

Supplementary Online Content 1

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Study Protocol

**INFLUENCE DE LA CORTICOTHERAPIE A DOSES FAIBLES
SUR L'ÉVOLUTION DES PNEUMOPATHIES AIGUËS COMMUNAUTAIRES GRAVES.**

**EFFECTS OF LOW-DOSE CORTICOSTEROIDS
ON SURVIVAL OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA**

CAPE COD

**Community-Acquired Pneumonia: Evaluation of Corticosteroids.
and sub-trial CAPE COVID19**

Community-Acquired Pneumonia: Evaluation of Corticosteroids in CoronaVirus Disease

Code: PHRN14-PFD / CAPE COD

BIOMEDICAL RESEARCH PROTOCOL

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Coordinating/Principal investigator

Pierre-François Dequin

Réanimation Polyvalente, CHU de Tours.
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 38 55
Fax: +33 2 47 39 65 36
pierre-françois.dequin@univ-tours.fr

Sponsor

CHU de Tours

2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 18 37 08 01
Fax: +33 2 47 47 82 04
recherche.clinique@chu-tours.fr

Methodology and Data Management Center

Bruno Giraudeau / Amélie Le Gouge

Elody Mureau
INSERM CIC 1415, CHU de Tours
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 34 37 96 57
Fax: +33 2 47 47 46 62
giraudeau@med.univ-tours.fr
legouge@med.univ-tours.fr
elody.murnat@med.univ-tours.fr

Coordinating pharmacy

Pharmaceutical service provider

Hélène Bourgoïn
Pharmacie Logipôle, CHU de Tours
37044 Tours cedex 9
Phone: +33 2 47 47 83 79
Fax: +33 2 47 47 60 16
h.bourgoïn@chu-tours.fr

Coordination Center

Sandrine Naturel

Caroline Caille-Fenerol

INSERM CIC 1435, CHU de Limoges
2, avenue Martin Luther King 87042 Limoges
cedex
Phone: +33 5 55 05 62 54
Fax: +33 5 55 05 80 57
sandrine.naturel@chu-limoges.fr
caroline.caille-fenerol@chu-limoges.fr

Clinical research study vigilance unit

Annie-Pierre Jonville-Béra

Céline Lengellé

Unité de Vigilance, CHU de Tours.
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 80 29
Fax: +33 2 47 47 38 26
jonville-bera@chu-tours.fr
c.lengelle@chu-tours.fr

HISTORY OF REVISIONS TO THE PROTOCOL

VERSION	DATE	REASON FOR THE REVISION
1.0	2015_06_02	Request for authorisation of a clinical trial
1.1	2015_07_07	Response to the ethics committee
1.2	2015_07_30	Response to the competent authority
2	2015_25_11	First amendment
3	2015_12_16	Second amendment
4	2016_04_06	Third amendment
5	2017_04_04	Fourth amendment
5.1	2017_07_25	Response to the competent authority
6	2017_09_22	Fifth amendment
7	2018_02_01	Sixth amendment
8	2018_07_04	Seventh amendment
9	2018_10_22	Eighth amendment
10	2020_03_30	Ninth amendment
10.1	2020_04_23	Response to the competent authority

PREAMBLE

On March 8th 2020, 105 586 cases of coronavirus disease (COVID19) due to SARS-CoV-2 have been reported, of whom 3 584 died (fatality rate 3.4%). Over 100 countries have reported laboratory-confirmed cases. In France, at the same date, 1 126 patients were contaminated and 19 have died (fatality rate 1.7%). Rational to use corticosteroids (CTx) in patients suffering from severe community-acquired pneumonia still holds for SARS-CoV-2 infected patients. Moreover, although controversial, some Chinese experts recommend short courses of CTx at low-to-moderate doses in the treatment of severe SARS-CoV-2 pneumonia. The need for a randomized clinical trial was strongly advocated. All CAPE-COD inclusion criteria were valid also for SARS-CoV-2 infected patients; moreover, these patients weren't excluded from our ongoing trial as Covid-19 infection didn't exist when CAPE-COD protocol was written. We then faced two major issues. The first one was how could we use the legal, administrative and ethical framework of the active CAPE-COD trial to help in providing an answer regarding CTx to the scientific community while the pandemic was going on. The second was that we did not want this new type of patients to jeopardize our initial trial. We finally decided to embed a sub-trial, the CAP-COVID trial, within the CAPE-COD trial. This meant that 1) inclusions of non- SARS-CoV-2 infected patients had to be temporarily stopped, 2) the CAPE-COVID trial would be conducted and 3) once the CAPE-COVID trial terminated, and after the pandemic had been contained, the CAPE-COD trial would be re-activated.

The CAPE-COVID trial was planned with substantial changes, as compared to the CAPE-COD trial. First, the primary outcome was defined as failure at Day 21 with failure defined as death or dependence from respiratory support, including mechanical ventilation or high-flow oxygen therapy. This outcome makes sense at both individual and community levels. Indeed, prolongation of respiratory support, especially mechanical ventilation, is associated with several complications (e.g. ventilator-associated pneumonia, ventilator-induced lung injury, acquired muscle weakness or sleep deprivation) and increase ICU stay. Moreover, in the context of rapidly progressive pandemic with a risk of exceeding critical care capacities, diminishing the duration of respiratory support will permit to decrease ICU length-of-stay and to liberate ICU beds for other patients. This beneficial effect of CTx is consistent with previous studies in non-severe community-acquired pneumonia that have shown that CTx decrease the time for clinical stability and hospital length-of-stay. Second, while the CAPE-COD trial was blinded we considered the

possibility to switch the CAPE-COVID trial from a blinded trial to an open while it is ongoing. Indeed, therapeutic units that will be used in CAPE-COVID will be those we planned to use for the original CAPE-COD trial. However, when starting the CAPE-COVID trials we had only about 290 remaining therapeutic units. Because obtaining new placebo units seemed impossible while the pandemic is going on, we decided (and specified it to both the ethic committee and the regulatory agency) that although the CAPE-COVID trial was planned as being blinded, in case we need to include more patients than we have units, we would end the trial as an open trial. Third, the CAPE-COVID trial was planned as a group sequential trial. The sample size has been calculated with an assumption on the failure rate associated to the control group which is not well documented. We will therefore allow ourselves to revise this sample size while the trial is going on.

These modifications appear in specific CAPE-COVID sections in the document.

MAIN CORRESPONDENTS

Coordinating / Principal investigator:

Pierre-François Dequin

Réanimation Polyvalente, Hôpital Bretonneau, CHU de Tours.
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 38 55 / Fax: +33 2 47 39 65 36
pierre-françois.dequin@univ-tours.fr

Sponsor:

CHU de Tours

2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 08 01 / Fax: +33 2 47 47 82 04
recherche.clinique@chu-tours.fr

Regulatory affairs and quality control center

Christelle Meunier et Marie Leclerc

Délégation à la Recherche Clinique et à l'innovation, CHU de Tours
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 46 64 / Fax: +33 2 47 47 46 62
c.meunier@chu-tours.fr / marie.leclerc@med.univ-tours.fr,

Methodology and data-management center:

Bruno Giraudeau / Amélie Le Gouge et Elody Mureau

INSERM CIC 1415, Hôpital Bretonneau, CHU de Tours
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 34 37 96 57 / Fax: +33 2 47 47 46 62
giraudeau@med.univ-tours.fr / legouge@med.univ-tours.fr / elody.marnat@med.univ-tours.fr

Coordinating pharmacy / Pharmaceutical service provider:

Hélène Bourgoïn

Pharmacie Logipôle, Hôpital Trousseau, CHU de Tours
37044 Tours cedex 9
Phone: +33 2 47 47 83 79 / Fax: +33 2 47 47 60 16
h.bourgoïn@chu-tours.fr

Clinical research study vigilance unit:

Annie-Pierre Jonville-Béra / Céline Lengellé

Unité de Vigilance des Recherches Biomédicales, Hôpital Bretonneau, CHU de Tours.
2, boulevard Tonnellé 37044 Tours cedex 9
Phone: +33 2 47 47 80 29 / Fax: +33 2 47 47 38 26
jonville-bera@chu-tours.fr / c.lengelle@chu-tours.fr

Coordination center:**Sandrine Naturel / Caroline Caille-Fenerol**

INSERM CIC 1435, CHU de Limoges

2, avenue Martin Luther King 87042 Limoges cedex

Phone: +33 5 55 05 62 54 / Fax: +33 5 55 05 80 57

sandrine.naturel@chu-limoges.fr / caroline.caille-fenerol@chu-limoges.fr**Biomarkers study:****Mustapha Si Tahar / Antoine Guillon :**Centre d'Etudes des Pathologies Respiratoires (CEPR) – INSERM U1100, Faculté de Médecine
10, boulevard Tonnellé 37032 Tours cedexmustapha.si-tahar@univ-tours.fr / antoine.guillon@univ-tours.fr<http://cepr.inserm.univ-tours.fr/>**Research networks supporting the study:****CRICS-TriGGERSep** (Clinical Research in Intensive Care and Sepsis - Trial Group for Global Evaluation and Research in Sepsis), a research network affiliated to the F-CRIN infrastructure.http://www.fcrin.org/sites/default/files/public/u350/fcrin-meeting_triggersep_20140318.pdf**Data and safety monitoring board** (cf. §12.2):

(in alphabetic order)

Jean CHASTRE (Paris)**Béatrice GUYOMARCH** (Nantes)**Sylvain MARCHAND-ADAM** (Tours)**Véronique SEBILLE** (Nantes)**Liem Binh LUONG** (Paris)**Scientific committee:**

(in alphabetic order)

Djillali Annane (Garches)**Thierry Boulain** (Orléans)**Pierre-François Dequin** (Tours)**Bruno François** (Limoges)**Bruno Giraudeau** (Tours)**Jean-Paul Mira** (Paris)**Pierre-François Laterre** (Brussels)**Philippe Vignon** (Limoges)

(all members of the CRICS-TriGGERSep network)

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CAPE COD : Community-Acquired Pneumonia: Evaluation of COrticosteroiDs.

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Sponsor

CHU Tours

2, boulevard Tonnellé 37044 Tours cedex 9

Tours, 30/03/2020

Signature

Directeur de la Recherche
et de l'Innovation
Julien LECHEVAT IEC

Coordinating investigator

Pierre-François Dequin

Réanimation Polyvalente, hôpital Bretonneau, CHU de Tours

Tours,

Signature

Pierre-François DEQUIN, MD, PhD

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LIST OF ABBREVIATIONS

ABG	Arterial Blood Gas
AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic Society
CAP	Community-Acquired Pneumonia
CEPR	Centre d'Etudes des Pathologies Respiratoires
CIC	Centre d'Investigation Clinique
CPP	Comité de Protection des Personnes
CRA	Clinical Research Associate
CRICS	Clinical Research in Intensive Care and Sepsis
CURB-65	Confusion Urea Respiratory rate Blood pressure 65 years
CTx	Corticosteroids
DSMB	Data and Safety Monitoring Board
e-CRF	electronic Case Report Form
ED	Emergency Department
F-CRIN	French Clinical Research Infrastructure Network
FiO ₂	Fraction of Inspired O ₂
I.C.H.	International Conference of Harmonisation
IDSA	Infectious Diseases Society of America
ICU	Intensive Care Unit
IL	Interleukin
INSERM	Institut National de la Santé et de la Recherche Médicale
ITT	Intention To Treat
IV	Intravenous
LOS	Length-of-stay
MRSA	Methicillin-Resistant Staphylococcus Aureus
P/F	PaO ₂ /FiO ₂ ratio
PaO ₂	Partial pressure of Arterial O ₂
PaCO ₂	Partial pressure of Arterial CO ₂
PCR	Polymerase Chain Reaction
PEEP	Positive End-Expiratory Pressure
PSI	Pneumonia Severity Index
SAE	Serious Adverse Events
SAPS2	Simplified Acute Physiology Score 2
SF-36	Short Form health survey - 36 items
SOFA	Sequential Organ Failure Assessment
SOP	Standardized Operating Procedure
SpO ₂	Pulse O ₂ Saturation
SUSAR	Suspected Unexpected Serious Adverse drug Reaction
TNF	Tumor Necrosis Factor
TriGGERSep	Trial Group for Global Evaluation and Research in Sepsis

1. SUMMARY OF THE RESEARCH STUDY CAPE COD

SPONSOR	CHU de Tours 2, boulevard Tonnellé 37044 Tours cedex 9
COORDINATING/PRINCIPAL INVESTIGATOR	Pierre-François Dequin, MD, PhD Réanimation Polyvalente, hôpital Bretonneau, CHU de Tours Phone: +33 2 47 47 38 55, Fax: +33 2 47 39 65 36 pierre-françois.dequin@univ-tours.fr
TITLE	Effects of low-dose corticosteroids on survival of severe community-acquired pneumonia (CAPE COD - Community-Acquired Pneumonia: Evaluation of COrticosteroiDs)
JUSTIFICATION/CONTEXT	Mortality of severe Community-Acquired Pneumonia (CAP) has not declined over time and is between 25 and 30% in sub-groups of patients. Corticosteroids (CTx) could down-regulate pulmonary and systemic inflammation, accelerate clinical resolution and decrease the rate of inflammation-associated systemic complications. Two recent meta-analyses suggest a positive effect on severe CAP D-28 survival when CTx are added to standard therapy. However they are based on only four trials gathering less than 300 patients, of which only one was positive. Recently published guidelines do not recommend CTx as part of CAP treatment. Therefore a well-powered trial appears necessary to test the hypothesis that CTx – and more specifically hydrocortisone – could improve D-28 survival of critically-ill patients with severe CAP, severity being assessed either on a Pulmonary Severity Index ≥ 130 (Fine class V) or by the use of mechanical ventilation or high-FiO ₂ high-flow oxygen therapy.
OBJECTIVES	<p><u>Primary objective:</u></p> <p>Demonstrate that hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for four to seven day at full dose (and then tapered for another four or seven days period) to patients admitted to the Intensive Care Unit (ICU) for severe CAP could improve the D-28 survival when compared to placebo.</p> <p><u>Secondary objectives:</u></p> <ol style="list-style-type: none"> 1. Demonstrate that hydrocortisone could decrease: <ul style="list-style-type: none"> ⇒ The need for intubation (for patients not-intubated at inclusion) ⇒ The need for non-invasive ventilation (for patients not-ventilated at inclusion) ⇒ The length of mechanical ventilation ⇒ The need for vasopressors ⇒ The vasopressors length of administration ⇒ The ICU and/or intermediate care unit length-of-stay (LOS) ⇒ The D-90 mortality ⇒ The level/activity of inflammation biomarkers

	<p>2. Demonstrate that hydrocortisone could improve:</p> <ul style="list-style-type: none"> ⇒ The oxygenation parameters ⇒ The level of organ dysfunctions ⇒ The survivors quality of life <p>3. Evaluate the side-effects potentially linked to CTx administration in this clinical setting.</p>												
STUDY DESIGN	<p>A phase-III multicenter add-on randomized controlled double-blind superiority trial assessing the efficacy of hydrocortisone vs. placebo on D-28 all-causes mortality, in addition to antibiotics and supportive care, including the correction of hypoxemia.</p> <p>Randomization will be stratified on: (i) centers; (ii) use of mechanical ventilation at the time of inclusion.</p>												
BLINDING	<p>Placebo-controlled trial. Patients, investigators and care-providers will be blinded for the patient-arm.</p>												
INCLUSION CRITERIA	<ul style="list-style-type: none"> • Age \geq 18 years • Patients affiliated to social security scheme (“Sécurité sociale”) • Admission to an ICU or intermediate care unit participating to the trial • Diagnosis of CAP suggested by at least two of the following: cough, purulent sputum, chest pain and dyspnea • Focal shadowing/infiltrate on chest X-ray or CT-scan • Diagnosis of CAP during the 48 hours post-hospital admission • Study drug infusion initiated no longer than 24 hours post first severity criterion • Severity defined by at least one of the following: <ul style="list-style-type: none"> ○ Pneumonia Severity Index (PSI) $>$ 130 (Fine class V) ○ Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more ○ Patient treated by high-flow oxygen therapy with a FiO_2 of 50% or more and a PaO_2/FiO_2 (P/F) ratio lower than 300 ○ Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO_2 is less than (cf. table): <table border="1" data-bbox="618 1585 1401 1761"> <tr> <td>Oxygen flow (L/min)</td> <td>6</td> <td>7</td> <td>8</td> <td>9</td> <td>10 or more</td> </tr> <tr> <td>PaO_2 (mmHg) less than</td> <td>180</td> <td>210</td> <td>240</td> <td>270</td> <td>300</td> </tr> </table> • Patient already treated by antibiotics (at least one dose since admission to hospital) • Informed consent signed by the patient, its relatives or emergency procedure 	Oxygen flow (L/min)	6	7	8	9	10 or more	PaO_2 (mmHg) less than	180	210	240	270	300
Oxygen flow (L/min)	6	7	8	9	10 or more								
PaO_2 (mmHg) less than	180	210	240	270	300								

<p>NON-INCLUSION CRITERIA</p>	<ul style="list-style-type: none"> • Patient treated by vasopressors for septic shock <u>at the time of inclusion</u> • Clinical history suggesting of aspiration of gastric content • Patient treated by invasive mechanical ventilation within 14 days before current hospital admission • Patient treated by antibiotics for a respiratory infection for more than seven days at the admission to the hospital (except if a pathogen resistant to this antibiotics is isolated) • History of cystic fibrosis • Post-obstructive pneumonia • Patients in which rapid PCR-test is positive for flu • Active tuberculosis or fungal infection • Active viral hepatitis or active infection with herpes viruses • Myelosuppression • Decision of withholding mechanical ventilation or endotracheal intubation • Hypersensitivity to corticosteroids • Patient needing anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason • Patients under treatment by more than 15 mg/d of prednisone (or equivalent) for more than 30 days • Patient already enrolled in another drug trial with mortality as an end-point. If the patient is already participating in another therapeutic trial with a different endpoint, the investigator must verify that inclusion in CAPE COD can not prejudice it. • Pregnant or breastfeeding woman • Patient on judicial protection
<p>STUDY TREATMENT STRATEGIES/ PROCEDURES</p>	<p>Patients will receive state-of-the-art standard therapy for severe CAP, including antibiotics and supportive care. Correction of hypoxemia will use standard low-flow oxygen therapy, high-flow oxygen therapy, non-invasive-ventilation or invasive ventilation with endotracheal tube, as required. Patients in the treatment group will receive intra-venous hydrocortisone. Patients of the control group will receive an intravenous placebo by intravenous route at the same frequency.</p> <p>Hydrocortisone or placebo will be given in a double-blind fashion for 8 or 14 full days. The intravenous route will be used. The treatment course will include 4 or 7 days of full dose (200 mg/day by continuous infusion), 2 or 4 days of half dose (100 mg/day by continuous infusion), and 2 or 3 days of tapering dose (50 mg/day by continuous infusion). Duration of treatment is chosen upon patient initial improvement.</p>
<p>PRIMARY OUTCOME</p>	<p>D28 all causes mortality</p>
<p>SECONDARY OUTCOMES</p>	<ul style="list-style-type: none"> ⇒ In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation ⇒ In patients non-ventilated at inclusion, proportion of patients

	<p>requiring non-invasive ventilation and proportion of patients needing endotracheal intubation</p> <ul style="list-style-type: none"> ⇒ D28 ventilator-free-days. This outcome will be assessed applying the following rules: <ul style="list-style-type: none"> ○ The period of interest will begin at the randomization date ○ Patients who die before day 28 will be affected a 0 value ○ Days between two mechanical ventilation episodes will be taken into account ○ A successful extubation will be defined as a spontaneous breathing 48h after extubation ⇒ Number of patients with vasopressor therapy initiation from inclusion to D28 ⇒ D28 vasopressor-free-days. This outcome will be assessed applying the following rules: <ul style="list-style-type: none"> ○ The period of interest will begin at the randomization date ○ Patients who die before day 28 will be affected a 0 value ○ Days between two vasoconstrictor-therapy episodes will be taken into account ⇒ ICU and/or intermediate care unit LOS ⇒ All-causes mortality at D90 ⇒ SF-36 Health Survey at D90 ⇒ Biomarkers: procalcitonin, C-reactive protein and plasmatic concentration of pro-inflammatory cytokines (IL-6, IL-20, IL-22, IL-22BP, HBD2, TNFα) at baseline, D3 and D7 ⇒ P/F ratio measured daily from baseline to D7, at the end of treatment, at the end of ICU-stay and/or D28 ⇒ SOFA calculated daily from baseline to D7, at the end of treatment, at the end of ICU-stay and/or D28 ⇒ Proportion of patients experiencing secondary infection during their ICU-stay ⇒ Proportion of patients experiencing gastrointestinal bleeding during their ICU-stay ⇒ Daily amount of insulin administered to the patient from D1 to D7 ⇒ Weight-gain at baseline and D7
SAMPLE SIZE	1,200 patients
NUMBER OF CENTERS	33
DURATION OF THE STUDY	<p>Recruitment period: 74 months Patient follow-up: 3 months Total duration: 77 months</p> <p>Exclusion period: 28 days.</p> <p>During this period, the subject will not be allowed to participate to another drug trial.</p>

STATISTICAL ANALYSIS	Death rate at D28 will be compared using a chi-square test. Two interim analyses are planned (at 400 and 800 patients) according to Peto's approach.
EXPECTED CONSEQUENCES	The intervention tested (adding CTx to the standard treatment of severe CAP) is expected to improve survival. Moreover, it will potentially decrease ICU LOS and reduce the need for invasive supportive procedures like mechanical ventilation (and then use of sedative drugs) or use of vasoconstrictors. A shortened ICU LOS with less invasive procedures is associated with a high probability of less hospital-acquired adverse effects, better qualitative outcome (in terms of quality of life) and less use of expensive health-care resources.

2. SUMMARY OF THE SUB-TRIAL CAPE COVID19

TITLE	<p align="center">Community-Acquired Pneumonia: Evaluation of Corticosteroids in COronaVirus Disease - CAPE-COVID19</p>
CONTEXT/ JUSTIFICATION	<p>On 28 March 2020, 591 971 cases of coronavirus disease (COVID19) due to SARS-CoV-2 have been reported, of whom 27 090 died (fatality rate 4.6%). Over 175 countries have reported laboratory-confirmed cases. In France, at the same date, 37 575 patients were contaminated and 2 314 have died (fatality rate 6.1%). Although most patients progress well and do not require specific treatment, therapy of severe forms (which represent 15% of cases) remains a challenge, as there is a lack of effective drug in addition to supportive care. At this stage, ICU-mortality is estimated to be 50%. There is an urgent need for focusing funding into searching novel approaches to treat severe coronavirus-associated pneumonia.</p> <p>Chinese experience shows that 45% of patients with severe disease receive corticosteroids (CTx). In Severe Acute Respiratory Syndrome (SARS) as in Middle-East Respiratory Syndrome (MERS) - two viral pulmonary diseases due to other coronaviruses - pulmonary histology revealed inflammation and diffuse alveolar injury. In severe cases, COVID19 is associated with a cytokine storm. This excessive immune response leads to extensive lung damage. Theoretically, CTx could have a role to decrease lung inflammation in coronaviruses pneumonia.</p> <p>Our knowledge on clinical use of CTx in viral pneumonia is essentially based on observational cohorts. As clinicians use CTx in the most critically ill patients, careful attention must be paid to the interpretation of mortality. In SARS, adverse effects of CTx have been observed, generally linked to the use of high doses. Prolonged viremia has also been evoked, without clinical impact. In MERS, CTx did not influence D-90 mortality, but seemed to delay viral clearance.</p> <p>Although controversial, some Chinese experts recommend short courses of CTx at low-to-moderate doses in the treatment of severe SARS-CoV-2 pneumonia. In a recently-published observational cohort of 201 patients, CTx appears to decrease the risk of death in the sub-group of Acute Respiratory Distress Syndrome (ARDS) patients: hazard ratio 0.38; 95% CI, 0.20-0.72. The need for a randomized clinical trial is strongly advocated.</p> <p>We suggest adapting a trial already underway to test the efficacy and safety of moderate doses of CTx in COVID19 patients receiving</p>

	antivirals.
<p>MAJOR CHANGES IN THE ORIGINAL PROTOCOL – DESIGNS ISSUES</p>	<p>Due to the pandemic context, the original Cape-Cod project is revised by including a “sub-trial” within the original trial. This allows beneficiating of an existing logistical, regulatory and ethical framework to help in providing very quickly results that could help the scientific community in the management of the ongoing crisis.</p> <p>COVID19 patients comply with selection criteria of the original Cape-Cod trial and actually from March 13th patients included in the Cape Cod trial are COVID19 patients. We therefore face two issues:</p> <ol style="list-style-type: none"> 1) Those patients may jeopardize the original trial 2) We urgently need answers to manage COVID19 patients <p>As a consequence, we propose:</p> <ol style="list-style-type: none"> 1) to stop the inclusion of non- COVID19 patients in the original trial 2) to conduct a new “sub-trial” named Cape COVID in which only COVID19 patients will be included 3) to re-start the original Cape Cod trial, once the current epidemic will be back, including non-COVID19 patients <p>Methodological issues are the following:</p> <ul style="list-style-type: none"> - Cape-COVID is planned as a group sequential randomized trial - The primary outcome is different as the one of the original trial. We will now consider failure at Day 21 were failure corresponds to death or dependence from respiratory support, including mechanical ventilation or high-flow oxygen therapy. This outcome makes sense at both individual and community levels. Indeed, prolongation of respiratory support, especially mechanical ventilation, is associated with several complications (e.g. ventilator-associated pneumonia, ventilator-induced lung injury, acquired muscle weakness or sleep deprivation) and increase ICU stay. Moreover, in the context of rapidly progressive pandemic with a risk of exceeding critical care capacities, diminishing the duration of respiratory support will permit to decrease ICU length-of-stay and to liberate ICU-beds for other patients. This beneficial effect of CTx is consistent with previous studies in non-severe community-acquired pneumonia who have shown that CTx decrease the time for clinical stability and hospital

	<p>length-of-stay.</p> <ul style="list-style-type: none"> - The sample size has been calculated with an assumption on the failure rate associated to the control group which is not well documented. We will therefore allow ourselves to revise this sample size while the trial is going on - Therapeutic units will be those we planned to use for the original trial. However, we presently have about 290 therapeutic units, knowing that about 50 COVID19 patients have already been included. It is presently impossible to obtain new placebo units. As a consequence, the trial is planned as being blinded, but in case we need to include more patients than we have units, we plan to end the trial as an open trial.
OBJECTIVE	<p>Primary objective</p> <p>Demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection could decrease the rate of treatment failure at D21, failure being defined either by patients death or persistent use of ICU respiratory support.</p> <p>Secondary objectives</p> <p>Demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> - could improve oxygenation parameters - could decrease: <ul style="list-style-type: none"> ▪ the need for intubation (for patients not-intubated at inclusion) ▪ the need for rescue therapies: prone-position, extra-corporeal membrane oxygenation (ECMO), nitric oxide inhalation (iNO) - will not increase the incidence of secondary infections - as measured at D21
STUDY DESIGN	<p>The Cape-COVID19 trial is a multi-center, blinded, two parallel group trial with group sequential analysis. An analysis will be performed every 50 patients.</p>

BLINDING	<p>Cf. original protocol</p> <p>Placebo-controlled trial. Patients, investigators and care providers will be blinded for the patient-arm.</p> <p>If necessary (lack of therapeutic units due to placebo manufacture that is unavailable during the pandemic) the trial will be ended as an open trial. Up-to-date there are still 290 therapeutic units available.</p>
INCLUSION CRITERIA	<ul style="list-style-type: none"> • Age \geq 18 year • Patients affiliated to social security scheme (“Sécurité sociale”) • Admission to an ICU or intermediate care unit participating to the trial • Diagnosis of COVID19 either as certain (PCR) or probable (evocative clinical and radiological features AND epidemic context AND absence of other microbiological documentation). • Focal shadowing/infiltrate on chest X-ray or CT-scan • Study drug infusion initiated no longer than 24 hours post first severity criterion ; in case of transfer from another hospital, this period will be prolonged to 48 hours. • Severity defined by at least one of the following: <ul style="list-style-type: none"> ○ Pneumonia Severity Index (PSI) $>$ 130 (Fine class V) ○ Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more ○ Patient treated by high-flow oxygen therapy with a FiO₂ of 50% or more and a PaO₂/FiO₂ (P/F) ratio lower than 300 ○ Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO₂ is less than (cf. table):

	Oxygen flow (L/min)	6	7	8	9	10 or more	
	PaO2 (mmHg)	180	210	240	270	300	
NON INCLUSION CRITERIA	<ul style="list-style-type: none"> • Patient receiving the best available treatment as define by up-to-date scientific knowledge • Informed consent signed by the patient, its relatives or emergency procedure <p>Patient treated by vasopressors for septic shock at the time of inclusion (vasopressors administered for the correction of a sedation- and high-PEEP-induced hypotension are allowed)</p> <ul style="list-style-type: none"> • Clinical history suggesting of aspiration of gastric content • History of cystic fibrosis • Post-obstructive pneumonia • Patients in which rapid PCR-test is positive for flu, if needed by epidemiologic context • Active tuberculosis or fungal infection • Active viral hepatitis or active infection with herpes viruses • Myelosuppression • Decision of withholding mechanical ventilation or endotracheal intubation • Hypersensitivity to corticosteroids • Patient needing anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason • Patients under treatment by more than 15 mg/d of prednisone (or equivalent) for more than 30 days • Patient already enrolled in another drug trial with similar endpoint. If the patient is already participating in another therapeutic trial with a different endpoint, the investigator must verify that inclusion in CAPE COD cannot prejudice it. 						

	<ul style="list-style-type: none"> • Pregnant or breastfeeding woman • Patient on judicial protection
TREATMENT	Hydrocortisone or placebo will be given in a double-blind fashion for 8 or 14 full days. The intravenous route will be used. The treatment course will include 4 or 7 days of full dose (200 mg/day by continuous infusion), 2 or 4 days of half dose (100 mg/day by continuous infusion), and 2 or 3 days of tapering dose (50 mg/day by continuous infusion). Duration of treatment is chosen upon patient initial improvement.
PROCEDURES ADDED TO CAPE COD TRIAL	Respiratory samples will be taken at the time of inclusion, at D3, D7, D10, D14 et D16. This examination will quantify the virus present in the airways. These coded samples will be stored on site at -80°C in triple packaging. At the end of the study, they will be sent back for analysis at the virology laboratory in Tours.
PRIMARY OUTCOME	D21 failure, where a failure is defined as death or need of respiratory support (mechanical ventilation or high-flow oxygen therapy).
SECONDARY OUTCOME	<p>Secondary outcomes (as measured at D21):</p> <ul style="list-style-type: none"> ⇒ P/F ratio measured daily from D1 to D7, at D14 and at D21 and/or at the end of ICU-stay ⇒ In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation <ul style="list-style-type: none"> ⇒ Number of prone-position sessions ⇒ Days on ECMO ⇒ Days on iNO ⇒ Proportion of patients experiencing secondary infection during their ICU-stay
SAMPLE SIZE	The event rate is assumed to be 30% in the control group. The trial is designed to demonstrate superiority of experimental treatment over control with an assumed event rate of 15% in the experimental group with 80% power and a one-sided Type I error rate of 2.5. Symmetric two-sided group sequential, requires sample size 290, for 6 interim analyses (5 during the trial and one final). Bounds were determined using a Kim-DeMets alpha spending function (Lan et al, Biometrika 1983;70:659-63; kim et al Biometrics 1987;4:857-64; DeMets et al Statist Medicine 1994;13:1341-52) with a conservative bound for efficacy and an aggressive bound for futility. That is, stopping for

	<p>high evidence of superiority while stopping early if the experimental treatment is not effective and can be potentially harmful for patients.</p> <p>Due to uncertainty of the failure rate in the control group, we plan to re-calculate this sample size while the trial is going-on. Indeed, data about mortality rate of COVID patients in ICU are diverging and ranging from 50% to 5%. We choose to assume a 30% rate considering mortality or need of respiratory support for the control arm but this is uncertain. This is why sample size re-estimation could be necessary during the trial when up-dated knowledge will be available.</p>
<p>NUMBER OF CENTERS</p>	<p>31 (same centers as CAPE COD)</p>
<p>DURATION OF THE STUDY</p>	<p>Recruitment period: 6 months</p> <p>Patient follow-up: 90 days</p> <p>Total duration: 9 months</p> <p>Exclusion period: NA.</p>
<p>STATISTICAL ANALYSIS</p>	<p>The statistical design for this phase III two arms clinical trial will follow a group sequential design with a total of 6 analyses (5 interim analyses and a final). The group sequential will use a Kim-DeMets alpha spending function with a conservative bound for efficacy and an aggressive bound for futility. That is, a conservative O'Brien Fleming type of bound for superiority bound and a an aggressive bound for futility design. The alpha spending function has the advantage to be a continuous function of the information time in group sequential procedures for interim analyses. As inclusions can be fast during this pandemic or that data monitoring will be more complex than usual, it can be possible that interim analysis will not follow the initial plan. So, using a continuous function will allow to re-calculate the boundaries if necessary.</p> <p>At each interim analysis, the Z statistics (for a difference of binary endpoints) is computed from the data of the two arms and will be compared to the efficacy and futility bounds.</p> <p>If the value of Z is higher than the interim analysis specific upper bound (or lower than the lower bound), the trial is stopped for reasons of demonstrated efficacy (or futility); otherwise the trial will continue.</p> <p>For interpretability, the plots and the results will be displayed on the maximum likelihood estimation (MLE) scale, but the final p-value</p>

	<p>will be computed using the log-odd-ratio normalized Z statistics. Analysis will be performed using R version 3.6.3 and the package gsDesign version 3.0-1.</p>
<p>EXPECTED CONSEQUENCES</p>	<p>The intervention tested (adding CTx to the supportive treatment of severe COVID19) is expected to improve survival and decrease the duration of respiratory support, thus improving individual health and well-being on one hand, and increasing ICU beds availability in the epidemic context.</p>
<p>EVALUATION OF SECURITY</p>	<p>Throughout the study, the safety will be in-live evaluated for each patient, in particular for the risk of secondary infections. All serious adverse event (with the exception of those listed in the protocol as specificities of protocol which do not require immediate reporting) occurring during the study from the day of the written informed consent until 14 days after the last study drug administration will be reported as thorough as possible by fax through the serious adverse event reporting form (initial or follow-up declaration).</p> <p>The data safety monitoring board (DSMB) is constituted by (in alphabetical orders) Jean Chastre, Béatrice Guyomarch, Sylvain Marchand-Adam, and Véronique Sébille. It will be systematically meet through teleconference at least every analysis (5 interim analysis and one final), and will meet in case of Suspected Unexpected Serious Adverse reaction (SUSAR), new facts or new safety information which could lead to a reevaluation of the benefit/risk ratio of the subject and/or new scientific information challenging study continuation. The study may be stopped definitely or temporarily at any time by the sponsor on the basis of information provided by the DSMB.</p>

3. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

3.1. Current state of knowledge

3.1.1. Community-Acquired Pneumonia: still a challenge

Community-acquired pneumonia (CAP) is a common problem with significant morbidity, mortality and cost. CAP accounts for 3-5 cases for 1000 person-years. This incidence-rate is multiplied by 10 in the elderly [1,2]. CAP is the first infection leading to an admission to the Emergency Department (ED) and, for the most severe forms, to the Intensive Care Unit (ICU) [3]. In all industrialized countries, CAP is at the forefront from mortality of infectious cause, and is considered to be between the sixth and the eight most prevalent causes of overall mortality [4]. In the United States alone, over 1.0 million people are admitted to the hospital each year with severe CAP, with an estimated inpatient cost of approximately \$10 billion [5]. The number of hospitalized cases in the USA is expected to increase due to population-ageing; similar trends are observed in Europe. Therefore, CAP is marked by high social and economical costs.

The overall 28-days mortality for inpatients with CAP is about 5%. However, in the subgroup admitted to the ICU, it varies from 18 to 54% [3,6,7]. Moreover, prognosis of severe CAP has not improved since several decades. This in-hospital case-fatality rate for patients with severe CAP remains unacceptably high.

3.1.2. Corticosteroids and community-acquired pneumonia: rationale

The keystones of up-to-date therapy of CAP are antibiotics and supportive treatment, including the correction of hypoxemia. There is little to be expected from evolution in antibiotics approach, since CAP's morbidity and mortality are not due to resistance to antibiotics or poor diffusion of drugs in the lung.

Severe CAP includes a systemic cytokines response which is likely to cause multiple organ dysfunctions. CAP is the most frequent cause of acute respiratory distress syndrome (ARDS), a respiratory failure characterized by deregulated systemic inflammation.

Corticosteroids (CTx) could down-regulate pulmonary and systemic inflammation, accelerate clinical resolution, decrease the rate of inflammation-associated systemic complications like ARDS and septic shock. CTx reduce the production of inflammatory cytokines (TNF-alpha, IL-1beta, IL-6, IL-8) and the subsequent recruitment of inflammatory cells into the alveolar space [8,9]. Supra-physiologic dose of CTx are needed for an adequate response to infectious diseases. Numerous studies have shown that the ability to secrete these doses could be impaired in a significant percentage of critically-ill patients [10].

3.1.3. Previous studies: no definitive answer

At the time the 1.0 version of this project was wrote, nine clinical trials comparing CTx vs. placebo in CAP have been published, including four since 2010 [11-19]. Two recently published meta-analyses suggested a positive effect of CTx, in terms of survival, when administered to severe CAP, with a survival odds ratio of 0.26 [95% CI: 0.11-0.64] and 0.39 [0.17-0.90], respectively [20,21]. However, this positive effect was linked to only four trials gathering less than 300 patients [14,16,18,19], of which only one was positive (although including only 48 patients)

[14], and sensitivity analysis revealed instability of pooled estimates. Therefore, the results of these meta-analyses should be interpreted with caution, and no treatment recommendations have been made about the use of CTx in severe CAP. Interestingly, this positive effect was not observed for non-severe CAP [20], underlying the necessity to define robust severity criteria for inclusion into such a trial.

Despite two positive meta-analyses, the benefit of CTx as an adjunctive therapy for CAP remains controversial and CTx are not recommended in recently published guidelines about the treatment of CAP [22-24].

Recently was published the STEP trial [25], which included 785 patients admitted to the hospital for CAP without severity criteria and compared prednisone 50 mg/d vs. placebo; its primary end-point was the time to obtain clinical stability, defined at time (days) until stable vital signs for 24h or longer. Median time to clinical stability was shorter in the CTx group (3.0 d, IQR [2.5-3.4]) than in the placebo group (4.4 d, IQR [4.0-5.0]). The CTx group had an higher incidence of hospital-acquired hyperglycaemia; other adverse events (AE) were infrequent and similar in both groups. Investigators of this trial chose a surrogate outcome and did not focus on severe CAP, although no studies have been positive in this context. Even if this trial conclude on a positive effect of CTx, the benefit/risk balance of this approach will remain to determine in critically-ill patients, who are exposed to specific risks – especially to infectious complications.

Contrasting with this result, a retrospective epidemiologic study [26] involving 6,925 patients mechanically ventilated in 893 Japanese hospitals suggested that CTx did not improve the D28 mortality, excepted for patients receiving catecholamine. This study however suffers from several limitations: in addition to its retrospective design, important data are missing including severity scores and microbiological documentation. Moreover, the large use of anti-pseudomonal and anti-MRSA antibiotics could suggest that ventilator-associated pneumonia have been included.

A. Torres et al. recently published a trial conducted in three Spanish ICUs [27] involving 120 patients with severe CAP and high inflammatory response, defined as a level of C-reactive protein greater than 150 mg/L at admission. They tested a 5-days cure of methylprednisolone 0.5 mg/kg b.i.d. vs. placebo and showed that treatment failure was less common in the CTx group (difference between groups 18%, 95% CI [3-32]). Mortality did not differ between groups; however, this study suggests that anti-inflammatory properties of CTx could positively influence the evolution of severe CAP.

3.1.4. Ongoing studies: a real place for CAPE COD

Several trials are currently evaluating CTx in CAP [28]. The Santeon-CAP study is planned to include 600 patients without severity criteria; its primary end-point will be the length of hospital stay. Even if one or both trials conclude on a positive effect of CTx, the benefit/risk balance of this approach will remain to determine in critically-ill patients, who are exposed to specific risks – especially to infectious complications.

Only one trial will focus on severe CAP (IDSA/ATS criteria), the ESCAPE trial which will include 1,450 patients with D-60 mortality as main end-point. Completion date was initially planned on January 2018. It compares methylprednisolone to placebo, for a treatment duration of 20 days.

This choice of methylprednisolone seems questionable. Indeed, four published studies have compared CTx and placebo in severe CAP, including three with hydrocortisone [13,14,18] (all resulting in lower mortality in the CTx arm, although not significant in two of them), and one with

methylprednisolone [19], negative in terms of mortality. Another trial comparing prednisone to placebo in “mild to severe” CAP also failed to show a difference in survival [16]. Unlike methylprednisolone, hydrocortisone is a natural hormone, and was used in large trials testing the benefit of CTx in septic shock. The balance between anti-inflammatory properties and mineral corticoid effects of hydrocortisone seems more adequate than this of methylprednisolone.

Additionally, IDSA/ATS criteria include the use of vasopressors, which appears to be a confusing factor, as hemodynamic effects of CTx are well documented [29], including a decrease of catecholamine dose and treatment-duration. Therefore, inclusion of septic shock patients seems to be inadequate for a study testing CTx effects in CAP.

Lastly, treatment duration of 20 days appears questionable, as some patients will probably improve faster, and will not require such as long hospital-stay.

Therefore, a large multicenter randomized clinical trial appears necessary to determine if hydrocortisone could improve survival of patients suffering from severe CAP, without associated septic shock. The protocol will provide an adaptive scheme to adapt the treatment duration to the degree of clinical improvement. Such a trial would not find an industrial financial support, in the absence of economical issues for pharmaceutical industry. Therefore, a public funding will be essential.

This trial will be one of the first endorsed by the TriGGERSep network, including CRICS group.

The F-CRIN-labeled TriGGERSep network gathers together basic researchers with main interest in sepsis, clinicians who have led or collaborated in the last major sepsis trials, methodologists and statisticians who have participated in these trials. CRICS group and his partners have participated in numerous pharmaceutical and academic trials especially in sepsis and pneumonia, and have demonstrated their ability to meet their commitments in terms of recruitment.

3.1.5. Characterization of CAP's severity

The Pneumonia Severity Index (PSI) has been widely validated as a mortality prediction tool for CAP patients [30]. It classifies patients into five groups of increased risk for hospital mortality on the basis of 20 variables easily assessed at their presentation to the ED. Patients in risk classes IV and V (i.e. $PSI > 90$ and > 130 , respectively) are considered at high-risk. In his original paper, Fine found that class V patients (who represented 9.9% of all CAP admitted to the ED during the study period) had a 28-days mortality of 25.2% [30]. In the Pneumocom-1 and -2 studies (conducted in France and Spain, respectively), 28-days mortality from class V patients was 36.9 and 28.7%, respectively [31]. In the CAPTIVATE study, which tested the efficacy of recombinant human tissue factor pathway inhibitor in severe CAP admitted to the ICU, the 28-days mortality in the control group was 27.0% in the subgroup of PSI V-strata [32]. Therefore, it appears that mortality of CAP has not declined over time in this sub-group. Moreover, this high mortality was observed in the control group of a clinical trial who did not allow inclusion of patients with severe comorbidities. Therefore, we can assume a mortality remaining as high as 25-30% for most severe (PSI class V) patients susceptible to be included into a trial.

PSI is a mortality prediction tool. Additionally, severity of CAP could be easily assessed by the presence of two criteria: mechanical ventilator support or treatment with vasopressors. The necessity to use mechanical ventilation as a supportive therapy for CAP patients is directly based on respiratory failure and related to high mortality, which is as high as 25% in intubated patients [6]. On the other hand, vasopressors are generally indicated for the treatment of septic shock

complicating CAP. The usefulness of hydrocortisone in the therapy of septic shock is still debated. However, we consider that this is a specific question, which overlaps with the question of hydrocortisone in CAP but is in several points quite different. Therefore, we decided not to include patients with septic shock treated by vasopressors in this trial.

High-flow oxygen therapy with nasal cannula has been proposed as a supportive treatment in acute respiratory failure [33], and seems to be widely used in ICUs despite a low level of evidence. No data is available about the vital prognosis of patients treated by this device. However, it seems reasonable to assume that a $\text{PaO}_2/\text{FiO}_2$ (P/F) less than 200 mmHg despite high-flow oxygen therapy with a FiO_2 of 50% or more (i.e. the level of P/F defining mild ARDS in mechanically ventilated patients) is a surrogate marker of severity of CAP.

As a CTx effect on mortality has been suggested only for severe CAP, we designed this trial on patients mechanically ventilated or hypoxemic despite high- FiO_2 high-flow oxygen therapy and/or with a PSI higher than 130. This strict definition of severity appears crucial to show a survival benefit of CTx. It was not taken into account in most published trials.

3.1.6. Biomarkers study

Interleukin (IL)-10 is a cytokine that exerts several immune stimulation as well as inhibitory effects. There are at least five novel human IL-10 family-related molecules: IL-19, IL-20, IL-22, IL-24, and IL-26. Activated T cells produce IL-19, IL-22 and IL-26, while IL-24 is produced by activated monocytes and T-cells.

Among those cytokines, IL-22, which was discovered in 2000, has been identified as key mediator to efficient lung anti-microbial host defense and preservation of homeostasis [39]. The influence of CTx on the pro-inflammatory cytokine response (TNF-alpha, IL-1beta, IL-6, IL-8) in CAP is well described, but no information is currently available on the regulation of the IL-22 signaling pathway by CTx in this context. CTx seem to regulate the production of IL-22-producing cells in systemic inflammatory diseases [40,41]. However, in patients with severe chronic inflammatory lung disease, CTx have no effect on IL-22 regulation, indicating a potential role for this cytokine in steroid-resistant diseases [42].

In the present study, we aim to decipher the effects of CTx on the IL-22 signaling pathway, including the regulation of IL-22, IL-22BP and IL-20 secretion as well as the release of the antimicrobial peptide hBD2. The expected findings will provide a better understanding of the potential immunomodulatory effects of CTx in severe CAP.

3.2. Hypothesis of the study and results expected

Our hypothesis is that the down-regulation of systemic and pulmonary deregulated inflammation induced by hydrocortisone, as well as the maintaining of the hypothalamic-pituitary-adrenal axis integrity, will improve the survival of critically-ill patients with severe CAP. As the initial course of the disease will probably be improved in different ways (e.g. a decrease of ICU and hospital length-of-stay (LOS), less use of supportive treatment like mechanical ventilation and vasoconstrictors), we expect not only an initial reduction of mortality, but also an improvement of both medium-term survival and quality of life. This will potentially lead to a decrease of health-related costs, and to a more efficient use of ICU resources.

3.3. Methodological choices

Studied intervention

As already explained, the adjunction of CTx to standard therapy in the treatment of severe CAP admitted to the ICU could decrease mortality, according to recently published but insufficiently convincing meta-analyses [20,21]. More precisely, this is based on published studies that tested the efficacy of hydrocortisone [13,14,18]. As the digestive function of critically-ill patients is frequently impaired, the intra-venous route appears the only option. A continuous infusion will help to prevent excessive blood glucose variability. We choose a supra-physiological dose of hydrocortisone, similar to that used in precedent studies and in trials that have tested the efficacy of hydrocortisone in septic shock. Tapering the dose should prevent a rebound of inflammation. To take into account individual evolution of CAP, an adaptive scheme will be provided for patients whose clinical status will improve rapidly, in accordance with the concept of “personalized medicine”. Non-inclusion of septic shock patients will contribute to reduce confounding factors.

Primary outcome

The mortality of severe CAP remains high and has not improved since several decades. Therefore reduction of mortality appears the only outcome that will justify the economic cost of such a trial. Meta-analyses suggest an impressive effect-size of CTx in CAP, with a survival odds ratio of 0.26 [95% CI: 0.11-0.64] and 0.39 [0.17-0.90]. However, this is supported by very few modest size trials. Our hypothesis (a 25% decrease in D-28 mortality) appears more realistic.

3.4. Benefit/risk ratio

3.4.1. Individual benefit

Severe CAP is characterized by a high mortality rate. Additionally, patients surviving hospitalization experience a significant increase in long-term morbidity (cardiovascular and other organs complications, impaired functional status, and recurrent hospitalizations) decreasing their quality of life [34]. There is a high probability that these long-term complications are highly-related to their initial ICU-stay. LOS, need for mechanical ventilation and especially long-time mechanical ventilation (needed when CAP is complicated by ARDS) and prolonged use of sedative agents are associated with physical and psycho-social sequelae occurring after ICU stay. If CTx are able to decrease inadequate inflammatory response to lung infection, they will probably improve respiratory status, thus leading to less use of mechanical ventilation and sedative. This will decrease not only the ICU-LOS but also iatrogenic complications like hospital-acquired infections. Therefore, administration of CTx to patients experiencing severe CAP is able to decrease their overall mortality and to improve their long-term general well-being.

3.4.2. Collective benefit

In any developed country, CAP is the leading cause of death from infection, and the seventh most prevalent cause of overall mortality. Severe CAP requires admission to the ICU, committing scarce resources in times of economic crisis. Despite advances in bacteriological identification, antibiotics therapy and supportive measurements, the mortality of severe CAP (Fine class V) stays at about 25-30%, and has not decrease since two decades. Therefore, CAP is characterized by high economical and social costs.

The keystones of up-to-date therapy of CAP are antibiotics and supportive treatment. There is little to be expected from evolution in antibiotics approach, since CAP's morbidity and mortality are not due to resistance to antibiotics or poor diffusion of drugs in the lung.

In the critical care setting, many studies have failed to demonstrate any benefit of numerous approaches manipulating the inflammatory cascade with very costly pharmacological agents. On the contrary, our approach based on physiological effects of glucocorticoids (an intact hypothalamic-pituitary-adrenal axis is indispensable for host survival during stress upon exposure to an infectious agent) and their anti-inflammatory intracellular activity appears susceptible to improve prognosis of CAP at minimal cost.

Although published trial (and therefore meta-analyzes) had been centered on mortality end-point, limited available data suggest that CTx could decrease length of mechanical ventilation and ICU-LOS. If this is confirmed, it will offer exciting perspectives not only for patients' well-being but also for hospitals organization, considering that the increased incidence of CAP during the cold season entails a risk of ICUs saturation.

Provided that a beneficial effect of CTx on survival is not burdened by excessive side-effects, we can assume that a decrease of mechanical ventilation and ICU stay duration will be associated to a better quality of life for surviving patients.

Therefore, CTx appear to be a promising approach to improve prognosis of severe CAP, with significant impact on public health.

3.4.3. Individual risk and risk prevention policy

This trial is designed as an add-on study. All patients will receive the state-of-the-art treatment of severe CAP in a critical care setting. As already exposed, this is a high-risk situation, due to the high mortality and morbidity related to severe CAP.

Additionally to this standard therapy, they will receive hydrocortisone or placebo during an eight or 14 days period.

Published studies that compared CTx to placebo in CAP did not report an increase of side-effects in the CTx group. However, side-effects of CTx that could occur in this clinical setting are: secondary infections, hyperglycemia and glycemia variability, neuromuscular weakness, rebound inflammation at the end of treatment, sodium retention and gastrointestinal bleeding.

Two large trials have evaluated hydrocortisone therapy in the treatment of septic shock. The GER-INF005 study did not report increase of secondary infections [35]. Conversely, the CORTICUS study reported a significant excess of secondary septic shock in the hydrocortisone group, even if superinfections from any type were not significantly more frequent [36]. In CAPE COD trial, routine use of bundle to prevent ventilator-associated pneumonia (use of a semi-recumbent position, daily "sedation vacations" and assessment of readiness to extubate) will be highly recommended. Microbiological assessment of bronchial secretions will be realized according to local guidelines. Additionally, CTx may blunt the febrile response, leading to failed or delayed recognition of hospital-acquired infections. Therefore, patients included in CAPE COD trial will be carefully monitored to screen precociously the occurrence of a novel infection. Recommendations of the Surviving Sepsis Campaign [37] will be used to improve efficiency of early diagnosis and treatment in case of suspected secondary infection.

Hyperglycemia is a common tool in septic ICU patients and is correlated to overall mortality. Moreover, CTx given as intermittent boluses produce glycemic variability. The continuous infusion of hydrocortisone will help to prevent blood glucose variability. Regular monitoring of blood glucose will be use, and insulin therapy titrated to target an upper blood glucose ≤ 180 mg/dL.

Neuromuscular weakness is a complex syndrome complicating the evolution of most severely-ill patients, in particular in case of septic shock and ARDS. Its occurrence increase when neuromuscular blocking agents are administered, especially for a long time. Therefore, neuromuscular blocking agents will be avoided whenever possible, unless they will be clearly indicated according to available guidelines (e.g. for a short period in severe ARDS). In this case, they will be administered for the shorter period possible, and every 12 hours tests will be done to see if their administration can be stopped.

Rebound inflammation at the end of treatment has been previously described, and this leads us to progressively taper hydrocortisone over a period of four or seven days.

Sodium retention is a multifactor event that is frequent in severe ICU patients. As recommended, the input/output fluid balance and patient's weight will be monitored. Blood sodium concentrations will be obtained from routine monitoring.

Gastrointestinal bleeding is infrequent in ICU patients, unless they have coagulation disorders. Its prevention will be left to the discretion of the physician-in-charge, as no recommendation is currently available to justify the use of a specific drug. Significant bleeding (i.e. justifying the need for endoscopy and blood transfusion) will be monitored.

3.4.4. Collective risk

The sole collective risk related to this trial is directly bound to its financial cost. Indeed, the assumption raised needs to design and conduct a large multicenter trial including 1,200 patients whose budget is necessarily expensive. However, the survival benefit suggested by background studies justifies this cost. Additionally, we have planned interim analyses after inclusion of 400 and 800 patients, so as to stop the trial early if our hypothesis was not confirmed.

3.4.5. Adverse events

Cf. section 10.2.1.5.

3.4.6. Risk / benefit balance

This trial will test the hypothesis of a significant improvement in D-28 survival. When compared to this potential benefit, the risks of hydrocortisone therapy appear uncommon, partly possible to prevent, and easy to detect. Therefore, the risk/benefit ratio appears favourable.

3.5. Expected consequences

The intervention tested (adding CTx to the standard treatment of severe CAP) is expected to improve short-term (D28) and medium-term (D90) survival. Moreover, it will potentially decrease ICU LOS and reduce the need for invasive supportive procedures like mechanical ventilation (and then use of sedative drugs) or use of vasoconstrictors. A shortened ICU stay with less invasive procedures is associated with a high probability of less hospital-acquired adverse effects, better

qualitative outcome (in terms of quality of life) and less use of expensive health-care resources. Interestingly, hydrocortisone is a cheap and almost always well-tolerated drug.

4. OBJECTIVES OF THE STUDY

4.1. Principal objective

4.1.1 CAPE COD

Demonstrate that hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion (severity criteria: see below section 5.1.) and administered for four to seven days at full dose (and then tapered for another four to seven days period) to patients admitted to the ICU for severe CAP could improve the D-28 survival when compared to placebo.

4.4.2. CAPE COVID19

The principal objective of the sub-study CAPE COVID19 is to demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection could decrease the rate of treatment failure at D21, failure being defined either by patients death or persistent use of ICU respiratory support.

4.2. Secondary objectives

4.2.1 CAPE COD

1. Demonstrate that hydrocortisone started during the first 24 hours following the first severity criteria and administered for four or seven days at full dose (and then tapered for another four or seven days period) to patients admitted to the ICU for severe CAP, could decrease:
 - ⇒ The need for intubation (for patients not intubated at inclusion)
 - ⇒ The need for non-invasive ventilation (for patients not ventilated at inclusion)
 - ⇒ The length of mechanical ventilation
 - ⇒ The need for vasopressors
 - ⇒ The vasopressors length of administration
 - ⇒ The ICU and/or intermediate care unit LOS
 - ⇒ The D-90 mortality
 - ⇒ The level/activity of inflammation biomarkers
2. Demonstrate that hydrocortisone started during the first 24 hours following the first severity criteria and administered for four or seven days at full dose (and then tapered for another four or seven days period) to patients admitted to the ICU for severe CAP, could improve:
 - ⇒ The oxygenation parameters
 - ⇒ The level of organ dysfunctions
 - ⇒ The survivors quality of life
3. Evaluate the side-effects potentially linked to CTx administration in this clinical setting.

4.2.2 CAPE COVID19

The secondary objectives of the sub-study CAPE COVID19 is to demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection:

- could improve oxygenation parameters
- could decrease:
 - the need for intubation (for patients not-intubated at inclusion)
 - the need for rescue therapies: prone-position, extra-corporeal membrane oxygenation (ECMO), nitric oxide inhalation (iNO)
- will not increase the incidence of secondary infections
- as measured at D21

5. CONCEPTION OF THE STUDY

5.1. Study design

5.1.1. CAPE COD

A phase-III multicenter add-on randomized controlled double-blind superiority trial assessing the efficacy of hydrocortisone *vs.* placebo on day 28 mortality, in addition to antibiotics and supportive care, including the correction of hypoxemia.

The trial will be conducted in 33 French centers.

Patients in the control group will receive state-of-the-art standard therapy for severe CAP, including antibiotics and supportive care. Correction of hypoxemia will use standard low-flow oxygen therapy, high-flow oxygen therapy, non-invasive-ventilation or invasive ventilation with endotracheal tube, as required.

Patients in the treatment group will be treated in the same way. Additionally, they will receive intravenous hydrocortisone. Patients of the control group will receive an intravenous placebo at the same frequency.

5.1.2. CAPE COVID19

The Cape-COVID19 trial is a multi-center, blinded, two parallel group trial with group sequential analysis. The trial will be conducted in xx French centers.

5.2. Blinding

5.2.1. CAPE COD

Patients, caregivers and investigators will be blinded from the treatment administered (hydrocortisone or placebo). The adaptive scheme will not affect the blinding.

5.2.2. CAPE COVID19

If necessary (lack of therapeutic units due to placebo manufacture that is unavailable during the pandemic) the trial will be ended as an open trial. Up-to-date there are still 290 therapeutic units available.

5.3. Randomization methods

Allocation sequence generation

A computer process will be used to generate allocation sequences in a 1:1 ratio. The INSERM CIC 1415 will be in charge of this process, independently from the physicians who will recruit patients.

Stratification

Randomization will be stratified on: (i) centers; (ii) use of mechanical ventilation at the time of inclusion.

Implementation

Randomization will be centralized and performed electronically thanks to the Clinsight® software, also used for the electronic Case Report Form (eCRF) (*cf. infra*).

6. ELIGIBILITY CRITERIA

6.1. Inclusion criteria

6.1.1. CAPE COD

- Age \geq 18 years
- Patients affiliated to social security scheme (“Sécurité sociale”)
- Admission to an ICU or intermediate care unit participating to the trial
- Diagnosis of CAP suggested by at least two of the following:
 - Cough
 - Purulent sputum
 - Chest pain
 - Dyspnea
- Focal shadowing/infiltrate on chest X-ray or CT-scan *
- Diagnosis of CAP during the 48 hours post-hospital admission
- Study drug infusion initiated no longer than 24 hours post first severity criterion
- Severity defined by at least one of the following:
 - Pneumonia Severity Index (PSI) $>$ 130 (Fine class V)
 - Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more

- Patient treated by high-flow oxygen therapy with a FiO_2 of 50% or more and a P/F ratio less than 300
- Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO₂ is less than (cf. table):

Oxygen flow (L/min)	6	7	8	9	10 or more
PaO ₂ (mmHg) less than	180	210	240	270	300

- Patient already treated by antibiotics (at least one dose since admission to hospital)
- Informed consent signed by the patient, its relatives or emergency procedure
- * For COPD patients with acute respiratory failure, a strong evidence of CAP has to be present (e.g. newly emerged focal shadowing on chest X-ray or CT-scan)

6.1.2. CAPE COVID19

On the sub-group of patients included with COVID19 :

- Age \geq 18 year
- Patients affiliated to social security scheme (“Sécurité sociale”)
- Admission to an ICU or intermediate care unit participating to the trial
- Diagnosis of COVID19 either as certain (PCR) or probable (evocative clinical and radiological features AND epidemic context AND absence of other microbiological documentation).
- Focal shadowing/infiltrate on chest X-ray or CT-scan
- Study drug infusion initiated no longer than 24 hours post first severity criterion ; in case of transfer from another hospital, this period will be prolonged to 48 hours.
- Severity defined by at least one of the following:
 - Pneumonia Severity Index (PSI) $>$ 130 (Fine class V)
 - Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more
 - Patient treated by high-flow oxygen therapy with a FiO_2 of 50% or more and a PaO₂/FiO₂ (P/F) ratio lower than 300
 - Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO₂ is less than (cf. table):

Oxygen flow (L/min)	6	7	8	9	10 or more
PaO2 (mmHg)	180	210	240	270	300

- Patient receiving the best available treatment as defined by up-to-date scientific knowledge
- Informed consent signed by the patient, its relatives or emergency procedure

6.2. Non-inclusion criteria

- Patient treated by vasopressors for septic shock at the time of inclusion[£]
- Clinical history suggesting of aspiration of gastric content
- Patient treated by invasive mechanical ventilation within 14 days before current hospital admission
- Patient treated by antibiotics for a respiratory infection for more than seven days at the admission to the hospital (except if a pathogen resistant to this antibiotics is isolated)
- History of cystic fibrosis
- Post-obstructive pneumonia
- Patients in which rapid PCR-test is positive for flu[§]
- Active tuberculosis or fungal infection
- Active viral hepatitis or active infection with herpes viruses
- Myelosuppression
- Decision of withholding mechanical ventilation or endotracheal intubation
- Hypersensitivity to corticosteroids
- Patient needing either anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason. For patients who will require a vasopressor therapy for septic shock after their inclusion, hydrocortisone will not be added, unless the clinician decides (cf. 6.5.).
- Patients under treatment by more than 15 mg/d of prednisone (or equivalent) for more than 30 days
- Patient already enrolled in another drug trial with mortality as an end-point. If the patient is already participating in another therapeutic trial with a different endpoint, the investigator must verify that inclusion in CAPE COD can not prejudice it.
- Pregnant or breastfeeding woman
- Patient on judicial protection

[£] “Vasoconstrictors” means norepinephrine or epinephrine (whatever the dose), or more than 5 µg/kg/min of dopamine. Vasoconstrictors administered for the treatment of septic shock are not allowed at inclusion. A patient admitted for CAP without sign of circulatory failure whose condition requires vasoconstrictors after the initiation of invasive mechanical ventilation could be included provided that: (i) circulatory failure is reported to the effects of positive pressure ventilation and sedative drugs, at discretion of the physician-in-charge; (ii) blood lactate level is lower than 4 mmol/L; (iii) the dose of epinephrine or norepinephrine is lower than 0.25 µg/kg/min.

A patient developing septic shock after inclusion may receive vasoconstrictors at any dose. He will not receive extra-trial hydrocortisone, unless biological demonstration of adrenal insufficiency.

§ In the case of a patient whom flu will be diagnosed after the inclusion, the study treatment will be stopped ; nevertheless the patient will be follow-up according to study protocol.

6.3. Methods of recruitment

Patients admitted to the participating ICUs (including intermediate care beds) for suspicion of CAP will be screened at admission for inclusion and non-inclusion criteria, on a 24/7 basis. When all inclusion criteria will be present except severity criteria, patient will be monitored at least at 6-hours intervals by physicians and/or study nurses to detect the onset of severity criteria.

Additionally, EDs of participating hospitals will be closely associated to the study. Emergency physicians will be encouraged to use a severity score for all suspected CAP, and trained to use it if necessary. Both PSI and CURB-65 [35] scores will be allowed in this pre-screening phase, as the PSI is more complicated than the CURB-65, especially in the context of EDs.

Emergency physicians will propose the transfer to participating ICU not only for patients with severe CAP whose severity has been defined on standard clinical criteria, e.g. obvious respiratory failure (usual care), but also for patients with either a $PSI \geq 90$ (i.e. assigned to Fine risk classes IV or V) or a $CURB-65 \geq 4$. In the absence of obvious immediate need for an ICU-admission, patients will be admitted to the intermediate care unit (e.g. for patients identified with a PSI from 90 to 129 (class IV) or a CURB-65 at 4).

PSI will be systematically calculated in the ICU, as it will be the sole severity index qualifying for inclusion to the study.

PSI and CURB-65 will be available on both paper and electronic forms, in both ICUs and EDs.

Feasibility of recruitment is discussed in section §9.11

7. STUDY TREATMENTS, STRATEGY AND PROCEDURES

7.1. Study treatment

7.1.1. Drug characteristics

The experimental treatment is hydrocortisone presented in powder and solvent for injection. The form used in the study is hydrocortisone hemisuccinate 100 mg in vial of powder and ampoule of solvent (Serb laboratory, 40 Avenue George V, 75008 Paris).

The composition is for one vial: hydrocortisone hemisuccinate - sodium salt – amount expressed in hydrocortisone: 100 mg ; the excipients are: disodium phosphate anhydrous, sodium dihydrogen phosphate anhydrous, for one ampoule of solvent: water for injection 2 mL.

7.1.2. Administration

Hydrocortisone or placebo will be given in a double-blind fashion during 8 or 14 full days. The intra-venous route will be used. The treatment course includes 4 or 7 days of full dose (200 mg/day by continuous infusion), 2 or 4 days of half dose (100 mg/day by continuous infusion), and 2 or 3 days of tapering dose (50 mg/day by continuous infusion). Patients whose status would improve

faster would interrupt treatment at the moment of their release from ICU or intermediate care unit. In this case, tapering will not be mandatory.

7.1.3. Contra-indications

Viral or fungal infections are usually considered as contra-indications for CTx. However, in the specific context of critically-ill patients, this contra-indication appears relative, provided that an adequate anti-infectious therapy is associated. Invasive fungal and viral infections are non-inclusion criteria. Flu pneumonia is also a non-inclusion criterion.

7.2. Comparative treatment

The placebo will be similar to the verum treatment but will not contain hydrocortisone. Placebo will be administered with the same scheme than hydrocortisone.

7.3. Medicinal product circuit

7.3.1. Supply of products

The Serb laboratory will supply hydrocortisone and placebo to the sub-contractor, which will distribute it in each investigational site in an adequate packaging.

7.3.2. Medicinal product packaging

The sub-contractor will prepare individual packages for each site; one kit will contain the full treatment for the 14-days treatment, that is to say either 21 vials of 100 mg of hydrocortisone for the active group or placebo for the comparative group. The same package will be used whatever the duration of treatment (i.e. 8 or 14 days).

The treatments (hydrocortisone or placebo) will be prepared and packed on a strictly same procedure. They will be labeled in accordance with the regulatory guidelines for experimental drugs and in order to keep the blinding.

7.3.3. Medicinal products labeling

The experimental treatments will be labeled in accordance with the regulatory guidelines in order to keep the blinding.

7.3.4. Distribution and management of medicinal products

Hydrocortisone and placebo will be supplied to the pharmacist of each investigational site, who will be in charge of the traceability and the storage. The products can be stored at room temperature (maximum 25°C). The study nurse will prepare either the hydrocortisone or placebo solution according to a standardized procedure.

7.3.5. Return and destruction of unused products

Hydrocortisone or placebo vial will be kept at the pharmacy until the monitoring visit by the Clinical Research Associate (CRA). Then they will be destroyed on site after a written agreement

by the Sponsor. Unused hydrocortisone and placebo will be destroyed on site after a written agreement by the Sponsor as well.

7.4. Placebo

7.4.1. Organization of blinding

The study will be performed in a double-blind manner. The patient, the investigator and study center staff will be blinded to study drug allocation. Hydrocortisone and placebo will be provided in identical packages. Vials will be labelled in an identical way.

7.4.2. Unblinding

Treatment will be unblinded in case of suspected unexpected Serious Adverse Event (SAE), in the situation where the clinical condition of the patient warrants to know whether or not he/she received hydrocortisone.

7.5. Allowed and forbidden treatments

Forbidden treatments

- ⇒ Hydrocortisone and other CTx whatever the dose and the route (except local administration, nebulization being not considered as a local administration) are not allowed. If an unavoidable indication appears during patient stay (e.g. biological demonstration of adrenal insufficiency) the patient should be treated. In this case, the study treatment will be stopped to avoid unnecessarily high-dose of hydrocortisone. However, short-duration administration of open CTx will be allowed for prevention of post-extubation laryngeal edema.
- ⇒ Continuous infusion of neuromuscular blocking agents is to be avoided. In the case it will be indicated (e.g. for severe ARDS), this will be for the shorter period possible and an interruption of the infusion will be planned every 12 hours, to insure not to prolong the treatment longer than necessary.
- ⇒ Vasoconstrictors administered for the treatment of septic shock are not allowed at inclusion. A patient admitted for CAP without sign of circulatory failure whose condition requires vasoconstrictors after the initiation of invasive mechanical ventilation could be include provided that: (i) circulatory failure is reported to the effects of positive pressure ventilation and sedative drugs, at discretion of the physician-in-charge; (ii) blood lactate level is lower than 4 mmol/L; (iii) the dose of epinephrine or norepinephrine is lower than 0.25 µg/kg/min. A patient developing septic shock after inclusion may receive vasoconstrictors at any dose. “Vasoconstrictors” means norepinephrine or epinephrine (whatever the dose), or more than 5 microg/kg/min of dopamine.

Allowed treatments

- ⇒ Antibiotics are at discretion of the clinician-in-charge, but should be started prior to inclusion.
- ⇒ All other treatments are allowed. Sedative agents will be used with respect of available guidelines, to avoid over-sedation.
- ⇒ “Rescue” treatments are allowed in case of severe ARDS (including prone-position, inhaled nitric oxide, veno-venous Extra-Corporeal Membrane Oxygenation). Rescue corticosteroids are not allowed as there is no evidence of their benefit in such circumstances.

8. OUTCOME

8.1. Primary outcome

8.1.1. CAPE COD

All-causes mortality at D28.

8.1.2. CAPE COVID19

For the sub-group of patients included with COVID19, the primary outcome is failure at D21. A failure is defined as death or need of respiratory support (mechanical ventilation or high-flow oxygen therapy).

8.2. Secondary outcomes

8.2.1. CAPE COD

- ⇒ In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation
- ⇒ In patients non-ventilated at inclusion, proportion of patients requiring non-invasive ventilation and proportion of patients needing endotracheal intubation
- ⇒ D28 ventilator-free-days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 28 will be affected a 0 value
 - Days between two mechanical ventilation episodes will be taken into account
 - A successful extubation will be defined as a spontaneous breathing 48h after extubation
- ⇒ Number of patients with vasopressor therapy initiation from inclusion to D28
- ⇒ D28 vasopressor-free-days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 28 will be affected a 0 value
 - Days between two vasoconstrictor-therapy episodes will be taken into account
- ⇒ ICU and/or intermediate care unit LOS
- ⇒ All-causes mortality at D90
- ⇒ SF-36 Health Survey at D90
- ⇒ Biomarkers: procalcitonin, C-reactive protein and plasmatic concentration of pro-inflammatory cytokines (IL-6, IL-20, IL-22, IL-22BP, HBD2, TNF α) at baseline, D3 and D7
- ⇒ P/F ratio measured daily from baseline to D7, at the end of treatment, at the end of ICU-stay and/or D28
- ⇒ SOFA calculated daily from baseline to D7, at the end of treatment, at the end of ICU-stay and/or D28
- ⇒ Proportion of patients experiencing secondary infection during their ICU-stay
- ⇒ Proportion of patients experiencing gastrointestinal bleeding during their ICU-stay
- ⇒ Daily amount of insulin administered to the patient from D1 to D7
- ⇒ Weight-gain at baseline and D7

8.2.2. CAPE COVID19

For the sub-group of patients included with COVID19, the secondary outcomes are:

- ⇒ P/F ratio measured daily from D1 to D7, at D14 and at D21 and/or at the end of ICU-stay
- ⇒ In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation
 - ⇒ Number of prone-position sessions
 - ⇒ Days on ECMO
 - ⇒ Days on iNO
- ⇒ Proportion of patients experiencing secondary infection during their ICU-stay

9. STUDY PROCEDURE

9.1. Timelines

Duration of the inclusion period: 74 months

Duration of each patient's participation: 3 months

Total duration of the study: 77 months

An exclusion period will be required during 28 days (assessment of the primary outcome). During this period, the subject will not be allowed to participate to another drug trial.

9.2. Flow chart

Cf below



Flow-chart CAPE COD:

	Pre-treatment period	Treatment period								Follow-up period		
	Screening Baseline T0	D1	D2	D3	D4	D5	D6	D7	End of treatment (D8 or D14)	End of ICU stay ¹	D28	End of study visit D90
Inclusion/non inclusion criteria	√											
Information of patient or relatives	√											
Written informed consent	√									√ ¹		
Randomization	√											
Medical history and demographics	√											
Pneumonia Severity Index	√											
SAPS2	√											
SOFA score	√	√	√	√	√	√	√	√	√	√	√ ²	
Pregnancy test ³	√											
Physical examination	√											
Height	√											
Weight	√							√ ⁴				
Vital signs ⁵	√	√	√	√	√	√	√	√	√	√		
Status ⁶											√	√
Chest X-ray or CT-scan	√											
ABG and P/F ratio ⁷	√	√	√	√	√	√	√	√ ⁴	√ ^{4,8}	√ ^{4,8}	√ ^{2,4,8}	
Respiratory parameters ⁹	√	√	√	√	√	√	√	√ ⁴	√ ⁴	√ ⁴	√ ^{2,4}	
Hematology ¹⁰	√							√ ^{4,8}	√ ^{4,8}			
Serum chemistry ¹¹	√			√				√ ^{4,8}	√ ^{4,8}			
Glucose		√	√					√ ^{4,12}	√ ^{4,12}			
Cortisol	√											
Microbiology ¹³	√										√	
Endotracheal intubation Y/N [T0-D28]											√	
Mechanical ventilation Y/N [T0-D28]											√	
Ventilator-free days											√	
Vasoconstrictors Y/N [T0-D28]											√	
Vasoconstrictors-free days											√	
Insulin dose		√	√	√	√	√	√	√				
Hospital-acquired infection [T0-D28]											√	
Digestive hemorrhage [T0-D28]											√	
Biomarkers (optional) ¹⁴	√			√				√				
Antibiotics	√	√	√	√	√	√	√	√	√			
SF-36												√
AEs/SAEs ¹⁵	√	√	√	√	√	√	√	√	√	√	√	√

Notes: When the end of ICU stay correspond at the end of treatment, only end of treatment visit must be complete.

- ¹: end-of-ICU-stay visit will take place when the patient will leave the ICU (including intermediate-care beds). For an inclusion with emergency procedure, pursuit informed consent will be obtained before the end-of-ICU-stay
- ²: if patient still stays in the ICU
- ³: serum beta-HCG or urine pregnancy test will be performed on all women of childbearing potential
- ⁴: a \pm 24-hours window will be tolerated
- ⁵: blood pressure, heart rate, respiratory rate, and temperature
- ⁶: alive or deceased
- ⁷: ABG (Arterial Blood Gas) : partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH. For patients on low-flow oxygen therapy, P/F will be calculated using equivalence tables
- ⁸: if needed for care of patient. Hematology and serum chemistry not will be performed at D8 if the results are already available at D7.
- ⁹: oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, SpO₂] and/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, SpO₂]
- ¹⁰: white blood cell count, platelet count
- ¹¹: potassium, glucose, creatine phosphokinase, C-reactive protein, procalcitonin
- ¹²: only if there is no sample for serum chemistry at this time
- ¹³: microbiological assessment will be guided by clinical context, as a piece of usual care. It will include at least blood cultures and research of urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila*. When those tests will not identify the cause of CAP, blood samples will be obtained at two weeks interval to assess antibodies for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia spp.* Other tests (including research of viruses) will be left to discretion of the clinician in charge; however, in epidemiological context, a rapid-diagnostic will be used for flu.
- ¹⁴: central lab (CEPR - UMR INSERM U1100)
- ¹⁵: adverse events will be recorded once the informed consent is signed



Flow-chart CAPE COVID19 :

	Pre-treatment period	Treatment period										Follow-up period			
	Screening Baseline T0	D1	D2	D3	D4	D5	D6	D7	D10	End of treatment (D8 or D14)	D14	D16	End of ICU stay ¹	D21	End of study visit D90
Inclusion/non inclusion criteria	√														
Information of patient or relatives	√														
Written informed consent	√												√ ¹		
Randomization	√														
Medical history and demographics	√														
Pneumonia Severity Index	√														
SAPS2	√														
SOFA score	√	√	√	√	√	√	√	√		√			√		
Pregnancy test ³	√														
Physical examination	√														
Height	√														
Weight	√							√ ⁴							
Vital signs ⁵	√	√	√	√	√	√	√	√		√			√		
Status ⁶														√	√
Chest X-ray or CT-scan	√														
RT-PCR	√														
ABG and P/F ratio ⁷	√	√	√	√	√	√	√	√ ⁴		√ ^{4,8}			√ ^{4,8}	√ ^{2,4,8}	
Respiratory parameters ⁹	√	√	√	√	√	√	√	√ ⁴		√ ⁴			√ ⁴	√ ^{2,4}	
Hematology ¹⁰	√							√ ^{4,8}		√ ^{4,8}					
Serum chemistry ¹¹	√			√				√ ^{4,8}		√ ^{4,8}					
Glucose		√	√					√ ^{4,12}		√ ^{4,12}					
Cortisol	√														
Microbiology ¹³	√													√	
Endotracheal intubation Y/N [T0-D21]														√	
Mechanical ventilation Y/N [T0-D21]														√	
Ventilator-free days														√	
Vasoconstrictors Y/N [T0-D21]														√	
Vasoconstrictors-free days														√	
Insulin dose		√	√	√	√	√	√	√						√	
Hospital-acquired infection [T0-D21]														√	
Digestive hemorrhage [T0-D21]														√	
Biomarkers (optional) ¹⁴	√			√				√							
Respiratory samples	√			√				√	√		√	√			
Antibiotics	√	√	√	√	√	√	√	√		√					
SF-36															√
AEs/SAEs ¹⁵	√	√	√	√	√	√	√	√		√			√	√	√

Notes: When the end of ICU stay correspond at the end of treatment, only end of treatment visit must be complete.

1: end-of-ICU-stay visit will take place when the patient will leave the ICU (including intermediate-care beds). For an inclusion with emergency procedure, pursuit informed consent will be obtained before the end-of-ICU-stay

2: if patient still stays in the ICU

3: serum beta-HCG or urine pregnancy test will be performed on all women of childbearing potential

4: a \pm 24-hours window will be tolerated

5: blood pressure, heart rate, respiratory rate, and temperature

6: alive or deceased

7: ABG (Arterial Blood Gas) : partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH. For patients on low-flow oxygen therapy, P/F will be calculated using equivalence tables

8: if needed for care of patient. Hematology and serum chemistry not will be performed at D8 if the results are already available at D7.

9: oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, SpO₂] and/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, SpO₂]

10: white blood cell count, platelet count

11: potassium, glucose, creatine phosphokinase, C-reactive protein, procalcitonin

12: only if there is no sample for serum chemistry at this time

13: microbiological assessment will be guided by clinical context, as a piece of usual care. It will include at least blood cultures and research of urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila*. When those tests will not identify the cause of CAP, blood samples will be obtained at two weeks interval to assess antibodies for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia spp.* Other tests (including research of viruses) will be left to discretion of the clinician in charge; however, in epidemiological context, a rapid-diagnostic will be used for flu.

14: central lab (CEPR - UMR INSERM U1100)

15: adverse events will be recorded once the informed consent is signed

9.3. Obtaining consent

During the screening visit, the investigator provides patient or patient's family (when present) with information and answers all his or her questions about the objective, the nature of constraints, foreseeable risks and benefits expected from the study. He also explains the patient's rights in relation to a biomedical research study and checks his eligibility criteria. Before any clinical examination or procedure related to the study, the investigator will obtain informed, written and freely given consent from patient or its relative when patient will not be able to consent itself. An emergency procedure will be used when patient's family could not come to the ICU.

When a subject is no longer incapacitated, informed consent to continue participation will be obtained from the subject at that time.

9.4. Pretreatment period

The pretreatment phase or screening visit is conducted by the investigator. The screening visit will occur on the same day than the inclusion visit.

The purpose of the pretreatment phase is to confirm subject eligibility for enrolment in the study based on the inclusion and exclusion criteria and to obtain written informed consent. Subjects may be rescreened.

Subjects who meet all of the inclusion criteria and none of the non inclusion criteria will be randomly assigned to study drug and will undergo the procedures and evaluations stated in the Time and Events Schedule.

During the pre-treatment period, and after obtaining an informed consent or with emergency procedure, following data will be obtained:

- ⇒ Medical history and demographics
- ⇒ Date of current hospital admission, ICU admission and initiation of mechanical ventilation
- ⇒ Pneumonia Severity Index
- ⇒ SAPS2
- ⇒ Sequential Organ Failure Assessment (SOFA)
- ⇒ Serum or urine pregnancy test in all women of childbearing potential
- ⇒ Physical examination, including weight and height
- ⇒ Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- ⇒ Chest X-ray or CT-scan
- ⇒ Blood sample for ABG. P/F will be calculated, using equivalence tables for non-ventilated patients.
- ⇒ Oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ and/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ Blood sample for hematology, serum chemistry and cortisol
- ⇒ Bacteriological assessment of CAP (at least blood cultures and urinary antigens research for *Streptococcus pneumoniae* and *Legionella pneumophila*).
- ⇒ Blood sample for central laboratory (biomarkers for centers participating)

- ⇒ Documentation of antibiotics
- ⇒ Randomization

9.5. Treatment period

Days 1 to 4 or 1 to 7:

After randomization, IV study drug therapy will be administered at full dose (i.e. 200 mg/day diluted in 48 mL of saline for hydrocortisone arm, or 48 mL of saline for placebo arm) for 4 to 7 days.

During this period, the following parameters will be obtained for each day from D1 to D7:

- ⇒ Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- ⇒ Sequential Organ Failure Assessment (SOFA)
- ⇒ Blood sample for ABG. P/F will be calculated, using equivalence tables for non-ventilated patients.
- ⇒ Oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ and/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or not-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ Documentation of antibiotics
- ⇒ Total dose of insulin administered by day
- ⇒ Collection of AEs and SAEs

Additionally:

- ⇒ Weight at D7. A \pm 24-hours window will be tolerated
- ⇒ Blood sample for hematology at D7 (if needed by patient care). A \pm 24-hours window will be tolerated.
- ⇒ Blood sample for serum chemistry at D3 and D7 (if needed by patient care). A \pm 24-hours window will be tolerated.
- ⇒ Blood sample for glucose at D1 and D2 (and at D7 if no blood sample will be obtained for serum chemistry / with a \pm 24-hours window).
- ⇒ Blood sample for central laboratory for participating centers (biomarkers) at D3 and D7

Day 5: Modulation of treatment period

At the end of the fourth day of full-dose hydrocortisone therapy, a decision will be made by the local investigator on the treatment scheme:

- ⇒ If the patient's respiratory and general status have sufficiently improved during this treatment period to consider the end of ICU-stay (including intermediate-care beds) before D14, an adaptive scheme will be used. In this case, the full-dose treatment will last 4 days and tapering will last 4 additional days. Dates of visit will not change. All behind criteria will have to be present to consider this adaptive scheme:
 - Patient breathing spontaneously
 - P/F > 200 as calculated with equivalence tables

- SOFA D4 inferior or equal to SOFA D1
- High-probability to be discharged from the ICU (including intermediate-care beds) before D14, according to clinician judgment

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
HC dose (mg/d) in the treatment arm	Full treatment:													
	200	200	200	200	200	200	200	100	100	100	100	50	50	50
	Adaptive scheme in case of prompt improvement:													
	200	200	200	200	100	100	50	50	0	0	0	0	0	0

⇒ All other patients will be treated at full dose from D1 to D7, and then hydrocortisone (or placebo) will be tapered from D8 to D14

However, patients whose status would improve faster would interrupt treatment at the moment of their release from ICU or intermediate care unit, irrespective of their theoretical duration of treatment. In this case, tapering will not be mandatory.

Days 5 to 8 or 8 to 14:

Intravenous study drug therapy will be administered at tapered dose, successively at 100 mg/day diluted in 48 mL of saline for hydrocortisone arm, or 48 mL of saline for placebo arm, for 4 days (D8-D11) or 2 days (D5-D6); then at 50 mg/day diluted in 48 mL of saline for hydrocortisone arm, or 48 mL of saline for placebo arm, for 3 additional days (D12-D14) or 2 days (D7-D8).

During this period, the following parameters will be obtained at the end of treatment (D8 or D14):

- ⇒ Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- ⇒ Sequential Organ Failure Assessment (SOFA)
- ⇒ Blood sample for ABG (if needed by patient care). A \pm 24-hours window will be tolerated P/F will be calculated, using equivalence tables for non-ventilated patients.
- ⇒ Oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ and/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ A blood sample for hematology and serum chemistry (if needed by patient care). A \pm 24-hours window will be tolerated
- ⇒ Blood sample for glucose (if no blood sample will be obtained for serum chemistry). A \pm 24-hours window will be tolerated
- ⇒ Documentation of antibiotics
- ⇒ Collection of AEs and SAEs

9.6. Post treatment period (follow-up)

9.6.1. CAPE COD

At the end of ICU-stay and/or at D28:

The following parameters will be obtained:

- ⇒ Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- ⇒ Sequential Organ Failure Assessment (SOFA)
- ⇒ Blood sample for ABG (if needed by patient care). A \pm 24-hours window will be tolerated. P/F will be calculated, using equivalence tables for non-ventilated patients.
- ⇒ Oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ And/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ Collection of AEs and SAEs

When the end of ICU stay correspond at the end of treatment, only end of treatment visit must be complete.

Additionally, at D28 (regardless the patient is still in ICU or not):

The following parameters will be obtained:

- ⇒ Status (alive or deceased)
- ⇒ Microbiological documentation of the CAP, as usually assessed
- ⇒ Need for endotracheal intubation from T0 to D28 (yes or no)
- ⇒ Need for mechanical ventilation from T0 to D28 (yes or no)
- ⇒ Need for vasoconstrictors from T0 to D28 (yes or no)
- ⇒ D28 ventilator-free days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 28 will be affected a 0 value
 - Days between two mechanical ventilation episodes will be taken into account
 - A successful extubation will be defined as a spontaneous breathing 48h after extubation
- ⇒ D28 vasoconstrictors-free days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 28 will be affected a 0 value
 - Days between two vasoconstrictors treatment episodes will be taken into account
- ⇒ Type and documentation of hospital-acquired infections from T0 to D28
- ⇒ Documentation of significant digestive haemorrhages (i.e. requiring endoscopy and blood transfusion) from T0 to D28

At D90:

The following parameters will be obtained by phone contact with the patient:

- ⇒ Status (alive or deceased)
- ⇒ SF-36 assessment of quality of life
- ⇒ Collection of AEs and SAEs

9.6.2. CAPE COVID19

At the end of ICU-stay and/or at D21:

The following parameters will be obtained:

- ⇒ Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- ⇒ Sequential Organ Failure Assessment (SOFA)
- ⇒ Blood sample for ABG (if needed by patient care). A \pm 24-hours window will be tolerated. P/F will be calculated, using equivalence tables for non-ventilated patients.
- ⇒ Oxygenation and respiratory parameters for non-ventilated patients [respiratory rate, type of oxygen device, oxygen flow, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ And/or ventilator and respiratory parameters for mechanically-ventilated patients [invasive or non-invasive ventilation, ventilation patterns, fraction of inspired oxygen (FiO₂), PEEP level, respiratory rate, partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂), pH, SpO₂]
- ⇒ Collection of AEs and SAEs

When the end of ICU stay correspond at the end of treatment, only end of treatment visit must be complete.

Additionally, at D21 (regardless the patient is still in ICU or not):

The following parameters will be obtained:

- ⇒ Status (alive or deceased)
- ⇒ Microbiological documentation of the CAP, as usually assessed
- ⇒ Need for endotracheal intubation from T0 to D21 (yes or no)
- ⇒ Need for mechanical ventilation from T0 to D21 (yes or no)
- ⇒ Need for vasoconstrictors from T0 to D21 (yes or no)
- ⇒ D28 ventilator-free days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 21 will be affected a 0 value
 - Days between two mechanical ventilation episodes will be taken into account
 - A successful extubation will be defined as a spontaneous breathing 48h after extubation
- ⇒ D21 vasoconstrictors-free days. This outcome will be assessed applying the following rules:
 - The period of interest will begin at the randomization date
 - Patients who die before day 21 will be affected a 0 value
 - Days between two vasoconstrictors treatment episodes will be taken into account
- ⇒ Type and documentation of hospital-acquired infections from T0 to D21
- ⇒ Documentation of significant digestive haemorrhages (i.e. requiring endoscopy and blood transfusion) from T0 to D21

At D90:

The following parameters will be obtained by phone contact with the patient:

- ⇒ Status (alive or deceased)

- ⇒ SF-36 assessment of quality of life
- ⇒ Collection of AEs and SAEs

9.7. Rules for interrupting the study

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason. The investigator and sponsor also have the right to withdraw participants from the study.

The treatment studied will be interrupted for the following reasons:

- ⇒ Withdrawal of consent: when a subject withdraws consent before completing the study, the reason for withdrawal of consent is to be documented on the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.
- ⇒ Adverse experiences
- ⇒ At the request of the investigator or sponsor, whether for administrative or other reasons

If the reason for interruption of the studied treatment is an adverse experience, the specific event and any related test results will be recorded on the eCRF. If an emergency occurs where the volunteer's condition requires knowledge of the study drug, the study code (patient number) may be broken for the specific subject. Any broken code will be clearly justified and explained by a comment on the e-CRF.

The study may be stopped definitely or temporarily at any time by the sponsor on the basis of information provided by the Data and Safety Monitoring Board (DSMB).

For the Sub-study CAPE-COVID19, the DSMB will meet at each interim analysis for efficacy, futility and safety analysis. Analysis will be conducted every 50 patients. The DSMB will also meet in case of a Suspected Unexpected Serious Adverse reaction (SUSAR), new facts, new safety information which could lead to a reevaluation of the benefit/risk ratio of the subject and/or new scientific information challenging study continuation. In the event of early termination of the study, the information will be forwarded immediately by the sponsor to the French Health Authorities (ANSM) and to the Ethics Committee (CPP).

When the studied treatment is interrupted, all observations collected up to the time of termination will be recorded on the e-CRF along with the reason for termination, and scheduled safety evaluations and follow-up examinations will be conducted, if possible.

If a subject is lost-to-follow-up, every possible effort must be made by the study center personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow-up must be documented.

9.8. Possible remuneration for subjects / patients

This study does not give rise to compensation.

9.9. Biomarkers

The biomarkers study will be realized in centers experienced in achieving this type of sample (CRICS group) and will include 400 patients (approximately 200 patients of each arm / i.e. hydrocortisone and placebo).

This study requires three additional blood samples of 7 mL each (i.e. a total of 21 mL). Blood samples will be collected at the inclusion of the patients (baseline) and at D3 and D7 post-inclusion for centralized assay of cytokines at CEPR, INSERM U1100, Tours. Samples will be collected in EDTA tubes and rapidly centrifuged (2000 g during 15 min at room temperature); the serum fraction will be aliquoted in triplicate (1.5 mL tube) and stored at -20°C for a short period (maximum 7 days), then stored at -80°C.

Cytokines will be quantified in serum by sandwich enzyme-linked immunosorbent assay (ELISA), using commercially available assays: IL-6, IL-22, IL-22BP, IL-20, hBD2 and TNF α .

9.10. CAPE COVID19

Respiratory samples will be taken at the time of inclusion, at D3, D7, D10, D14 et D16. This examination will quantify the virus present in the airways. These coded samples will be stored on site at -80°C in triple packaging. At the end of the study, they will be sent back for analysis at the virology laboratory in Tours.

9.11. Feasibility

The feasibility is a key-factor of such a trial and will be detailed in four points:

Study design

The trial has been designed from a very simple manner: an add-on study with two parallel arms. Hydrocortisone and placebo will be provided in similar packages, simplifying respect of blinding. Randomization will be possible 24/7 by e-CRF with two stratification variables (mechanical ventilation at inclusion or not / center). Data will be entered into an e-CRF in order to facilitate their processing and to limit and detect input errors.

According to the complexity of ICU-patients files (very high number of monitored parameters and measurement points, high frequency of multi-organ involvement), sufficient time of CRA has been budgeted.

The follow-up visits at D28 and D90 will be conducted by phone for outcome criteria (death or alive) and submission of SF-36. If we are unable to reach a patient, the knowledge of its place of birth will allow obtaining its vital status from the city hall (public data, according to French law).

The adaptive scheme will not only permit to adapt the duration of treatment to patient's clinical evolution (personalized medicine) but to simplify the follow-up during ICU-stay. Indeed, the study of 1,541 episodes of *Streptococcus pneumoniae* CAP (of all degrees of severity) hospitalized in the central area of France between 2004 and 2008 showed that mean and median hospital LOS were 9.9 and 7.0 days, respectively [unpublished data]. A lower hospital LOS of eight days (short treatment duration in our adaptive scheme) seems therefore reasonable for severe CAP requiring ICU admission. This is supported by a retrospective analysis of patients hospitalized for CAP which found a mean(SD) hospital LOS of 12(10) days for the subgroup of patients admitted to the ICU [43]. Patients included in the CAPE COD trial whose clinical status will allow transfer from the ICU before D8 will be transferred to the intermediate-care unit attached to the ICU (when it exists) or to a general ward unit in the nearest possible place from the ICU. In this case the administration of the tapering dose of hydrocortisone or placebo and the data collection will be supervised by ICU's research nurses and/or investigators.

Research organization

The coordinator has a strong experience in respiratory critical care medicine and sepsis. He leads the Work Package 1 (clinical investigation) of the TriGGERSep network, and coordinates the scientific council of CRICS group. He is Investigator or Principal Investigator in many studies (inclusion rates always above initial expectations).

Limoges INSERM CIC 1435 is experimented in emergency, sepsis and intensive care research, has a strong expertise in research clinical trials coordination and will be responsible of global organization of the current trial.

The methodologist (Tours INSERM CIC1415) involves in many multicenter trials, is responsible for several large population study analysis and is recognized in intensive care field. He is responsible for methodology of an ICU research network.

Coordination unit will associate coordinating investigator, methodologist from Tours INSERM CIC 1415, a project manager and a CRA. A delegation task will be established to define precisely the responsibilities of each partner.

In every participating site a principal investigator and a clinical research technician (or a study nurse) will be identified and responsible for:

- ⇒ Implementation of study procedures
- ⇒ Quality and data reporting
- ⇒ Archives and confidentiality
- ⇒ Patient screening
- ⇒ Data collection and CRF completion
- ⇒ Archives and confidentiality

Networks and investigation centers involved

This trial is endorsed by the TriGGERSep network (<http://www.triggersep.org/>), which is a F-CRIN-labeled structure gathering basic researchers with main interest in sepsis, clinicians who have led or collaborated in the last major sepsis trials, and methodologists and statisticians who have participated in these trials.

The TriGGERSep partners have conducted several trials to explore potential adjunct therapies for sepsis. This group of investigators showed that a prolonged treatment with low doses of hydrocortisone plus fludrocortisone was associated with a survival benefit in septic shock patients at high risk of dying (Ger-Inf-O5). This trial constituted a breakthrough in the field more than 10 years ago. Subsequently, the partners showed in a European trial (CORTICUS), that a treatment with hydrocortisone alone in patients at low risk of dying from septic shock did not provide any survival benefit although resolution of shock and organ failures was faster. In another trial (COITSS), the partners showed, that glucocorticoid-induced hyperglycemia in septic shock was not associated with an increased risk of death or long-term sequels. Indeed, in this trial, tight blood glucose control by intensive insulin therapy yielded similar outcomes than conventional management, i.e. maintenance of blood glucose levels below 150 mg/dl. The partners have conducted the only academic trial on activated protein C for septic shock (APROCCHS) and showed that this drug did not improve outcome in patients with septic shock and a high risk of dying. Finally, the partners are conducting a new trial (APROCCHS II) of hydrocortisone plus fludrocortisone in septic shock to confirm that this treatment continues to be helpful in a modern

era of critically ill patients’ management. The partners have substantially contributed to large industry-driven trial evaluating several potential adjunct therapies among them are activated protein C, Eritoran (TLR4 antagonist), and tissue factor pathway inhibitor.

The investigation work-package of CRICS-TriGGERSep who will act as the core of the investigation function of the network, and more particularly of the CAPE COD trial. All centers involved in the trial are strongly involved in clinical research and have been chose for both their experience in sepsis trials and the quality of their organization as investigation centers.

CRICS group and his partners have participated in numerous pharmaceutical and academic trials especially in sepsis and pneumonia, and have demonstrated their ability to meet their commitments in terms of recruitment. In order to optimize and to ensure high quality recruitment, sites have a 24/24 7/7 organization with dedicated resources. CRICS has also developed its own tools and specific computerized tracking system. CRICS centers impact positively the recruitment in multi-center international trials, as show in the table behind:

	CAPTIVATE	OASIS	CYTOFAB	ZANAMIVIR	RESPOND	ACCESS	MIDEX
Domain	CAP	sepsis	sepsis	flu	sepsis	sepsis	Sedation
Number of worldwide centers	188	108	45	30	54	197	44
CRICS centers participating	4 (2.1%)	8 (7.4%)	9 (20.0%)	3 (10.0%)	5 (9.2%)	5 (2.5%)	5 (11.4%)
Total inclusions	2,138	309	300	125	557	1984	501
CRICS inclusions	185 (8.6%)	84 (27.2%)	109 (36.3%)	30 (24.0%)	79 (14.2%)	214 (10.8%)	147 (29.3%)

As an example, in the CAPTIVATE trial, which tested the efficacy of recombinant human tissue factor pathway inhibitor in severe CAP admitted to the ICU, the four participating CRICS centers (representing 2.1% of all centers) have recruited 8.7% of all patients included (i.e. 186 patients) during the 36 months period when CRICS centers where opened – i.e. 1.3 patient/month/center.

Taking into account the high incidence of severe CAP in ICUs, the strong relationship existing between ICUs involved and EDs from their hospitals, and on the basis of one to two inclusions per month in each center (depending of the number of beds), 30 centers will have the recruitment facility to conduct the trial in a 54-month period – i.e. including 0.7 patient par month and per center at average.

Risk mitigation plan

Inclusions of each center will be followed in real time. The principal investigator and the coordination structure (CIC 1435), with help of the project managers of TriGGERSep and CRICS, will eventually contact a center whose inclusions are too inferior to its commitments (less than 3 inclusions in the first trimester following opening of “small centers”, less than 6 for “big centers”). The first step of this intervention will be helping the centers to improve their organization for inclusions in the study. As a second step, centers whose inclusions’ volume remains too low will be closed and substituted by others. The scientific committee and coordination structure will constitute a site selection committee before beginning of the trial, to evaluate and pre-select back-up sites.

10. EVALUATION OF SECURITY. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

For the sub study CAPE-COVID 19, the safety will be in-live evaluated for each patient, in particular for the risk of infectious complications mainly with secondary infections and viral reactivations.

10.1. Definitions

Adverse event (article R.1123-46 of the French Public Health Act)

Any harmful event occurring in a person taking part in a research study involving person, whether or not that event is linked to the study or to the product being investigated in the study.

Serious adverse event (article R.1123-46 of the Public Health Act and the ICH E2B guide)

Any undesirable event which:

- ⇒ Leads to death
- ⇒ Endangers the life of the person taking part in the research study
- ⇒ Necessitates admission to hospital, or prolongation of hospitalization
- ⇒ Causes serious or sustained incapacity or handicap
- ⇒ Is expressed by a congenital anomaly or malformation
- ⇒ Or any event considered to be medically serious, and concerning the drug, whatever the dose administered

Adverse Reaction: any untoward and unintended reaction to an investigational medicinal product, whatever the dose administered.

Serious Adverse Reaction: a serious adverse event with a causal relationship to an investigational medicinal product.

Unexpected adverse reaction (article R.1123-46 of the French Public Health Act): an adverse reaction whose type, severity, frequency or outcome does not agree with information contained in the summary of product characteristics for an authorized investigational medicinal product or investigator's brochure for an unauthorised investigational product.

Causal relationship: relation between the adverse event and the study treatment. An adverse event related to an investigational medicinal product will become an adverse reaction.

New fact (article R.1123-46 12° of the French Public Health Act):

New information which could lead to:

- ⇒ re-evaluation of the benefit/risk ratio of the study or the investigational product,
- ⇒ or which may be sufficient to envisage modifications to the way the product is used, to documents concerning the study, or if necessary to the way the study is conducted,
- ⇒ or to suspend or interrupt or modify the protocol of the research or similar researches.

10.2. Investigator's responsibilities

10.2.1. Notification of serious adverse events

During hospitalization, only serious adverse events that lead to prolonged hospitalization or that are considered to be life-threatening or have resulted in a death (except those listed in 9.2.1.5.) must be reported immediately to the sponsor.

When the patient is discharged from the ICU, serious adverse events (leading to death, endangering the life of the person taking part in the research study, requiring admission to hospital, or prolonging hospitalization, causing serious or sustained incapacity or handicap, or any event considered to be medically serious, and concerning the drug) will be reported immediately to the sponsor except those listed in 9.2.1.5.

10.2.1.1. Information to be submitted to the sponsor

Each serious adverse event must be reported as “Adverse Event” in the appropriate CRF pages trying to be as thorough as possible. The information to be transmitted is as follows:

- ⇒ Patient identification (number, code, date of birth, date of inclusion, sex, weight, height),
- ⇒ Severity of the adverse event,
- ⇒ Start and end of the adverse event,
- ⇒ Clear and detailed description of the adverse event (diagnosis, symptoms, intensity, timing, actions and results)
- ⇒ Evolution of the adverse event,
- ⇒ Disease course or relevant patient history,
- ⇒ Treatment received by the patient,
- ⇒ Relationship of the adverse event with the experimental drug or with any associated treatment or study procedure.

The investigator shall also attach to the adverse event report, whenever possible:

- ⇒ A copy of the report of hospitalization or prolongation of hospitalization,
- ⇒ Possibly a copy of the autopsy report
- ⇒ A copy of all results of additional tests performed, including relevant negative enclosing normal laboratory values,
- ⇒ Any other documents if necessary and appropriate.

These documents will be anonymized and bear the identification number of the patient. Whenever a serious adverse event persists at the end of the study, the investigator must follow the patient until the event is considered resolved.

10.2.1.2. How to notify the sponsor

Every serious adverse event must be sent by fax to the +33 2 47 47 46 62. The persons in charge of vigilance are Dr Annie-Pierre JONVILLE-BERA and Dr Céline LENGELLE (phones: +33 2 47 47 36 01 / +33 2 47 47 80 37, e-mail addresses: jonville-bera@chu-tours.fr / c.lengelle@chu-tours.fr).

For the sub-study CAPE-COVID19, every serious adverse event must be sent by mail to uvrb@chu-tours.fr.

The persons in charge of vigilance are Dr Annie-Pierre JONVILLE-BERA and Dr Céline LENGELLÉ (phones: +33 2 47 47 36 01 / +33 2 47 47 80 37, e-mail addresses: jonville-bera@chu-tours.fr / c.lengelle@chu-tours.fr).

10.2.1.3. Time notification to the sponsor

The investigator has to notify to the sponsor, immediately, to the day when he heard, all serious adverse event occurred in the trial, with the exception of those listed in the protocol or in the investigator's brochure requiring not an immediate notification (cf. 10.2.1.5). This initial notification is subject to a written report and should be quickly followed by one or detailed written supplementary reports.

10.2.1.4. Reporting period to the sponsor

The investigator has the responsibility to record and report all serious adverse events occurring during the study from the day of the written informed consent until 14 days after the last study drug administration.

Moreover, regardless of the time of occurrence after the end of the study, all serious adverse events likely to be due to the research must be reported to the sponsor, since no other cause that the research cannot reasonably be attributed (e.g. serious events that may occur at great distances from drug exposure, such as cancer or birth defects).

All these events must be monitored until they are completely resolved. The investigator will send the sponsor additional information (additional declaration form) concerning the evolution of the event not mentioned in the initial report.

10.2.1.5. Specificity of the trial

The following circumstances requiring hospitalization not covered by the criteria of seriousness "hospitalization / prolongation of hospitalization", should not be reported as serious adverse events:

- ⇒ Predefined protocol hospitalization
- ⇒ Admission on social or administrative condition
- ⇒ Passing day hospital
- ⇒ Hospitalization for routine treatment or monitoring of the disease, not associated with a worsening of the patient's condition
- ⇒ Hospitalization for medical or surgical treatment scheduled before the start of the research.

The adverse events will be recorded in the e-CRF during the study and could be reported in the final report for analysis at the end of the study.

Additionally, following expected adverse events which are related to the patient's disease or comorbidity and are frequent in the setting of critically-ill patients will not require an immediate notification as SAEs but will be noticed in the e-CRF (according to health authorities):

- ⇒ Respiratory events: decreased P/F, use of mechanical ventilation, acute respiratory distress syndrome
- ⇒ Acute renal failure
- ⇒ ICU delirium and confusion
- ⇒ Septic shock occurring in the first 48 hours following inclusion
- ⇒ Deaths which are attributable to another cause than the experimental treatment

For the sub-study CAPE-COVID19, specificities of protocol are the same with the exception of deaths which are attributable to another cause than the experimental treatment, which must be reported as through as possible to the Sponsor.

10.2.2. Notification of non-serious adverse events

The non-serious adverse events will be reported in the e-CRF specifying the date of occurrence, the description, intensity, duration, method of resolution, etiology, causal relationship, and the decisions made.

10.3. Sponsor's responsibilities

10.3.1. Analysis of serious adverse events

The sponsor must evaluate the following:

- ⇒ the causal relationship of serious adverse events (all adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably expected, are considered as suspected adverse reactions. If the sponsor's evaluation of the event differs from the investigators' evaluation, both opinions will be mentioned in the statement sent to the competent authority, if this statement is necessary),
- ⇒ and their expected or unexpected feature, using the reference document in force (IB Investigator's Brochure).

The sponsor shall keep detailed records of all adverse events reported by the investigators.

These records will be sent to the National Security Agency of Medicines and Health Products (ANSM), upon request.

10.3.2. Scoring of causal relationship

The method used by the sponsor in evaluating the relationship of the event is as follows:

- ⇒ *Unrelated*: the event occurred within a time period not compatible compared to administration of the medicinal product, and/or a sufficient amount of information exist showing that the observed reaction is unrelated to the medicinal product, and/or a probable alternative explanation exists
- ⇒ *Doubtful*: the event has a chronology (occurrence, outcome) that is little compatible with administration of the medicinal product, and most probably is attributable to factors other than the medicinal product such as the patient's clinical condition or concomitant administration of other medicinal products.
- ⇒ *Possible*: the event occurred within a period compatible, after administration, of the medicinal product and although the responsibility of the product cannot be ruled out, other factors can be implicated, such as the patient's clinical condition or concomitant administration of other medicinal products. Information on the outcome upon discontinuation of the medicinal product can be absent or inconclusive.
- ⇒ *Probable*: the event occurred within a time period compatible after administration of the medicinal product. It cannot reasonably be due to another factor, such as the patient's clinical condition or concomitant administration of other medicinal products. The outcome upon

discontinuation of the medicinal product must be clinically compatible. Information on re-challenge with the medicinal product is not essential.

- ⇒ *Highly probable*: the event appeared within a very suggestive time period after administration of the medicinal product. It cannot be explained by another factor such as the patient's clinical condition or concomitant administration of other medicinal products. The outcome upon discontinuation of the medicinal product must be clinically compatible. The event can be explained pharmacologically or based on disease physiopathology, or a recurrence upon re-challenge with the medicinal product.

Adverse events whose relationship with the investigational medicinal products is doubtful, possible, probable or highly probable are considered as related to the product(s). If they are unexpected, they are qualified as being Suspected Unexpected Serious Adverse Reactions (SUSAR) and must be notified in a report by the sponsor (see Following paragraph).

10.3.3. Declaration of suspected unexpected serious adverse reactions

The sponsor reports all SUSAR to Eudravigilance (European vigilance database), to the French Health Authorities (ANSM), and to the investigators within the regulatory time periods for reporting:

- ⇒ Immediately* for fatal or life-threatening SUSAR. In these cases, relevant additional information should be sought and transmitted within a further period of eight days.
- ⇒ 15 calendar days for all other SUSAR. Also relevant additional information should be sought and transmitted within a further period of eight days.

**As soon as the sponsor is aware of the treatment received by the patient, patient identification (number, code, date of birth), the serious adverse event, identifiable investigator, EUDRACT number and if applicable the causal relationship.*

In case of blind research, the declaration of suspected unexpected serious adverse reaction must be preceded by unblinding.

10.3.4. Transmission of annual safety reports

On the anniversary date of authorization of the study delivered by the Health Authorities or at the request of French Health Authorities, the sponsor will write a safety report containing:

- ⇒ the list of serious adverse events which may be related to the investigational medicinal product studied, including expected and unexpected serious effects,
- ⇒ a succinct and critical analysis of safety of patients who are subjects in the study.

This will be sent to local regulatory agency, to the ethics committee and to the independent surveillance committee within 60 days following the anniversary of authorization of the trial.

10.3.5. Declaration of other data security

The sponsor will notify immediately the ANSM and the ethics committee (CPP) of new fact and if applicable solutions taken.

Additional relevant information must be provided in a new period of 8 days.

10.4. Pregnancy

Pregnancy occurring during the period or immediately after a study does not constitute an SAE. However, a pregnancy must be notified in the same way as an SAE because it requires particular monitoring throughout its duration. Any anomaly observed in the fetus or child will then be notified. Any elective termination of pregnancy, medical termination of pregnancy or spontaneous abortion must give rise to a notification of pregnancy, and if it necessitated hospitalization, it must be passed on in the same manner as an SAE.

11. STATISTICS

11.1. Sample size

1,200.

With α fixed to 5%, β to 20%, a bilateral test, an estimated mortality in the control group of 27% [29], 1,146 patients are needed to show a relative decrease of mortality of a quarter in the experimental group (i.e. a mortality of 20%). This effect-size is much lower, but more realistic, than that suggested by the meta-analyses.

With two interim analyses, 1,165 are needed (Peto's rule [44]), and 1,200 to take into account the possibility of pursuit-consent refusal.

Sample size for CAPE-COVID: The event rate is assumed to be 30% in the control group. The trial is designed to demonstrate superiority of experimental treatment over control with an assumed event rate of 15% in the experimental group with 80% power and a one-sided Type I error rate of 2.5. Symmetric two-sided group sequential, requires sample size 290, for 6 interim analyses (5 during the trial and one final). Bounds were determined using a Kim-DeMets alpha spending function (Lan et al, *Biometrika* 1983;70:659-63; kim et al *Biometrics* 1987;4:857-64; DeMets et al *Statist Medicine* 1994;13:1341-52) with a conservative bound for efficacy and an aggressive bound for futility. That is, stopping for high evidence of superiority while stopping early if the experimental treatment is not effective and can be potentially harmful for patients. Due to uncertainty of the failure rate in the control group, we plan to re-calculate this sample size while the trial is going-on. Indeed, data about mortality rate of COVID patients in ICU are diverging and ranging from 50% to 5%. We choose to assume a 30% rate considering mortality or need of respiratory support for the control arm but this is uncertain. This is why sample size re-estimation could be necessary during the trial when up-dated knowledge will be available.

11.2. Statistical methods used

11.2.1. General principles

The statistical analyses will be performed by the INSERM CIC 1415 unit and supervised by Bruno Giraudeau. SAS 9.2 and R 2.12.1 (or further versions) softwares will be used.

A detailed analysis plan will be *a priori* defined. Later modifications must occur before unblinding the database.

The statistical analysis will be conducted according to the intention to treat (ITT) principle. A statistical report will be written in agreement with the standards as specified in the CONSORT Statement (<http://www.consort-statement.org/>).

11.2.2. Baseline characteristics

Baseline characteristics will be reported per group using descriptive statistics. No statistical test will be performed.

11.2.3. Groups to be compared

The ITT principle will be applied. Nevertheless, patients who would withdraw consent to study participation will be discarded, as required by the French legislation.

Because patients are ICU patients, it is expected to have no lost-to-follow-up patient. We moreover plan to collect the location of birth, so that we will be able to collect the vital status asking to the city halls. In case there would be some lost to follow-up, we plan to use multiple imputation.

11.2.4. Statistical analysis of the primary outcome

The primary outcome will be analyzed using a chi-square test.

Two interim analyses will be performed (after the inclusion of 400 and 800 patients, respectively) using Peto's rule [44].

Subgroup analyses will be performed. Subgroup considered will be:

- ⇒ patients mechanically-ventilated at inclusion, or not
- ⇒ patients whose evolution will be complicated by septic shock, or not
- ⇒ different pathogens causing CAP

The primary outcome of CAPE-COVID trial (D21 failure) will be analyzed using a two-proportion z-test based on normal approximation.

The statistical design for CAPE-COVID trial will follow a group sequential design with a total of 6 analyses (5 interim analyses and a final). The group sequential will use a Kim-DeMets alpha spending function with a conservative bound for efficacy and an aggressive bound for futility. That is, a conservative O'Brien Fleming type of bound for superiority bound and an aggressive futility boundary for futility design. The alpha spending function has the advantage to be a continuous function of the information time in group sequential procedures for interim analyses. As inclusions can be fast during this pandemic or that data monitoring will be more complex than usual, it can be possible that interim analysis will not follow the initial plan. So, using a continuous function will allow to re-calculate the boundaries if necessary. At each interim analysis, the Z statistics (for a difference of binary endpoints) is computed from the data of the two arms and will be compared to the efficacy and futility bounds. If the value of Z is higher than the interim analysis specific upper bound (or lower than the lower bound), the trial is stopped for reasons of demonstrated efficacy (or futility); otherwise the trial will continue. For interpretability, the plots and the results will be displayed on the maximum likelihood estimation (MLE) scale, but the final p-value will be computed using the log-odd-ratio normalized Z statistics.

11.2.5. Statistical analysis of secondary outcomes

In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation will be compared using a competing risk approach (with death and end of ICU stay as competing events).

In patients not ventilated at inclusion, proportion of patients requiring non-invasive ventilation and proportion of patients needing endotracheal intubation will be compared using a competing risk approach (with death and end of ICU stay as competing events).

D28 ventilator-free-days and D28 vasopressors-free-days will be compared using the Wilcoxon test.

Number of patients with vasopressor therapy initiation from inclusion to D28 will be compared using a competing risk approach (with death and end of ICU stay as competing events).

Length of ICU and/or intermediate care unit stay will be compared in the framework of a competing risk model, with death considered as a competing event of end of stay.

All-causes mortality at D90 will be compared using the chi-square test.

SF-36 Health Survey at D90 will be compared using a Wilcoxon test.

Repeated data (i.e., plasmatic concentration of pro-inflammatory cytokines, biomarkers, P/F ratio, SOFA) will be analyzed in the framework of a mixed model.

Proportion of patients experiencing secondary infection during their ICU-stay and proportion of patients experiencing gastrointestinal bleeding during their ICU-stay will be analyzed in the framework of a competing risk model with death and end of stay considered as competing events.

Daily amount of insulin administered to the patient from D1 to D7 and weight-gain from baseline to D7 will be compared using a Wilcoxon test.

The secondary outcomes of CAPE-COVID trial will be analyzed as follow:

- In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation will be compared using a competing risk approach as for CAPE-COD trial.
- The need for rescue therapies (prone-position, extra-corporeal membrane oxygenation (ECMO), nitric oxide inhalation (iNO)) will be compared using a competing risk approach (with death and end of ICU stay as competing events)
- Days (prone-position, ECMO, iNO) divided by the length of ICU stay will be compared using Wilcoxon tests.
- P/F ratio measured daily will be analyzed in the framework of a mixed model as for CAPE-COD trial.
- Proportion of patients experiencing secondary infection during their ICU-stay will be analyzed in the framework of a competing risk model with death and end of stay considered as competing events as for CAPE-COD trial.

12.COMMITTEES

12.1. Scientific committee

A scientific committee has been constituted to help the principal investigator to define the study, to write the protocol and to conduct the trial. It is constituted by (in alphabetical orders):

- ⇒ Djillali Annane, MD, PhD (University of Versailles and ICU, Raymond Poincaré hospital, Garches), who past-coordinates the TriGGERSep network
- ⇒ Thierry Boulain, MD (ICU, de la Source hospital, Orléans), who is member of the scientific council of CRICS-TriGGERSep group
- ⇒ Pierre-François Dequin, MD, PhD (University of Tours and ICU, Bretonneau hospital, Tours), principal investigator of the CAPE COD trial, who co-leads the investigation work package of the CRICS-TriGGERSep network
- ⇒ Bruno François, MD (CIC 1435 and ICU, Dupuytren hospital, Limoges), who is coordinator of the CRICS-TriGGERSep network
- ⇒ Bruno Giraudeau, PhD (CIC 1415, University of Tours and Bretonneau hospital, Tours) who is statistician and methodologist of the CAPE COD trial, and is member of the scientific council of CRICS-TriGGERSep group
- ⇒ Pierre-François Laterre, MD, PhD (Saint-Luc University hospital, Brussels, Belgium), who leads the Europe work package of the CRICS-TriGGERSep network
- ⇒ Jean-Paul Mira, MD, PhD (University of Paris V and ICU, Cochin hospital, Paris), who co-leads the scientific board of the CRICS-TriGGERSep network
- ⇒ Philippe Vignon, MD, PhD (University of Limoges and ICU, Dupuytren hospital, Limoges).

12.2. Data and safety monitoring board

The Data and Safety Monitoring Board (DSMB) is an advisory committee responsible for giving its opinion to the sponsor and the coordinator / principal investigator of the study benefit/risk ratio and conducting a clinical trial. Its members, qualified in clinical trials (pathology, methodology ...) are not involved in the study. The selection of members of the DSMB is made collegially by the coordinator / principal investigator and the sponsor.

They are appointed and authorized by the sponsor for the period of the study. They are involved in participation as the confidentiality of data.

The DSMB may be requested at any time by the sponsor if a SUSAR or a SAE presents a particular difficulty of analysis, if data may change the benefit and risk ratio during clinical trial.

The DSMB analyzes the transmitted data, may request additional information. It makes recommendations about the future of the clinical trial (pursuit, amendment, stop).

The DSMB will held a phone-conference after each interim analysis to recommend interruption of the study in case of futility. It will held additional phone-conferences at the request of the sponsor or at its own initiative.

The DSMB will receive annual safety reports and will meet at least once a year before sending the annual safety report.

It is constituted by (in alphabetical orders):

- ⇒ Jean Chastre, MD, PhD (University Pierre et Marie Curie and ICU, Pitié-Salpêtrière hospital)
- ⇒ Béatrice Guyomarch, MD, PhD (University of Nantes, CHU Nantes)
- ⇒ Sylvain Marchand-Adam, MD, PhD (University François Rabelais and Respiratory Diseases Department, Tours)

For the sub-study CAPE-COVID 19, the data safety monitoring board (DSMB) is constituted by (in alphabetical orders) Jean Chastre, Béatrice Guyomarch, Sylvain Marchand-Adam, Véronique Sébille, and Liem Binh LUONG. It will be systematically meet through teleconference at each every interim analysis for efficacy, futility and safety analysis. It will meet in case of Suspected Unexpected Serious Adverse reaction (SUSAR), new facts or new safety information which could lead to a reevaluation of the benefit/risk ratio of the subject and/or new scientific information challenging study continuation. The study may be stopped definitely or temporarily at any time by the sponsor on the basis of information provided by the DSMB.

13.ACCESS RIGHTS

13.1. Access to data

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

The investigators will make available to the people with a right of access to these documents under the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control and auditing the biomedical research.

13.2. Source data

Any original document or object helping to prove the existence or accuracy of a piece of information or fact recorded during the study is defined as a source document.

13.3. Confidentiality of data

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to investigational drugs, research studies and people taking part in them, particularly as regard to their identity and the results obtained. These people, such as like the investigators themselves, are subject to professional secrecy.

During the biomedical research study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be coded. Under no circumstances may the uncoded names or addresses of the people concerned appear in it.

For coding subjects the first letter of the first name and first letter of the last name of the subject will be recorded, accompanied by a code showing the order of inclusion of the subject.

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to the individual data concerning him which is strictly necessary for quality control of the study.

14.QUALITY CONTROL AND INSURANCE

14.1. Instructions for collecting data

All the information required by the protocol will be entered in an eCRF and an explanation will be provided for each missing piece of information. The data must be collected as they are obtained, and transcribed into these forms.

14.2. Quality control and monitoring of the study

A CRA appointed by the sponsor will regularly visit each study center during the process of setting up, one or more times during the study depending on the frequency of inclusions, and at the end of the study. He/she will work in accordance with the Standardized Operating Procedures (SOP) setting up by the sponsor. Each visit will be recorded in a written monitoring report.

During these visits, the following aspects will be reviewed:

- ⇒ informed consent,
- ⇒ compliance with the study protocol and the procedures set out in it,
- ⇒ quality of the data collected in the eCRF: accuracy, missing data, consistency with the source documents (medical records, appointment diaries, originals laboratory results etc.),
- ⇒ management of medicinal products

The CRA will be also responsible for:

- ⇒ The logistics of the study,
- ⇒ Producing reports concerning its state of progress,
- ⇒ Verifying that the eCRF are updated (request for additional information, corrections, etc.),
- ⇒ Sending samples,
- ⇒ Transmitting SAEs to the sponsor.

14.3. Data management

Data management will be performed by the INSERM CIC 1415. An eCRF will be developed using the Clinsight® software. The eCRF will be managed in agreement with the INSERM CIC 1415 SOP. CRA in charge of the study will be trained to the eCRF and will then carry physicians training. In investigating centers, data will be entered through a secure web site monitored by CRAs and queries will be edited by data-managers, in agreement with an *a priori* specified data management plan.

A blind review will be done before locking the database. The database will be locked in agreement with the INSERM CIC 1415 SOPs and data will be extracted in a SAS format or other, according to statistical requirements.

14.4. Audit and inspection

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

15. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator or investigators undertake to conduct this study in compliance with French Law n° 2004-806 of 9th August 2004 and with Good Clinical Practice (I.C.H. version 4 of 1st May 1996 and the decision of 24th November 2006) and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004).

The study is being conducted in accordance with this protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards to obtaining consent and the notification and follow-up of serious adverse events.

This study was approved by the ethics committee of CPP Ouest I and was authorised by the ANSM.

CHU Tours, the sponsor of this study, has taken out an insurance policy covering third party liability with SHAM complying with the provisions of article L1121-10 of the French Public Health Act.

The data recorded in this study will be subject to computer processing by INSERM CIC 1415 – CHU Tours in compliance with the Law n°78-17 of 6th January 1978 concerning data processing, files and civil liberties modified by the Law 2004-801 of 6th August 2004.

This research falls within the framework of the "Reference methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the modified Law of 6th January 1978 relating to information, files and civil liberties. This change has been approved by the decision of 5th January 2006. CHU Tours signed a commitment to comply with this "Reference methodology".

This research is registered in the European EudraCT database in accordance with art. L1121.15 of the French Public Health Act.

This research is registered on the web site <http://clinicaltrials.gov/> before inclusion of the first patient.

The collection of physiological samples to be undertaken for this study was declared to ANSM at the same time as the request was made to authorize the study. After the study, storage of the collection of physiological samples will be declared to the Minister for Research and to the director of the Regional Hospitalization Agency (and submitted to the ethics committee for approval if there is any change in the aim of the study).

Amendments to the protocol

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the investigational medicinal products, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is subject to a written amendment to be submitted to the sponsor; prior to implementing it. The latter must obtain approval from the ethics committee and authorization from ANSM.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of patients or the benefits, risks or constraints of the study is the subject of a new patient information and informed consent form which must be completed and collected according to the same procedure as used for the previous one.

16. STORAGE OF DOCUMENTS AND DATA CONCERNING THE STUDY

The following documents relating to this study are archived in accordance with Good Clinical Practice:

By the investigating doctors:

- **For a period of 15 years following the end of the study**
 - The protocol and any amendments to the protocol
 - The case record forms
 - The source files of participants who signed a consent form
 - All other documents and letters relating to the study
- **For a period of 30 years following the end of the study**
 - The original copies of informed consent forms signed by participants

The investigator is responsible for all these documents for the regulation period of archiving.

By the sponsor:

- **For a period of 15 years following the end of the study**
 - The protocol and any amendments to the protocol
 - The originals of the case record files
 - All other documents and letters relating to the study
- **For a period of 30 years following the end of the study**
 - A copy of the informed consent forms signed by the participants
 - Documents relating to serious adverse events

The sponsor is responsible for all these documents for the regulation period of archiving.

No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

17. RULES RELATING TO PUBLICATION

17.1. Scientific communication

Analysis of the data provided by the study centers is performed by INSERM CIC 1415 Tours. Any written or oral communication of the results of the study must have been previously agreed by the coordinating investigator and, if necessary, by any committee constituted for the study.

Publication of the main results will mention the name of the sponsor, all the investigators who recruited or monitored patients in the study, the methodologists, biostatisticians and data managers who took part in the study, the members of the committee or committees set up for the study and the source of finance. The international rules for writing and publication (Vancouver Agreement, February 2006) will be taken into account.

Primary publication ranking rule will be the following:

- ⇒ First author: Principal investigator
- ⇒ Second author: Investigator from highest recruiter site
- ⇒ Third author: Investigator from second highest recruiter site
- ⇒ Fourth author: Investigator from the third highest recruiter site
- ⇒ Other authors up to the number of authors authorized by the targeted journal: depending both on recruitment and scientific involvement in the project, including the coordinator of the study from the CIC 1435 and the coordinating pharmacist
- ⇒ Penultimate author: Methodologist
- ⇒ Last author: member of TriGGERSep board (from highest recruiter TriGGERSep-board-site)
- ⇒ The CRICS group and TriGGERSep network will be cited at the end of authorship
- ⇒ All investigators not cited in the authorship will be listed at the end of the article

17.2. Communication of the results to patients

In accordance with the Law n° 2002-303 of 4th March 2002, patients are informed, at their request, of the overall results of the study.

17.3. Data transfer

The collection and management of data will be carried out by CHU Tours. The conditions for transferring all or part of the database of the study will be decided by the sponsor of the study and will be the subject of a written contract.

18. BUDGET EVALUATION

This trial is funded through a grant from the French Ministry of Health (PHRC n°14-XX). Funding comprises 1 619 512 Euros. The financial management of the funding will be under the responsibility of the sponsor.

19. BIBLIOGRAPHICAL REFERENCES

[1] Almilar J et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. *Eur Resp J* 2000;15:757-63.

[2] Ewig S et al. New perspectives on community-acquired pneumonia in 388,406 patients. Results from a nationwide mandatory performance measurement program in healthcare quality. *Thorax* 2009;64:1062-69.

[3] Restrepo MI et al. Severe community-acquired pneumonia: current outcomes, epidemiology, etiology and therapy. *Curr Opin Infect Dis* 2001;14:703-9.

[4] National Heart, Lung, and Blood Institute. Morbidity and mortality: 2012 chart book on cardiovascular, lung, and blood diseases. Bethesda, Maryland: US Department of Health and Human Services. Public Health Service. National Institutes of Health; Feb. 2012
www.nhlbi.nih.gov/resources/docs/2012_ChartBook.pdf [Accessed August 30, 2014]

- [5] Niederman MS et al. The cost of treating community-acquired pneumonia. *Clin Ther* 1998;20:820-37.
- [6] Angus DC et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society diagnostic criteria. *Am J Respir Crit Care Med* 2002;166:717-23.
- [7] Leroy O et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intens Care Med* 1995;21:24-31.
- [8] De Pascale G et al. Steroids in severe pneumonia : a literature review. *Minerva Anestesiol* 2011;77:902-10.
- [9] Annane D et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; 283:1038–1045.
- [10] Annane D. Adrenal insufficiency in sepsis. *Curr Pharm Des* 2008;14:1882-6.
- [11] Wagner HN et al. The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. *Bull John Hopkins Hosp* 1956;98:197-215.
- [12] Mc Hardy VU et al. Ampicillin dosage and use of prednisolone in treatment of pneumonia: co-operative controlled trial. *BMJ* 1972;4:569-73.
- [13] Marik P et al. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia: a randomized controlled study. *Chest* 1993;104:389-92.
- [14] Confalonieri M et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;171:242-8.
- [15] Mikami K et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. *Lung* 2007;185:249-55.
- [16] Snidjers D et al. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blind clinical trial. *Am J Respir Crit Care Med* 2010;181:975-82.
- [17] Mejjvis SCA et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomized, double-blinded, placebo-controlled trial. *Lancet* 2011;377:2023-30.
- [18] Sabry NA et al. Course of community-acquired pneumonia in Egyptian settings. *Pharmacology and Pharmacy* 2011;2:73-81.
- [19] Fernandez-Serrano S et al. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. *Crit Care* 2011;15:1-9.
- [20] Nie W et al. Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. *Plos One* 2012;7:e47926.
- [21] Cheng M et al. Corticosteroids therapy for severe community-acquired pneumonia: a meta-analysis. *Resp Care* 2014;59:557-63.

- [22] Woodhead M et al. Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect* 2011;17(suppl.6):E1-E59.
- [23] Wiersinga WJ et al. SWAB /NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Neth J Med* 2012;70:90-101.
- [24] Spindler C et al. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults--Swedish Society of Infectious Diseases 2012. *Scand J Infect Dis* 2012;44:885-902.
- [25] Blum CA et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomized, placebo-controlled trial. *Lancet* 2015 (published online January 19, 2015).
- [26] Tagami T et al. Low-dose corticosteroid use and mortality in severe community-acquired pneumonia patients. *Eur Respir J* 2014;45:463-72.
- [27] Torres A et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015;313:677-86.
- [28] <https://clinicaltrials.gov> [Accessed lastly September 14, 2014]
- [29] Bellissant E, Annane D. Effect of hydrocortisone on phenylephrine--mean arterial pressure dose-response relationship in septic shock. *Clin Pharmacol Ther* 2000;68:293-303.
- [30] Fine MJ et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243-50.
- [31] Renaud B et al. Investigation of the ability of the Pneumonia Severity Index to accurately predict clinically relevant outcomes: a European study. *Clin Microbiol Infect* 2007;13:923-31.
- [32] Wunderink RG et al. Recombinant Tissue Factor Pathway Inhibitor in severe community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2011;183:1561-8.
- [33] Sztrymf B et al. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. *J Crit Care* 2012;27:e9-13.
- [34] Restrepo MI et al. Long-term prognosis in community-acquired pneumonia. *Curr Opin Infect Dis* 2013;26:151-8.
- [35] Annane D et al. Effect of treatment with low-doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
- [36] Spring CL et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.

[37] Dellinger RP et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

[38] Lim WS et al. Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377-82.

[39] Sabat R et al. Therapeutic opportunities of the IL-22-IL-22R1 system. Nat Rev Drug Discov 2014 ;13:21-38.

[40] Zhao L et al. Immunoregulation therapy changes the frequency of interleukin (IL)-22+ CD4+ T cells in systemic lupus erythematosus patients. Clin Exp Immunol 2014;177:212-8.

[41] Cao J et al. Effects of high-dose dexamethasone on regulating interleukin-22 production and correcting Th1 and Th22 polarization in immune thrombocytopenia. J Clin Immunol 2012;32:523-9.

[42] Sarinho ES et al. Evaluation of Th17 related cytokines and IFN production from blood mononuclear cells of moderate and severe asthmatic children reveals methylprednisolone does not decrease IL-22 levels. J Asthma 2014;sep 9:1-18.

[43] Restrepo MI et al. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. Chest 2008;133:610-7.

[44] Peto R et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patients. Br J Cancer 1976;34:585-612.

APPENDIX

Appendix 1: list of investigators

Name	City	Hospital
Pierre-François Dequin	Tours	Bretonneau
Kamel Toufik	Orléans	La Source
Bruno François	Limoges	Dupuytren
Jean-Pierre Frat	Poitiers	La Milétrie
Gwenhael Colin	La Roche sur Yon	Les Oudairies
Christophe Cracco	Angoulême	Saint-Michel
Ferhat Meziani	Strasbourg	NHC
Francis Schneider	Strasbourg	Hautepierre
Jean-Pierre Quenot	Dijon	Bocage Central
Sylvie Vimeux	Montauban	CH Montauban
Gaëtan Plantefève	Argenteuil	Victor Dupouy
Jean-Paul Mira	Paris	Cochin
Djillali Annane	Garches	Raymond Poincaré
Erwann l'Her	Brest	La Cavale Blanche
Arnaud Gacouin	Rennes	Pontchaillou
Sébastien Gibot	Nancy	Central
Nicolas Terzi	Grenoble	Albert Michallon
Muriel-Sarah Fartoukh	Paris	Tenon
Charlotte Quentin	Saint-Malo	Broussais
Mercé Jourdain	Lille	Salengro
Jean Reignier	Nantes	Hôtel-Dieu
Bertrand Souweine	Clermont Ferrand	G Montpied
Laurent Papazian	Marseille	Hôpital Nord
Abdelkader Ouchenir	Chartres	Louis Pasteur
Jean-Damien Ricard	Colombes	Hôpitaux Universitaires Paris Nord Val de Seine
Christophe Giacardi	Brest HIA	HIA Clermont-Tonnerre
Nicolas Barbarot	Saint Briec	CH de Saint Briec
Christophe Guitton	Le Mans	CH Le Mans
Henri Faure	Aulnay sous Bois	CHI Robert Ballanger
Guillaume Louis	Metz	Mercy

Aurélie JORET	Caen	Côte de Nacre
Rémi BRUYERE	Bourg-en-Bresse	CH de Fleyriat
Julio BADIE	Belfort	Hôpital Nord Franche Comte