers, je vous demande de veiller à reporter dans l'objet du message la mention : **MSA/ N° EUDRACT** pour les MS soumises pour autorisation ou pour les dossiers mixtes (comportant des modifications soumises pour autorisation et d'autres pour information).

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION DE MODIFICATION (S) SUBSTANTIELLE (S) D'ESSAI(S) CLINIQUE(S) DE MEDICAMENT A USAGE HUMAIN (MSA)

Date : 17 SEP. 2020

Identifiants de la (des) modification(s) et du (des) essai(s) concerné(s)		
Promoteur	**AP-HP Délégation à la Recherche Clinique et à l'Innovation (GIRCI Ile de France)**	
Réf. Essai(s)	**Réf. Modification(s)**	
N° EudraCT	**Réf à rappeler**	**Réf. Promoteur** (item E.1 du formulaire de demande d'AMS)
2020-001457-43	MEDMSANAT-2020-07-00121	APHP 200388 / MS n°2/ Protocole V3 du 09/07/2020

Expéditeur
ANSM / Direction Produit CARDIO

Destinataire (**demandeur** : nom / société / tél.)	
Fadila Amerali AP-HP Délégation à la Recherche Clinique et à l'Innovation (GIRCI Ile de France) 01 44 84 17 17	
Mél	fadila.amerali@aphp.fr

Vu le code de la santé publique et notamment l'article L. 1123-9, et les dispositions réglementaires prises pour son application, et vu la ou les autorisations d'essais cliniques délivrées par l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) pour le ou les essais cliniques ci-dessus référencés ;

Vu le dossier de demande d'autorisation de modification(s) substantielle(s) adressé à l'ANSM ;

Vu les compléments versés par le promoteur en date des 13 août, 09 et 10 septembre 2020 et notamment le protocole modifié (protocole version 4 du 07/09/2020) de l'essai cité en objet, suite à la demande de l'ANSM ;

L'autorisation mentionnée à l'article L. 1123-9 du code de la santé publique est accordée pour la (les) modification(s) substantielle(s) identifiée ci-dessus, pour les aspects relevant de la compétence de l'ANSM.

Dr Christelle RATIGNIER-CARBONNEIL

Directrice générale adjointe

Je vous demande de transmettre toute demande de modifications concernant ce dossier par courriel adressé à la boite : **ams-essaiscliniques@ansm.sante.fr** . Lors de l'envoi de ces dossiers, je vous demande de veiller à reporter dans l'objet du message la mention : **MSA/ N° EUDRACT** pour les MS soumises pour autorisation ou pour les dossiers mixtes (comportant des modifications soumises pour autorisation et d'autres pour information).

CPP Ile de France XI
Comité de Protection des Personnes

St-Germain-en-Laye, le 8 Avril 2020

APHP
Mme Fadila AMERALI
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75475 PARIS

Titre de l'essai :	**Dexamethasone et stratégies d'oxygénation des patients hospitalisés en réanimation atteints de pneumonies à Covid-19**
Promoteur :	**APHP**
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Demande d'avis valant autorisation sur une recherche de catégorie 1	**X**
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Demande d'avis consultatif sur un projet de déclaration de constitution d'une collection d'échantillons biologiques humains (art. L. 1243-3 du CSP)	

Documents examinés Numéro et date de version	
Le courrier de demande d'autorisation ANSM	01/04/2020
Courrier de demande d'avis	01/04/2020
Courrier de réponse du promoteur	06/04/2020
CTAForm	01/04/2020
Le document additionnel à la demande destiné au CPP	01/04/2020
Protocole	Version 1-1 du 06/04/2020
Résumé	Version n°1 du 31/03/2020
La lettre d'information et le formulaire de consentement : poursuite proche	V1-1 du 06/04/2020
La lettre d'information et le formulaire de consentement : proche	V1-1 du 06/04/2020
La lettre d'information et le formulaire de consentement : poursuite	V1-1 du 06/04/2020

Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

La lettre d'information et le formulaire de consentement : majeur	V1-1 du 06/04/2020
Lettre d'information d'utilisation des données après le décès du patient	V1 du 04/04/2020
La carte patient	Jointe
Les CV des Investigateurs Principaux	Joints
La liste des investigateurs	V1-1 du 06/04/2020
La justification de l'adéquation des moyens	Jointe
La copie de l'attestation d'assurance	30/03/2020
La charte du CSI	Version n°1 du 01/04/2020
RCP produits utilisés	Joints

J'ai bien reçu les modifications demandées lors de la séance du **3 AVRIL 2020** concernant le projet de recherche référencé ci-dessus.

Ont participé à la délibération :

I – PREMIER COLLEGE

Didier ARMENGAUD	**Pédiatre**
Annie DURAND	**Pharmacien**
Axel LEVIER	**Ingénieur**
Gérard LOEB	**Médecin**
Kolia MILOJEVIC	**Biostatisticien**
Sabine de la PORTE	**Chercheur**
Ariane QUEFFELEC	**Médecin**

II - DEUXIEME COLLEGE

Michèle CATZ	**Psychologue**
Jean-François LAIGNEAU	**Avocat**
Odile LACHAUD	**Représentant UDAF 78**
Olivier LANTRES	**Avocat**

Aucun membre délibérant du comité n'est affecté par un conflit d'intérêt.

Par conséquent je donne **l'AVIS FAVORABLE** de notre Comité pour cette recherche.

Veuillez croire, Madame, Monsieur, l'assurance de mes sentiments les meilleurs.

Michèle CATZ, Secrétaire Générale du CPP IDF XI

Sabine de la PORTE, Présidente – **Léon LOISEAU**, Vice-président – Michèle **CATZ**, Secrétaire générale
Kolia MILOJEVIC, Vice-secrétaire Général
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Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

Sabine de la PORTE, Présidente – **Léon LOISEAU**, Vice-président – Michèle **CATZ**, Secrétaire générale
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CPP Ile de France XI
Comité de Protection des Personnes

St-Germain-en-Laye, le 30 Avril 2020

APHP
Mme Fadila AMERALI
Carré Historique de l'Hôpital Saint-Louis
Secteur Gris - Porte 23
1 avenue Claude Vellefaux
75475 PARIS

Titre de l'essai :	**Dexamethasone et stratégies d'oxygénation des patients hospitalisés en réanimation atteints de pneumonies à Covid-19**
Promoteur :	**APHP**
Investigateur :	**Pr Jean-François TIMSIT**
Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

Demande d'avis valant autorisation sur une recherche de catégorie 1	**X**
Demande d'avis valant autorisation sur une recherche de catégorie 2	
Demande d'avis valant autorisation sur une recherche de catégorie 3	
Demande d'avis consultatif sur un changement substantiel de finalité dans l'utilisation d'une collection d'éléments biologiques humains (art. L. 1211-2 du CSP)	
Demande d'avis consultatif sur un projet de déclaration de constitution d'une collection d'échantillons biologiques humains (art. L. 1243-3 du CSP)	

Modification Substantielle 1

Documents examinés Numéro et date de version	
Formulaire de demande de MS	Non daté
Courrier de demande d'avis	29/04/2020
Tableau des modifications	Joint
Protocole	Version 2 du 23/04/2020
La lettre d'information et le formulaire de consentement : poursuite proche	Version 2 du 23/04/2020
La lettre d'information et le formulaire de consentement : proche	Version 2 du 23/04/2020
La lettre d'information et le formulaire de consentement : poursuite	Version 2 du 23/04/2020
La lettre d'information et le formulaire de consentement : majeur	Version 2 du 23/04/2020

Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

Lettre d'information d'utilisation des données après le décès du patient	Version 2 du 23/04/2020
CV des nouveaux investigateurs Principaux	Joints
La liste des investigateurs	Version 2 du 23/04/2020

Le CPP Ile de France XI a examiné dans sa séance en comité restreint du 30 AVRIL 2020, la modification substantielle n°1 au projet de recherche référencé ci-dessus.

Ont participé à la délibération :

I – PREMIER COLLEGE

Annie DURAND	**Pharmacien**
Axel LEVIER	**Ingénieur**
Kolia MILOJEVIC	**Biostatisticien**
Sabine de la PORTE	**Chercheur**
Ariane QUEFFELEC	**Médecin**

II - DEUXIEME COLLEGE

Michèle CATZ	**Psychologue**
Odile LACHAUD	**Représentant UDAF 78**
Olivier LANTRES	**Avocat**
Léon LOISEAU	**Philosophe**
Christine GHESTEM	**Association des familles du Vésinet**

Aucun membre délibérant du comité n'est affecté par un conflit d'intérêt.

J'ai l'honneur de vous informer que le comité a donné pour cette modification substantielle :

UN AVIS FAVORABLE

Cette modification substantielle consiste principalement en :

- L'ajout de deux études ancillaires
  - La première propose d'étudier le devenir à long terme des sujets
  - La seconde vise à étudier les paramètres thrombo-inflamatoires des patients ayant une infection à Covid-19 (la relation entre l'administration de corticoïdes et le fonctionnement des globules blancs) dans deux centres, le CHU Bichat et le CHU de Strasbourg).

- L'ajout d'un questionnaire en fin de suivi à J60 : questionnaire de qualité de vie à réaliser au téléphone pour les patients sortis d'hospitalisation afin d'évaluer le retour à leur niveau d'activité avant l'infection COVID.

- Des précisions apportées à la description de la population concernée par oxygénothérapie.

- L'ajout d'objectifs secondaires concernant l'étude de l'oxygénothérapie.

- L'actualisation de la liste des investigateurs : il manque la formation au BPC du Dr. GARCON et l'autorisation des lieux de recherche.

Sabine de la PORTE, Présidente – **Léon LOISEAU**, Vice-président – Michèle **CATZ**, Secrétaire générale
Kolia MILOJEVIC, Vice-secrétaire Général
Anne-Elisabeth DECARIS, Assistante
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Réf. Promoteur :	**APHP 200388-COVIDICUS**
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Le CPP a étudié en séance la V2 d'une LETTRE D'INFORMATION RELATIVE A L'UTILISATION DES DONNEES POUR UN PARENT/PROCHE/PERSONNE DE CONFIANCE APRES LE DECES DU PATIENT qui n'était pas dans le dossier d'origine mais avait été ajoutée à la réponse du promoteur (courrier du 06/04/2020).

Remarques/corrections à faire :

Page 1 : « ….*la loi (Art. L. 1122-1-2 du CSP) nous a permis de l'inclure* … » .

Page 2 Fin du §3 : « *Vous avez la possibilité à tout moment de demander au médecin investigateur qui suivait votre proche dans le cadre…* ».

Page 2 §4 : « … données médicales concernant votre proche qui sont eterecueillies» Corriger.

Page 3 fin du § 5 : Supprimer la phrase inadaptée : « *Si vous décidez d'arrêter sa participation à la recherche, les données recueillies... »*

Page 4 section 6 : Supprimer les formules inadaptées : « *La participation de votre proche nécessite que nous informions son médecin traitant sauf si vous vous y opposez*. » « *Après avoir lu toutes ces informations, discuté tous les aspects avec le médecin et après avoir bénéficié d'un temps de réflexion suffisant si vous acceptez que votre proche participe* »

Proche est masculin : supprimer les (e) dans toutes les occurrences, exemple : « *Votre proche Mme, M. (barrer les mentions inutiles) ……. (nom, prénom) avait été admis(e)… ».*

A la fin du document le recueil de l'« *Opposition exprimée par la personne de confiance ou le proche ou le parent* » n'est pas clair : s'agit-il d'un appel téléphonique ? Le CPP propose 2 options :

- soit prévoir le **recueil de la signature** du PARENT/PROCHE/PERSONNE DE CONFIANCE
- soit prévoir l'envoi d'un courrier précisant :

« En l'absence d'opposition de votre part dans un délai d'un mois à compter de l'envoi de la note d'information, les données de votre proche seront conservées et analysées dans le cadre de ce projet de recherche.
Pour exprimer votre droit d'opposition à l'utilisation de ses données dans le cadre de la recherche ou afin d'obtenir de plus amples informations sur cette étude, veuillez contacter le médecin investigateur (nom…) ayant pris en charge votre proche ou le Délégué à la Protection des données (DPO) à l'adresse suivante :…. »

Dans tous les cas prévoir de noter dans le dossier du patient, la date de la délivrance/l'envoi de l'information, le nom et la qualité du destinataire et le nom du médecin/responsable qui s'est chargé de l'envoi.

Clarifier

Sabine de la Porte, Présidente de Séance

Sabine de la PORTE, Présidente – **Léon LOISEAU**, Vice-président – Michèle **CATZ**, Secrétaire générale
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CPP Ile de France XI
Comité de **P**rotection des **P**ersonnes

St-Germain-en-Laye, le 22 juillet 2020

APHP
Mme Fadila AMERALI
Carré Historique de l'Hôpital Saint-Louis
Secteur Gris - Porte 23
1 avenue Claude Vellefaux
75475 PARIS

Titre de l'essai :	**Dexamethasone et stratégies d'oxygénation des patients hospitalisés en réanimation atteints de pneumonies à Covid-19**
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Modification Substantielle 2	
Documents examinés Numéro et date de version	
Formulaire de demande de MS	15/07/2020
Courrier de demande d'avis	17/07/2020
Tableau comparatif des modifications	Joint
Protocole	Version 3 du 09/07/2020
La lettre d'information et le formulaire de consentement : poursuite proche	Version 3 du 09/07/2020
La lettre d'information et le formulaire de consentement : proche	Version 3 du 09/07/2020
La lettre d'information et le formulaire de consentement : poursuite	Version 3 du 09/07/2020
La lettre d'information et le formulaire de consentement : majeur	Version 3 du 09/07/2020
CV du nouvel investigateur	Joint

Réf. Promoteur :	**APHP 200388-COVIDICUS**
N° IDRCB :	**2020-001457-43**
Réf. CPP :	**20037-25957**

La liste des investigateurs	Version 3 du 09/07/2020
Compte rendu du comité scientifique	Du 03/07/2020
Compte rendu du CSI	Du 06/07/2020

Le CPP Ile de France XI a examiné dans sa séance en comité restreint du 22 JUILLET 2020, la modification substantielle n°2 au projet de recherche référencé ci-dessus.

Ont participé à la délibération :

I – PREMIER COLLEGE

Axel LEVIER	Ingénieur
Kolia MILOJEVIC	Biostatisticien
Sabine de la PORTE	Chercheur
Ariane QUEFFELEC	Médecin

II - DEUXIEME COLLEGE

Léon LOISEAU	Philosophe
Christine GHESTEM	Association des familles du Vésinet
Nicole TAVERNY	Association des familles du Vésinet

Aucun membre délibérant du comité n'est affecté par un conflit d'intérêt.

J'ai l'honneur de vous informer que le comité a donné pour cette modification substantielle :

UN AVIS FAVORABLE

Cette modification substantielle consiste principalement en :

1. Modification du protocole de prise en charge du bras pharmacologique « Placebo »

Justification du promoteur : A la suite des premiers résultats de l'étude RECOVERY le comité scientifique de l'étude COVIDICUS s'est réuni le 3 juillet 2020, et, conscient de la possibilité d'un effet sur la mortalité des patients hospitalisés sous oxygène, propose de laisser à l'appréciation de l'investigateur en charge du patient la possibilité d'administrer 6 mg de dexamethasone selon le régime de l'étude RECOVERY à l'ensemble des malades inclus dans les 2 bras de randomisation.

Remarque du CPP :
Si l'étude RECOVERY ne remet pas en question l'étude COVIDICUS, l'adaptation du protocole est nécessaire pour des raisons éthiques. La solution proposée est un bon compromis entre la protection des patients et le maintien de la performance méthodologique de l'étude.

Il existe, sur le plan statistique, une perte de contraste par la division du groupe contrôle en 2 sous-groupes. Au lieu de comparer 20 mg à 0 mg, on va désormais comparer 20 mg à un groupe comprenant du 0 et du 6 mg.

Pour ne pas trop perdre en puissance méthodologique, il est important :

- **De verrouiller le groupe 6 mg à 6 mg. En effet, il ne faut pas qu'en plus de choisir 0 ou 6, l'investigateur ait la possibilité de prescrire 8 ou 15 mg, car alors, la comparaison devient totalement floue et inopérante.**

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- **De conserver la connaissance du sous-groupe 0 ou 6 afin de prévoir des analyses comparant en critère majeur : groupe 20 mg à groupe 0-6 mg, et en critères complémentaires 20 mg à 0 mg, 20 mg à 6 mg, 0 à 6 mg. Même si la décision entre 0 et 6 n'est pas un TAS, ces comparaisons séparément et rassemblées, auront un intérêt dans l'interprétation finale.**

2. Ajout d'un nouveau centre dans l'étude

3. Augmentation de la durée d'inclusion de l'étude de 8 mois.

Remarque du CPP : vérifier la validité de l'assurance

Sabine de la PORTE, Présidente de séance

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