Rapid rEcognition of COrticosteroid Resistant or sensitive Sepsis - RECORDS

A Multicentre Concealed-Allocation Multi-arms Blinded Randomized Controlled Trial to Identify the Best Sepsis Population for Corticotherapy

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

Version N°4.0 dated 03/03/2021
Project Code: APHP191110 / EUDRACT no: 2020-000296-21

Coordinating Investigator and Scientific Director :
Pr Djillali ANNANE
Department Intensive Care Unit
Hospital Raymond Poincaré - APHP
Tel. 33 1 47 10 77 87
Email : djillali.annane@aphp.fr

Sponsor:
Assistance Publique – Hôpitaux de Paris (AP-HP)
and by delegation: Délégation à la Recherche Clinique et à l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint-Louis, 1, avenue Claude Vellefaux
DRCI-Head Office project advisor : Myriem CARRIER / Akim SOUAG
Tel : 01 44 84 17 52/ 01 44 84 17 15.
Email : myriem.carrier@aphp.fr / akim.souag@aphp.fr

Entity responsible for Safety
Secteur Vigilance - DRCI, Hôpital Fernand Widal -
200, rue du Fbg Saint-Denis - 75475 Paris
Sarra DALIBEY / Tel.: +33 (0)1 40 27 57 85
Email: sarra.dalibey@aphp.fr

Entity responsible for monitoring the study:
Pr GRIMALDI Lamiae
URC (Clinical Research Unit) Paris Saclay Ouest
Address : Hôpital Ambroise Paré DRCI-URC
project advisor: Karima MESBAHI / Nawal.DERRIDJ
Tel : 01 49 09 47 47 / 01 49 09 48 14
Email : karima.mesbahi@aphp.fr / nawal.derridj@aphp.fr

Statistician:
Pr Sylvie Chevret
Department of Bioinformatics and Statistics,
Address: Hôpital Saint Louis,
1 avenue Claude Vellefaux, 75475 PARIS Cedex 10
Sec : +33 (0)1 42 49 97 42
Email : sylvie.chevret@paris7.jussieu.fr

Entity responsible for Pharmaceutical circuit :
Agence Générale des Equipements et Produits de Santé
Département des Essais Cliniques
7, rue du Fer à Moulin 75005 Paris Cedex 5
Pharmacien : Dr Blandine Lehmann
Chef de projets : Kévin Cardet
Tel : 01 46 69 14 02

Direction de la Recherche Clinique et de l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint Louis 75010 PARIS

SIGNATURE PAGE FOR A RESEARCH PROTOCOL

RESEARCH CODE NUMBER: APHP191110

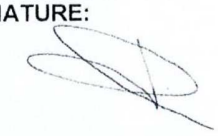
TITLE: RAPID RECOGNITION OF CORTICOSTEROID RESISTANT OR SENSITIVE SEPSIS – RECORDS

A MULTICENTRE CONCEALED-ALLOCATION MULTI-ARMS BLINDED RANDOMIZED CONTROLLED TRIAL TO IDENTIFY THE BEST SEPSIS POPULATION FOR CORTICOTHERAPY

VERSION NO.4.0 DATED: 03/03/ 2021

COORDINATING INVESTIGATOR:
PROFESSOR DJILLALI ANNANE
DEPARTMENT OF INTENSIVE CARE
HOSPITAL RAYMOND POINCARÉ
PARIS

DATE: 15/03/2021
SIGNATURE:



SPONSOR
ASSISTANCE PUBLIQUE – HOPITAUX DE PARIS
DELEGATION A LA RECHERCHE CLINIQUE ET A L'INNOVATION - DRCI (CLINICAL RESEARCH AND INNOVATION DEPARTMENT)
HOPITAL SAINT LOUIS
1 AVENUE CLAUDE VELLEFAUX
75010 PARIS

DATE: 23 MARS 2021
SIGNATURE:

This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.
Version 4.0 dated 31/05/2019

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AGEPS	Agence générale des équipements et produits de santé-APHP
ANSM	Agence nationale de sécurité du médicament et des produits de santé
APHP	Paris Public Hospital Assistance
CMU	Couverture Maladie Universelle
CRF	Case Report Form
CRP	C-reactive protein
CTA	Clinical Trial Application
DSMC	Data Safety Monitoring Committee
DRCI	Delegation of Clinical Research and Innovation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked ImmunoSorbent Assay
FiO2	Fraction of inspired oxygen
HRQoL	Health Related Quality of Life
ICU	Intensive Care Unit
IPDMA	Individual Patient Data Meta-Analysis
IRB	Institutional Review Board
PaO2	Partial pressure of arterial oxygen
PaCO2	Partial pressure of arterial carbon dioxide
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SOFA score	Sequential Organ Failure Assessment score
SUADR	Serious Unexpected Adverse Drug Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
URC HUPIFO	Paris Ile de France Ouest Clinical Research Unit
WHO	World Health Organization

STUDY SUMMARY

Title	Rapid rEcognition of COrticosteroid Resistant or sensitive Sepsis -
Acronym/reference	**RECORDS**
Coordinating investigator and Scientific Director	Pr Djillali ANNANE
Sponsor	Assistance Publique – Hôpitaux de Paris
Clinical Sites	French adult general ICUs
Background	WHO estimates that, yearly, 30 million people develop sepsis and 11million die. APROCCHS, a phase 3, placebo-controlled trial, demonstrated a 6% absolute reduction in sepsis mortality with hydrocortisone+fludrocortisone. A number of factors may positively/negatively impact corticosteroids (CS) benefits in sepsis
Main objective and primary endpoint	To compare the effect hydrocortisone plus fludrocortisone vs. placebo on a composite of death or persistent organ dysfunction – defined as continued dependency on mechanical ventilation, new renal replacement therapy, or vasopressors – assessed at 90 days on intensive care unit (ICU) adults and having different biological profiles for immune responses and corticosteroids bioactivity The primary endpoint is death or persistent organ dysfunction (defined as continued dependency on mechanical ventilation, renal replacement therapy, or vasopressors) and with SOFA score >6 up to 90 days.
Secondary objectives and endpoints	• Mortality and health-related quality of life at 6 months; • Daily organ function (SOFA score days 1, 2, 3, 4, 7, 10, 14, 28, and 90); • Daily secondary infections (up to 90 days) • Daily blood and urinary levels of glucose, sodium and potassium (up to 28 day) • Daily gastroduodenal bleeding (up to 28 day) • Daily cognitive function and muscles' strength (days 1 to 28, 90 and 180 days)
Study design	Multi-arms Parallel blinded randomized controlled trial preceded by a 6-month run-in observational period. - Observational phase (run-in period) - Interventional phase.
Inclusion Criteria **observational phase:** (N°1,2,3,4,6,7,8,9) **interventional phase:** (N°1,2,3,4,5,6,7,8).	1. Patients ≥18 years old; 2. Admitted to ICU with proven or suspected infection as the main diagnosis; 3. Community acquired pneumonia related sepsis OR vasopressors dependency (norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine) OR septic shock (Singer 2016: vasopressor to maintain mean blood pressure of at least 65 mmHg and lactate levels above 2 mmol/l) OR acute respiratory distress syndrome (ARDS – Ranieri 2012: a- acute onset, i.e. within one week of an apparent clinical insult and with progression of respiratory syndrome, b- bilateral opacities on chest imaging not explained by other pulmonary pathologies, e.g. pleural effusion, atelectasis, nodules etc, c- no evidence for heart failure or volume overload, d- PaO2/FiO2 ≤ 300 mm Hg, - PEEP ≥ 5 cm H2O 4. Patient who has signed an informed and written consent whevener he/she is able of consent, if not, if not ascent from his/her representant whenever he/she is present at time of screening for inclusion

	5. Patients who have been tested for one or more RECORDS specific biomarkers: a. CIRCI b. Endocan c. GILZ d. CPD e. Transcriptomic SRS2 f. Endotype B g. PCR COVID-19 h. PCR Influenza i. PCR other respiratory virus 6. Affiliation to a social security system or to an universal health coverage (Couverture Maladie Universelle, CMU). 7. Patients under guardianship or curatorship will be included. 8. Patients in case of simple emergency (legal definition) will be included. 9. Patients managed with covid 19 and having biological samples available
Exclusion Criteria observational phase: (N°1,2,3) **interventional phase:** (N°:1,2,3,4,5,6,7,8).	1. Pregnancy; 2. Expected death or withdrawal of life-sustaining treatments within 48 hours; 3. Previously enrolled in this study 4. Formal indication for corticosteroids according to most recent international guidelines 5. Vaccination with live virus within past 6 months 6. Hypersensitivity to hydrocortisone or fludrocortisone or any of their excipients (spc) 7. Women of childbearing potential not using contraception 8. Nursing women
Study Intervention	-**Observational phase (run-in period):** additional biological samples For the **restrospective part** (Covid patients): telephone follow-up **-Interventional phase:** Investigational products or their placebo will be administered to patients on the basis of RECORDS signatures Investigational products included: - Hydrocortisone hemisuccinate 50 mg: one intravenous injection every 6 hours, and - 9 alpha fludrocortisone 50 µg: one tablet per day via a nasogastric tube. All treatments will be stopped after 7 days or until the patient has left the intensive care unit (whichever occurs first) without tapering off.
Randomization (Interventional phase)	Web-based randomization system available 24/7. Eligible patients will be randomized in a 1:1 ratio to corticoseroids or matching placebo. We will use permuted blocks of undisclosed and variable size and stratify randomization by site and biomarkers.
Sample Size	We will enroll a total of at most 1800 patients in this adaptative trial. Sites are expected to enroll at least 1or 2 patients per month. By enrolling 376 evaluable patients per arm, the study will have 80% power to detect a 10% absolute risk reduction (from 45% to 35%, which corresponds to a 20% relative risk reduction).
Study duration	Inclusion period: 48 months: Treatment 7 days and follow-up: 6 months.Daily during ICU stay and telephone follow-up at 6 months. Total study period: 54 months

1 INTRODUCTION

1.1 SEPSIS

Sepsis occurs when a site of infection is apparent and evidence shows dysregulated host response (Singer 2016). The dysregulated host response is usually defined by the presence of a sequential organ failure assessment (SOFA) score (Vincent 1996), of two or more (Singer 2016). Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater, and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia. The deregulated response may result in systemic inflammation and organs damage, or immune paresis and secondary infections (van der Poll 2017). In 2017 the World Health organization estimated that around 31 million people develop sepsis each year, and about 10 million die (WHO 2018). According to a recent retrospective cohort study of adult patients admitted to 409 USA academic, community, and federal hospitals from 2009 to 2014, sepsis was present in 6% of adult hospitalizations (Rhee 2017). Another study of electronic health records from 27 USA academic hospitals reported an annual incidence of septic shock of about 19 per 1000 hospitalizations in 2014 (Kadri 2017). People usually die from hypotension or from progressive multiple organ failure (Angus 2013; Annane 2003; Annane 2005; Parrillo 1993). There is no current diagnostic test for sepsis. Its standard management includes control of source of infection with antibiotics and surgery whenever needed, and control of tissue oxygenation with fluids replacement, oxygen with or without respiratory support, and vasopressor whenever needed (Rhodes 2017). There are still no specific interventions to control immune responses to invading pathogens (Rhodes 2017). The financial burden to health care system due to sepsis has been calculated to be >24 billion US$, representing 6.2% of total hospital costs in 2013 (WHO 2018). Studies in Europe and Canada estimated the daily costs of hospital care of a septic patient to be between €710 and €1033 in 2000 (equivalent to about US$ 645 and US$ 939, respectively) (WHO 2018).

1.2 CORTICOSTEROIDS

Corticosteroids include the natural steroid hormones produced by adrenocortical cells and a broad variety of synthetic analogues. These substances have various effects that may be grossly classified into glucocorticoid and mineralocorticoid effects. Glucocorticoid effects include mainly regulation of carbohydrates, lipids and proteins metabolism, as well as regulation of inflammation. Mineralocorticoid effects include mainly regulation of electrolytes and water metabolism.

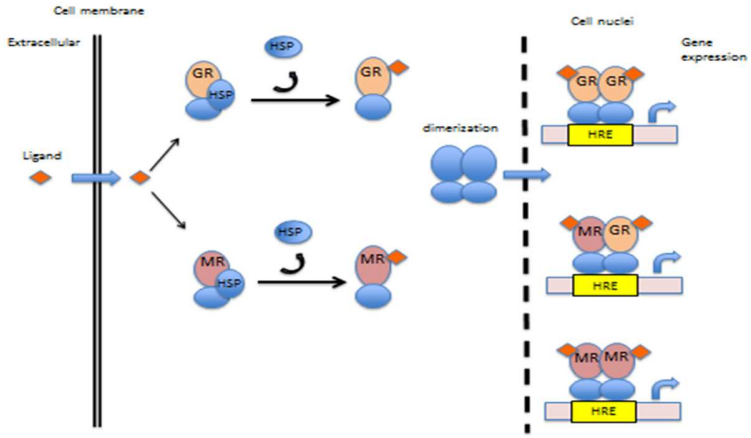


Figure 1: molecular mechanisms of actions of gluco- and mineralocorticoids.

At molecular levels, glucocorticoids have non-genomic and genomic effects (Annane 2017a; Cain 2017). Rapid (within minutes) non-genomic effects of glucocorticoids include a decrease in platelet aggregation, in cell adhesion and in intracellular phosphotyrosine kinases, and they include an increase in annexin 1 externalisation (Lowenberg 2005). These effects may result from interaction of glucocorticoids with

specific membrane sites (Norman 2004). Glucocorticoids have indirect genomic effects, called trans-repression (Rhen 2005). These occur within a few hours following exposure of cells to glucocorticoids. They result from physical interaction between the monomeric glucocorticoid-glucocorticoid receptor (G-GR) α complex and various nuclear transcription factors, such as nuclear factor (NF)-κB and activator protein (AP)-1. Subsequently, these nuclear transcription factors are sequestrated in the cytosol and cannot enter the nucleus, preventing expression of genes encoding for most if not all pro-inflammatory mediators. Glucocorticoids also have direct genomic effects, called transactivation. They require only a few days of cell exposure to glucocorticoids. Indeed, conformational changes (i.e. dimerization of the G-GRα complex) are needed before this complex can migrate to the nucleus to interact with glucocorticoid-responsive elements, that is, parts of genes encoding for regulators of termination of inflammation. Then, key anti-inflammatory factors are up-regulated, leading to phagocytosis, chemokinesis and anti-oxidative processes. The net effect of glucocorticoids involves reprogramming rather than inhibiting immune cell function (Erschen 2007). Glucocorticoids induce specific activated anti-inflammatory monocyte subtypes that migrate quickly to inflamed tissues (Varga 2008). They prolonged survival of this subtype of monocytes via A3 adenosine receptor-triggered anti-apoptotic effects (Barczyk 2010). Obviously, these molecular mechanisms of action of glucocorticoids are appropriate for counteracting the uncontrolled inflammation that may characterize sepsis.

1.3 CORTICOSTEROIDS AND SEPSIS

Researchers have explored the biological mechanisms of sepsis to explore potential interventions. Corticosteroids have been a topic of particular focus because of their influence on the immune response (Cain 2017). In sepsis, the hypothalamic-pituitary gland hormonal pathway to the adrenal glands stimulates corticosteroid production (Annane 2017a; Chrousos 1995; Cooper 2003; Heming 2018). These hormones affect inflammation through production of white blood cells, cytokines (proteins that influence the immune response) and nitric oxide. In sepsis, cytokines may suppress adrenocorticotropin hormone synthesis (Annane 2017a; Polito 2011; Sharshar 2003), and the cortisol response to exogenous adrenocorticotropin hormone (Annane 2017a; Hotta 1986; Jaattela 1991). Likewise, sepsis may be associated with alterations in scavenger receptor B1-mediated cholesterol delivery (Cai 2008). This causes poor adrenal activity in almost half of patients (Annane 2000; Lipiner 2007; Marik 2008; Rothwell 1991), and possible resistance of body tissues to corticosteroids (Meduri 1998a), due to fewer corticosteroid receptors or receptors with lower affinity (Barnes 1995; Huang 1987; Molijn 1995). Alteration in corticosteroid receptor numbers and in binding capacity may be related at least in part to nitric oxide (Duma 2004; Galigniana 1999). Recent works suggest that immune cells - not steroid-secreting cells - are key regulators of the interaction between the immune sytem and the adrenals (Kanczkowski 2013). In addition, acute illness such as sepsis may be associated with decreased cortisol clearance from plasma (Boonen 2013; Melby 1958), likely resulting from altered hepatic and renal inactivation of cortisol (Boonen 2013), Early studies showed that a pharmacological dose of corticosteroids prolonged survival among animals with sepsis (Fabian 1982). More recent studies in rodents have demonstrated that lower doses of corticosteroids, for example, 0.1 mg/kg of dexamethasone, improved haemodynamic and organ function, favourably modulated the inflammatory response and prolonged survival (di Villa Bianca 2003; Heller 2003; Tsao 2004; Vachharajani 2006). Protective effects of these glucocorticoids against sepsis may be mediated in part by the endothelial glucocorticoid receptor (Goodwin 2013). In healthy volunteers challenged with endotoxin, a low dose of corticosteroids, for example, 10 mg of prednisolone, blocked the release of pro-inflammatory cytokines, prevented endothelial cell and neutrophil activation and inhibited the acute phase response without altering coagulation and fibrinolysis balance (de Kruif 2007). Studies in patients with septic shock showed that a short course of corticosteroids may result in a rebound in the systemic inflammatory response (Briegel 1994; Keh 2003). In addition, it is now recognized that increased pro-inflammatory cytokine release can be sustained for longer than a week in patients with sepsis (Kellum 2007). Likewise, timing of initiation of corticosteroids may be an important factor in response to treatment. Indeed, in observational studies, short-term mortality increased with delayed initiation of hydrocortisone (Katsenos 2014; Park 2012). For these reasons, we would anticipate that corticosteroid treatment is

beneficial for patients with sepsis, and that differences in dose, timing or duration of corticosteroid treatment may differentially affect patient response to treatment. Finally, several authors have argued that in patients with sepsis, hydrocortisone should be given as a continuous infusion rather than as intermittent boluses to reduce the risk of metabolic complications (Rhodes 2017). In sepsis trials, continuous infusion of hydrocortisone was variably associated with better outcomes (Loisa 2007) or worse outcomes (Tilouche 2019) than intermittent intravenous boluses.

1.4 RATIONALE FOR THE STUDY

1.4.1 Clinical evidence for potential benefit from corticosteroids

Initially, researchers used high doses of corticosteroids, usually given as a single bolus, in an attempt to block potential bursts in pro-inflammatory cytokines. Two systematic reviews and meta-analyses of trials of corticosteroids in sepsis or in septic shock included 10 (Lefering 1995), and nine (Cronin 1995), randomized controlled trials (RCTs), respectively. These systematic reviews showed no significant effect on relative risk of death, on relative risk of gastrointestinal bleeding or superinfection associated with corticosteroids. Subsequently, most clinicians will not recommend use of high doses of corticosteroids in sepsis (Annane 2017b; Rhodes 2017).

The potential benefits of a lower dose (≤ 400 mg of hydrocortisone or equivalent per day), and a longer duration at full dose (≥ three days) of treatment, have been investigated in numerous RCTs over the past three decades (Annane 2017b; Lamontagne 2018; Rochwerg 2018). In the past two years, guidelines for clinical practices about corticosteroids use in sepsis have been released by at least five entities (Annane 2017b; Lamontagne 2018; Nishida 2018; Rhodes 2017; Tavaré 2017). All but one of the guidelines (Lamontagne 2018), recommended against the use of corticosteroids in sepsis, except in patients with septic shock and poorly responsive to fluid replacement and vasopressor therapy. Some guidelines suggested that corticosteroids should be given as a continuous infusion rather than intermittent boluses (Annane 2017b; Rhodes 2017). In the year 2018, there were five different systematic reviews and meta-analyses addressing the effects of corticosteroids in sepsis (Allen 2018; Fang 2018; Ni 2018; Rochwerg 2018; Rygard 2018). The number of included trials was different in all reviews and ranged from 14 to 42, the relative risk of death in the short-term varied from 0.91 to 0.96, and the upper limit of the 95% confidence interval varied from 0.98 to 1.03. Another systematic review and meta-analysis of one randomized trial and 17 observational studies, has examined the risk of acquired muscle weakness associated with exposure to corticosteroids in ICU patients (Yang 2018). This review found an odds ratio for acquired muscle weakness of 1.84 (95% CI 1.26 to 2.67) with corticosteroids compared to control.

1.4.2 The challenge of corticosteroids responsiveness in sepsis

The crude absolute reduction in mortality in these two trials was about 6.5%. It is likely that among the heterogeneous population of sepsis, some patients may draw much substantial survival benefit whereas others may be harmed. Corticosteroids survival benefit is not affected by age, gender, disease severity, type of infection, source of infection, or type of pathogens (Lamontagne 2018). There is currently no diagnostic test for CS sensitivity/resistance in sepsis. The scientific community is competing to identify markers delineating between patients who draw survival benefit from corticosteroids (CS-sensitive sepsis) and those who may be harmed (CS-resistant sepsis). In sepsis, the deregulated response may result in systemic inflammation and organs damage, or immune paresis and secondary infections (van der Poll 2017). Obviously, patients with systemic inflammation may benefit from CS whereas those with immune paresis may deteriorate. We looked for an interaction between survival in response to corticosteroids and the presence of CIRCI according to the ACTH test results (cortisol increment of less than 9μg/dL). The benefits from corticosteroids were more important in patients with CIRCI in the Ger-Inf-05 trial but not in

the APROCCHS trial. Thus, current sepsis guidelines suggest that the ACTH test may not reliably guide the use of corticosteroids (Rhodes 2017). Indeed, this test provides information neither on corticosteroids bioactivity nor on patient's immune status, when this information should precede any corticotherapy. Recent studies suggested that a transcriptomic signature based on 100 genes may identify a subset of paediatric sepsis that had increased risk of death when exposed to corticosteroids (Wong 2015). Another study found transcriptomic based sepsis response signatures (SRS) associated with immune paresis (SRS1) or with systemic inflammation (SRS 2) (Antcliffe 2018). In this study, patients with a SRS 2 transcriptomic signature had significantly higher mortality when treated with hydrocortisone. Thus, we have started exploring the mechanisms of sensitivity/resistance to corticosteroids in sepsis, namely by investigating endocan, as a surrogate of patient's inflammatory status, and GILZ expression as a marker of corticosteroids bioactivity. In two independent sepsis cohorts we found that the lower plasma endocan levels the greater the risk of organ dysfunction. In one study (n=20), serum endocan levels correlated significantly with hypoxia (P=0.005), a marker of severity of illness, and admission endocan levels of <2.54ng/ml accurately predicted early onset of ARDS. In a second cohort (n=100), plasma endocan levels of <2.54 ng/ml, had a positive predictive value to develop organ dysfunction of 1, and endocan levels >5.49 ng/ml a negative predictive value of 1 (Gaudet 2017).

ENDOCAN (NG/ML)	**SP**	**SE**	**PPV**	**NPV**	**RV+**	**RV-**	**YOUDEN**
<2.54	1.00	0.45	1.00	0.91		0.55	0.73
<5.49	0.77	1.00	0.44	1.00	4.36		0.89

Glucocorticoid-induced leucin zipper (GILZ) is a critical mediator of corticosteroids immune effects as shown by 1) GILZ up-regulation by glucocorticoids, 2) GILZ inhibition of a number of transcription factors including NF-kB, AP-1, Raf-1, and Ras, all involved in corticosteroids effects, 4) GILZ silencing abrogated the antiproliferative activity of dexamethasone and reduced GC inhibition of either cytokine-induced COX-2 expression or pro-inflammatory cytokines and chemokines. In previous animal and human studies, we showed that GILZ was a master regulator of macrophages down-regulating their synthesis of cytokines following endotoxin. As compared to controls, GILZ was significantly less expressed in patient's monocytes and mice' macrophages. Decreased GILZ expression correlated with higher TNF production. Transgenic mice overexpressing GILZ in macrophages had attenuated systemic inflammation in response to sepsis and prolonged survival. These results provided new evidence for a central role of GILZ expressed in monocytes/macrophages on the pathophysiology of sepsis. These results also suggest that GILZ expression in monocytes/macrophages may discriminate between corticosteroids sensitive and corticosteroids resistant sepsis. Strong evidence supports the pivotal role of corticosteroids induced subtypes of anti-inflammatory and highly mobile monocytes (Erschen 2007), and of monocytes expressed GILZ in regulating corticosteroids' immune effects (Ronchetti 2015). Patients with downregulated anti-inflammatory monocytes or downregulated GILZ may be corticosteroids CS resistant.

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

This adaptive multi-arms trial will adapt the different arms (to be stopped or continued) by sequentially detecting whether the treatment effect may be different according to biomarkers, that may potentially stop the recruitment of patients presenting with certain levels of that biomarker if there is any evidence that it interacts negatively with the outcome for instance.
Therefore, as the treatment effect will be assessed on safety measure (severe adverse events) and on early surrogate efficacy measure, research patients in the RECORDS trial are expected to have a substantial increase in the chance to survive free of sequels through this patient level customization of corticotherapy proposed in the RECORDS trial through dosing and randomizing patients on specific biomarkers. Also, they are expected to experience much less harm, that is indeed minimised at most, thanks to the surveillance and to the adaptive design.

2 STUDY OBJECTIVES

The overall objective of the study programme is to determine whether different signatures of immune status and/or corticosteroids biological activity influence the responses to hydrocortisone plus fludrocortisone of adults with sepsis. To this end, several predefined biomarker cohorts of patients will be randomly allocated to receive hydrocortisone plus fludrocortisone or their respective placebos with “primary objective” and “secondary oobjectives” defined below.

2.1 PRIMARY OBJECTIVES OF EACH ANALYSIS BY BIOLOGICAL MARKER

To compare the effect hydrocortisone plus fludrocortisone vs. placebo on a composite of death or persistent organ dysfunction – defined as continued dependency on mechanical ventilation, new renal replacement therapy, or vasopressors – assessed at 90 days on intensive care unit (ICU) adults and having different biological profiles for immune responses and corticosteroids bioactivity .

2.2 SECONDARY OBJECTIVES OF EACH ANALYSIS BY BIOLOGICAL MARKER

- To compare the effect of hydrocortisone plus fludrocortisone vs. placebo on:
  1) 6-month mortality;
  2) 6-month HRQoL;
  3) organ function (days 1, 2, 3, 4, 7, 10, 14, and 28 if in ICU);
  4) hyperglyceamia as defined by glucose levels of >8.3 mmol/L (150mg/dL) (daily up to day 28)
  5) hypernatremia as defined by serum sodium levels of >150mmol/L (daily up to day 28)
  6) secondary infection (daily up to day 90)
  7) beeding in the gastrointestinal tract defined by clinical evidence of active bleeding and need for blood transfusion OR hemostatic endoscopic or surgical procedures
  8) neurological cognitive dysfunction defined as by low score on the PROMIS Adult cognitive function score (appendix 15.4.7)
  9) neuromuscular weakness defined as a grade of 2 or more on Muscular Disability Rating Scale (MDRS) (appendix 15.4.6)

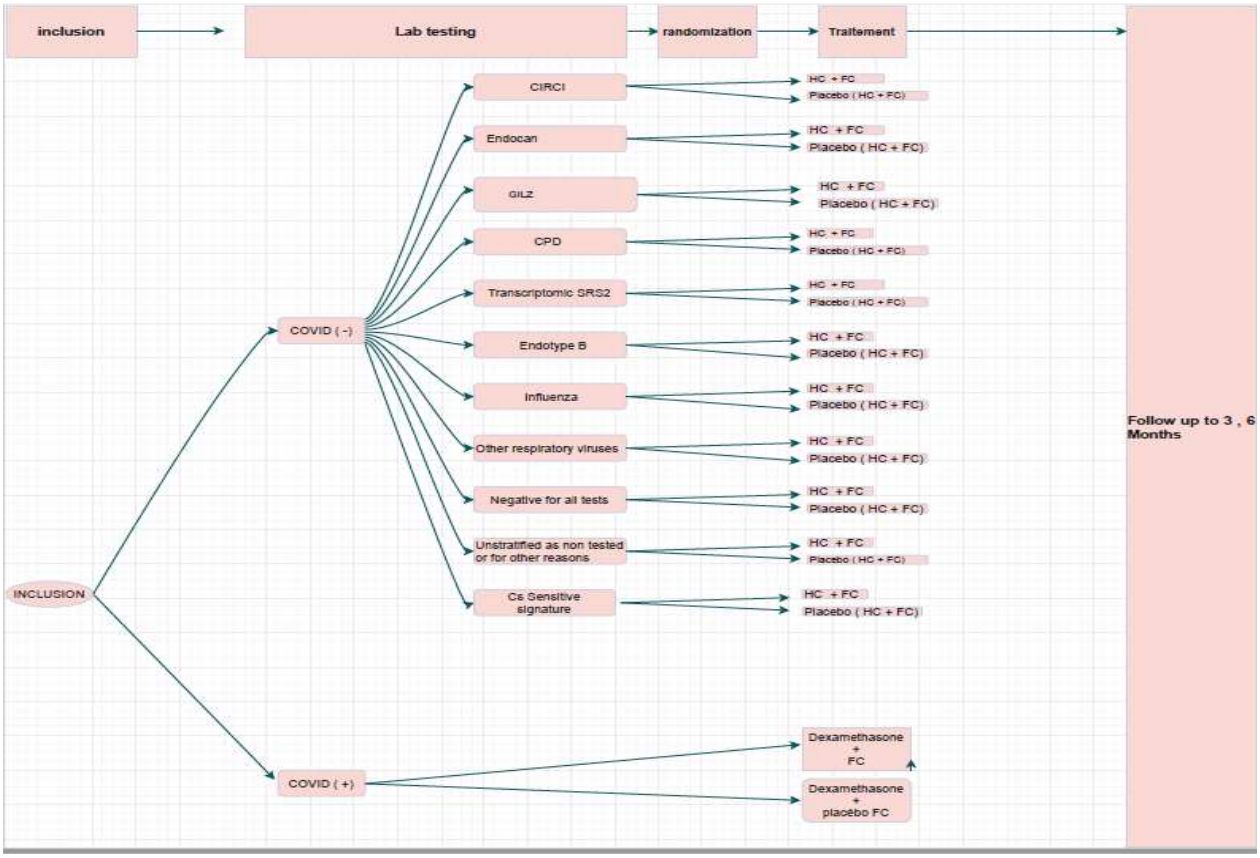
3 STUDY DESIGN

The RECORDS multicentre trial will be conducted within two stages. First, the run-in non-interventional, observational period will last 6 month. During this period, eligible patients will be treated with hydrocortisone and fludrocortisone. The clinical and laboratory data will be collected. This period will allow refining the incidence of elligible patients in participating centres and defining the biomarkers on which the interventional period will be based.

In addition, during this phase, we will retrospectively include COVID patients who were managed during the health crisis and who were collected as part of care within 3 months prior to the start of the research.

The second period will be interventional and last 54 months. This stage will be a multicentre concealed-allocation multi-arms, parallel-group, adaptive blinded RCT. Patients will be randomly assigned to hydrocortisone plus fludrcortisone or placebos for 7 days. Our maximum recruitment target is 1800 patients with full follow-up. Since loss to follow up is rare in critical care trials with outcomes measured at day 90, we do not expect missing data for the primary outcome. Study personnel at the clinical sites will document the composite of death or persistent organ dysfunction at day 90.

The sites will include on average 1 patient per month over 48 months of inclusion and 6 months of follow-up.



4 METHODS

4.1 STUDY SETTING

This study will be centrally coordinated by Paris Ile de France Ouest Clinical Research Unit (URC HUPIFO) attached to the Delegation of Clinical Research and Innovation (DRCI) of The Paris Public Hospital Assistance (APHP), at the Hospital Raymond Poincaré, Ile de France, France. URC PIFO will be responsible for programming and maintaining the randomization system and the electronic data capture (EDC) system. The Centre de Ressource Biologique (Biological resource centre) at the Hospital Ambroise Paré, Paris Saclay Ouest will be responsible for managing the storage and analysis of the blood samples. The RECORDS Trial will be conducted in French adult general ICUs, including sites from CRICS-TRIGERSEP, a F-CRIN labelled sepsis network.

The study will be conducted in two phases: an observational phase and an interventional phase.

4.1.1 Observational phase (run-in period)

The observational phase (Run in period) lasts at least 6 months. Its aim is to collect as much information as possible on biomarkers likely to influence responses to corticosteroids under the usual conditions of care and develop reference values for the biomarkers. These values will later be used during the second phase (interventional phase) to set up diagnostic tests in order to rapidly identify patients with sepsis who may be sensitive or resistant to corticoids

During the first stage, run-in observational period, all participants will receive as a standard of care, open-labeled, commercialized hydrocortisone and fludrocortisone , or dexamethasone or methylprednisolone, at equivalent doses, or no corticosteroids as left at physician discretion. Physicians will be asked to strictly follow before prescribing corticosteroids all available information on contraindications, caution in use and drug-drug interaction by referring to http://base-donnees-publiques.medicaments.gouv.fr. Hydrocortisone will be given as a 50mg intravenous bolus every 6 hours (6 to 8 mg equivalent of dexamethasone once daily, 40mg per day equivalent of methylprednisolone on continuous intravenous infusion) for seven days and fludrocortisone will be given orally/enteraly as a 50μg tablet once a day (in the morning) for seven days. Patients with COVID-19 will receive dexamethasone 6 mg once daily for 10 days (RECOVERY 2020), or equivalent dose of hydrocortisone (150 to 200mg), according to e recent WHO propective meta-analysis for corticosteroids in COVID-19 (Sterne 2020).
All consecutive eligible patients should be approached for participation in the run-in observational part of the study by the clinical investigators or person qualified to carry out the research. The clinical investigator will inform the eligible person of this study then collect the consent of this person to use his/her clinical data and biological samples routinely collected for the present research. If the patient is unable to confirm or not his/her consent within the time window allowed by the protocol, his or her authorized persons (members family, curator, guardianship, trusted person) may be approached in person4. The local research team could also enroll eligible patients.

For the observational phase, patients with Covid 19 who met the eligibility criteria as below, can be retrospectively included in the observational cohort. For these patients, we will use data from the analysis of samples collected as part of their care in the participating centres. The inclusion of this retrospective cohort may help shortening the duration of the run in period and may accelerate the identification of biomarkers to be investigated in the interventional phase.

4.1.1.1 Eligibility Criteria (observational phase)

The patients included in this phase should present the following selection criteria:

4. 1. 1.1.1 Inclusion Criteria (observational phase)

- Patients ≥18 years old;
- Admitted to ICU with proven or suspected infection as the main diagnosis;
- Community acquired pneumonia related sepsis OR vasopressors dependency (norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine) OR septic shock (Singer 2016: vasopressor to maintain mean blood pressure of at least 65 mmHg and lactate levels above 2 mmol/l) OR acute respiratory distress syndrome (ARDS – Ranieri 2012: a- acute onset, i.e. within one week of an apparent clinical insult and with progression of respiratory syndrome, b- bilateral opacities on chest imaging not explained by other pulmonary pathologies, e.g. pleural effusion, atelectasis, nodules etc, c- no evidence for heart failure or volume overload, d- PaO2/FiO2 ≤ 300 mm Hg, - PEEP ≥ 5 cm H2O
- Patient who has signed an informed and written consent whevener he/she is able of consent, if not, if not ascent from his/her representant whenever he/she is present at time of screening for inclusion

- Affiliation to a social security system or to an universal health coverage (Couverture Maladie Universelle, CMU).
- Patients under guardianship or curatorship will be included.
- Patients in case of simple emergency (legal definition) will be included.
- Patients managed with covid 19 and having biological samples available

4.1.1.1.2 Exclusion Criteria (observational phase)

- Pregnancy;
- Expected death or withdrawal of life-sustaining treatments within 48 hours;
- Previously enrolled in this study

The observational phase poses no risk to participants. Any adverse reactions observed in the patients during this phase are reported by the investigators as per the local vigilance procedures.
All adverse events will be recorded in the patient case report form (eCRF).

4.1.2 Interventional phase

4.1.2.1 ELIGIBILITY CRITERIA (INTERVENTIONAL PHASE)

4.1.2.1 Inclusion Criteria (interventional phase)

1) Patients ≥ 18 years old;
2) Admitted to the ICU with proven or suspected infection as the main diagnosis;
3) Community acquired pneumonia related sepsis OR vasopressors dependency (norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine) OR septic shock (Singer 2016: vasopressor to maintain mean blood pressure of at least 65 mmHg and lactate levels above 2 mmol/l) OR acute respiratory distress syndrome (ARDS – Ranieri 2012: a- acute onset, i.e. within one week of an apparent clinical insult and with progression of respiratory syndrome, b- bilateral opacities on chest imaging not explained by other pulmonary pathologies, e.g. pleural effusion, atelectasis, nodules etc, c- no evidence for heart failure or volume overload, d- PaO2/FiO2 ≤ 300 mm Hg, - PEEP ≥ 5 cm H2O
4) Patient who has signed an informed and written consent whevener he/she is able of consent, if not, if not ascent from his/her representant whenever he/she is present at time of screening for inclusion
5) Patients who have been tested for one or more RECORDS specific biomarkers
   - CIRCI
   - Endocan
   - GILZ <
   - CPD
   - Transcriptomic SRS2
   - Endotype B
   - PCR COVD-19
   - PCR Influenza
   - PCR other respiratory virus
6) Affiliation to a social security system or to an universal health coverage (Couverture Maladie Universelle, CMU);
7) Patients under guardianship or curatorship will be included;
8) Patients in case of simple emergency (legal definition) will be included.

4.1.2 Exclusion Criteria (interventional phase)

1) Pregnancy;
2) Expected death or withdrawal of life-sustaining treatments within 48 hours;
3) Previously enrolled in this study;
4) Formal indication for corticosteroids according to most recent international guidelines
5) Vaccination with live virus within past 6 months
6) Hypersensitivity to hydrocortisone or fludrocortisone or any of their excipients (SPC)
7) Women of childbearing potential not using contraception
8) Nursing women

4.1.3 Biomarker-defined subgroups

To remain pragmatic, this trial has broad eligibility criteria and includes all patients admitted to the ICU with a primary diagnosis of sepsis, community acquired pneumonia or ARDS. Patients will be further characterized at the cellular and molecular levels based on biomarkers whether measured in blood, urines, intracellularly, or exhaled air and whether being proteins, cells, metabolites or genes products (see trial flow chart 4.1.19).
The RECORDS Trial is based on the assumption that patients with sepsis regardless the pathogen (bacteria or virus) and demonstrable acute proinflammatory states or altered endogenous corticosteroids activity are the more likely to benefit from corticosteroids whereas those with evidence for a depressed immune state or preserved endogenous corticosteroids activity may be harmed by the corticotherapy.
Thus, we will investigate the following biomarker-defined "cohorts."

4.1.3.1 Biomarkers that are readilty available for bedside use for bedside use

1) ***CIRCI "cohort"***: defined by baseline total cortisol of 10 μg/dL or less OR a maximum increment in total cortisol of less than 9μg/dL at 30 and 60 minutes following a 250μg intravenous bolus of Synacthen (Annane et al). This biomarker is considered as the best available test for CIRCI, a syndrome of insufficient tissue activity of corticosteroids that may occur in critically ill patients like sepsis (Annane 2017a; Annane 2017b).
2) ***Low plasma endocan cohort***: defined by levels of less than 2 ng/ml. This biomarker is an endothelial peptidoglycan that contribute regulating the inflammation by counteracting the leukodiapesis that is also a key target for corticosteroids (De Freitas Caires 2018; Gaudet 2017). Low circulating levels of endocan may result from insufficient release of exaggerated clearance. Then, low endocan levels may identify patients with a proinflammatory state (Gaudet 2018) that can be corrected by corticosteroids.
3) ***CPD cohort***: defined by an increased circulating monocytes distribution width. Increased volume and other cell pathologic data (CPD) have been recently characterized as early index of sepsis and shown to correlate with severity and excesive systemic inflammation (Crouser 2017). This cellular biomarker has been approved by the FDA and can be very rapidly obtained as fast as the white blood cell count and on the same blood sample.
4) ***Transcriptomic SRS cohort***: transcriptomic analysis of peripheral leukocytes defined two distinct sespsis response signatures SS1 and SRS2 (Davenport 2018). SRS1 is characterized by features of endotoxin tolerance, T -cell exhaustion, and downregulation of human leucocyte antigen (HLA) class II suggesting immune suppression whereas SRS2 may correspond to relative immune competency. Grouping septic patients relatively to SRS1 or SRS2 can reliably be done by using a generalized linear model based on the set of seven genes (DYRK2, CCNB1IP1, TDRD9, ZAP70, ARL14EP, MDC1,and ADGRE3). Previous work in rather small sized cohort of sepsis suggested increased mortality with hydrocortisone in SRS2 patients (Antcliffe 2018).
5) ***Endotype B cohort***: as defined by endotyping of 100 genes reflecting adaptive immunitiy and glucocorticoid receptor signalling. This approach in children with sepsis identified two distinct endotypes A and B. Endotype A was characterized by repression of the majority of these genes (Wong 2011).

Patients presenting with an endotype A have a profile of immune suppression, and were at higher risk for mortality. Nevertheless, those patients with an endotype A at ICU day 1 that shifted for an endotype B later on draw benefit from corticosteroids (Wong 2018).

6) ***PCR COVID-19 cohort***: the emergence in the end of 2019, of a novel coronavirus, SARS-CoV-2, related disease, places a major burden on worll health care systems. The disease is characterized by viral sepsis with a key role of over-activation of the complement system and inflammatory mediators. Corticosteroids have been provent to reduce mortality at 28-day (RECOVERY 2020; Sterne 2020) The phenotype COVID-19 may identify among patients with sepsis those who may be benefit from corticosteroids. In this biomarker cohort, all patients will receive dexamethasone 6 mg per day for 10 days and will be assigned to fludrocortisone or its placebo. Indeed, dexamethasone has no mineralocorticoid activity. The added value of mineralococrticoid is worth being evaluated owing to the role of angiotensin-converting enzyme 2 receptor and endothelial dysfunction in the pathogenesis of COVID-19.

7) ***PCR Influenza cohort***: seasonal influenza causes yearly thousands of death primarily by pneumonia related sepsis. While retrospective observational studies reported controversial effects of corticosteroids in these patients, there are still no high quality randomized trial to inform routine practice.

8) ***PCR other respiratory viruses cohort***: likewise, seasonal non-influenza viral pneumonia causes thousands of death due to sepsis. While retrospective observational studies reported controversial effects of corticosteroids in these patients, there are still no high quality randomized trial to inform routine practice.

4.1.3.2 Biomarkers that will be provided by WP3 and WP4

During the RECORDS project based on samples from both APROCCHS and the ongoing RECORDS cohort, new potentially relevant biomarker will emerge and the RECORDS trial will be adapted by adding new bioamarker-defined cohort. This may include

1) ***GILZ cohort***: WP3 experiments will provide the cut-off value defining low monocyte expression of GILZ that will be used to characterized this cohort (Ellouze 2019).

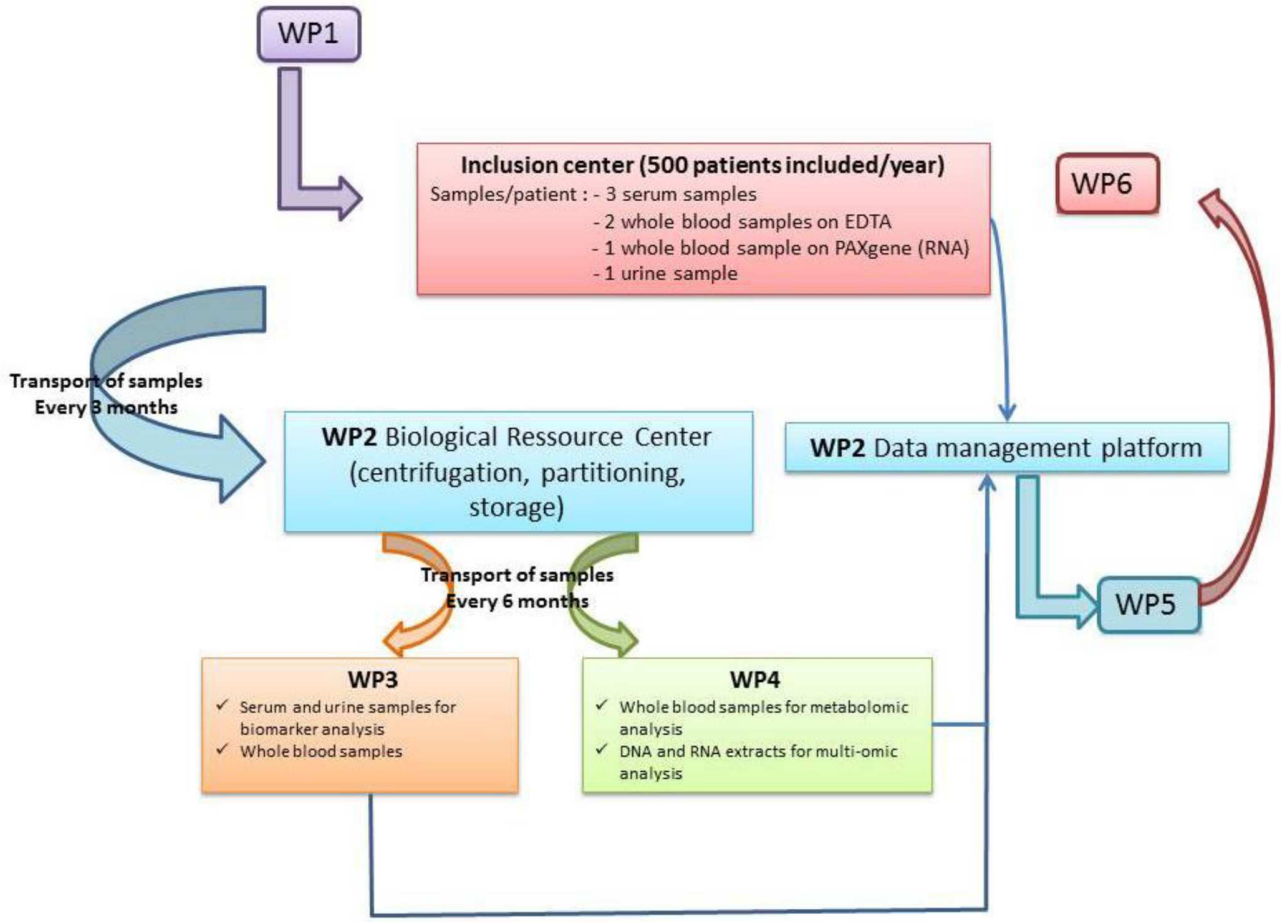
2) ***Uninary Cathepsin G endocan cohort***: Low blood endocan in sepsis involves at least partly proteolytic degradation by neutrophil elastase and cathepsin G, generating endocan catabolites of 10 to 15 kDa among which one major catabolite of 14 kDa induced by cathepsin G (CG) detected by ELISA in septic serum, and resistant to other neutrophil proteases. Endocan is cleaved at endothelial-leukocyte synapse when leukocytes are in contact with endothelial cell surface before entering into tissues. CG-cleaved endocan may reflect early step of inflammation. Glomerular filtration separates CG-cleaved endocan from endocan which apparent globular molecular weight is of 400 kDa when including its glycosaminoglycan chain. Preliminary data in sepsis confirmed larger amount of CG-cleaved endocan in urine than in blood (De Freitas Caires N, personal data).

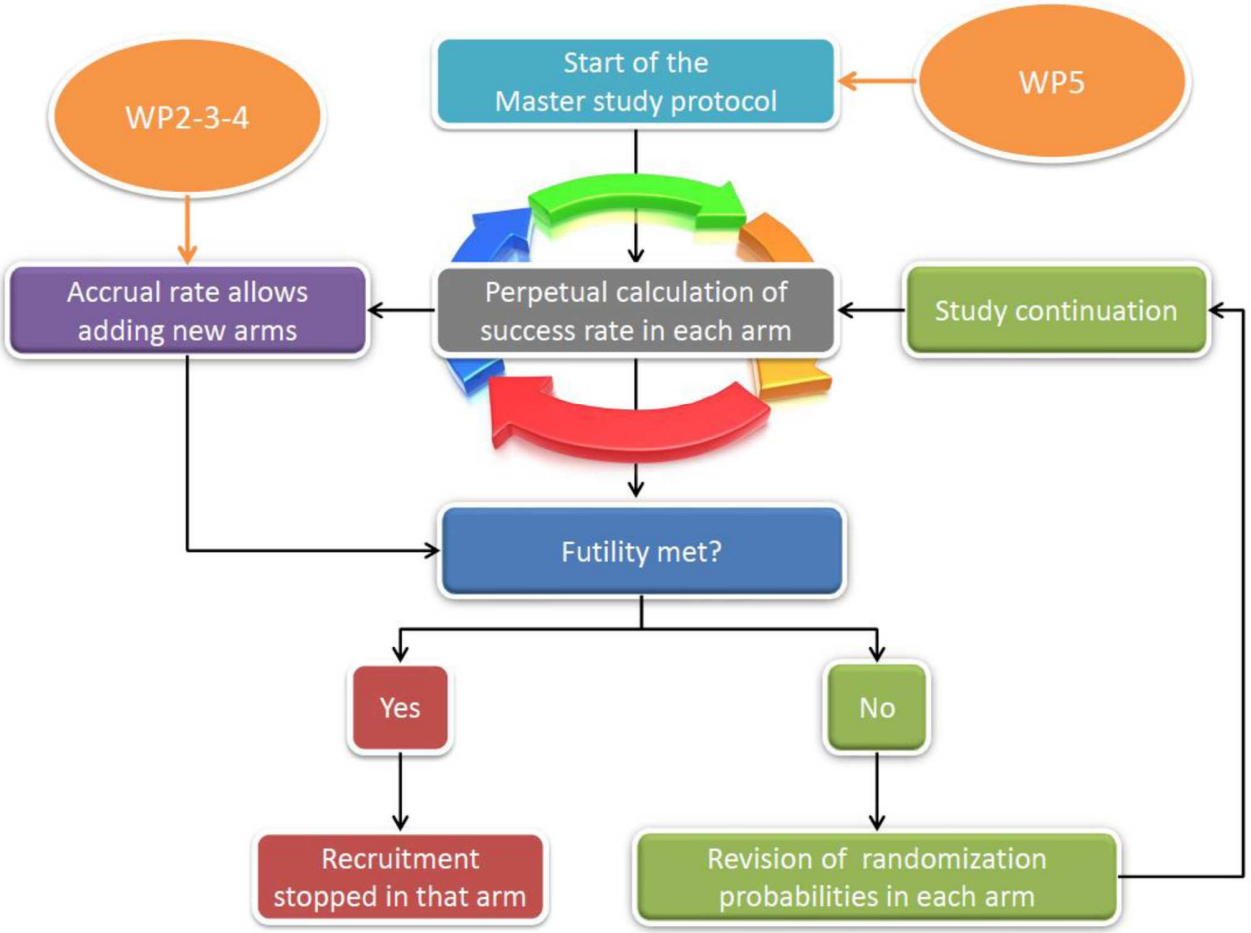
3) ***Multi-omic sepsis response signature cohort***: experiments in WP4 and WP5 will combined genotyping, whole genome sequencing and metabolome analyses from 500 patients of the APROCCHS cohort (Annane 2018) and from patients included in the run-in period of RECORDS to derive multi-omic signatures that will be delivered at month 9 of the RECORDS project. Then, corresponding new cohorts will be added to the RECORDS multi-arm trial. We anticipate that these multi-omic signatures may be changed by enrichment from accumulation of new data generated during the RECORDS trial, and subsequently the corresponding cohort is expected to be progressively enriched while RECORDS trial is progressing.

4.1.3.2 Biomarkers that will be released by other groups

Knowing that other groups are currently working on similar research program, we anticipate the possibility of adapting the RECORDS trial by adding new biomarker-defined cohort whenever they will become available.

- **Figure 1. Schema of the relations between the WPs and the positioning of the BRC**


WP1
Inclusion center (500 patients included/year)
Samples/patient : - 3 serum samples
- 2 whole blood samples on EDTA
- 1 whole blood sample on PAXgene (RNA)
- 1 urine sample
WP6
Transport of samples
Every 3 months
WP2 Biological Ressource Center (centrifugation, partitioning, storage)
WP2 Data management platform
Transport of samples
Every 6 months
WP5
WP3
✓ Serum and urine samples for biomarker analysis
✓ Whole blood samples
WP4
✓ Whole blood samples for metabolomic analysis
✓ DNA and RNA extracts for multi-omic analysis


WP2-3-4
Start of the Master study protocol
WP5
Accrual rate allows adding new arms
Perpetual calculation of success rate in each arm
Study continuation
Futility met?
Yes
No
Recruitment stopped in that arm
Revision of randomization probabilities in each arm

4.2 RECRUITMENT STRATEGY

As per standard practice for critical care research, before any examination or act related to the study, the clinical investigator will inform the eligible person, then collect the free and written consent of the person undergoing to the research if he/she is able to consent.

Given the management of intensive care patients, we will be confronted in this study with the case of simple emergency inclusion (France art. L. 1122-1 CSP). Therefore, the clinical investigator may include a patient without his or her written consent but with the written consent of his or her family members or the person of trust if they are present. The participant will be informed as soon as possible to consent to the continuation of the research (deferred consent).

Given the context, patients under guardianship or curatorship will be included. The consent of the guardian/curator will be sought, as well as the patient (

Once the consents are obtained, for both stages (the run-in observational and the interventional periods) participants samples will be used for the cellular and molecular testings. At the second stage (interventional period), consenting participant will be assigned to a biomarker cohort and randomized, then treatment will start immediately as per trial allocation.

We anticipate that each participating clinical site will enroll at least 1 or 2 patients per month, a conservative estimate given the experience in previous trials conducted in a similar population, by CRICS-TRIGERSEP network.

4.4 TERMINATION RULES

4.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

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

The investigator must:

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

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 1 month following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved.

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

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study.
  List the relevant criteria
    - Pregnancy;
    - Expected death or withdrawal of life-sustaining treatments within 48 hours;
    - Previously enrolled in this study, or in an other ineterventional study;
    - Hypersensitivity to hydrocortisone or fludrocortisone or any of their excipients (SPC)
    - Women of childbearing potential not using contraception
    - Nursing women

- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead. In this study vital status will be searched for in the National Registry of Deaths thanks to their family and first name and their date of birth and their place of residence.

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
In case of premature exit from the study, this will in no way affect their usual care for their condition.
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:
- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

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

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

4.4.4 Procedures for replacing participants,

No replacement of participants is planned in this study.

4.4.5 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, in the following situations:
- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study

- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy

However these situations are unlikely to occur as this trial is an adaptive multi arm trial that will, per essence, stop the arms that show patients with increased risk of toxicity or of a lack of efficacy.

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

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

In all cases in which a study is discontinued, this will in no way affect participants currently enrolled in the study that will benefit from usual care for their condition. Notably, the participants included in the study must be monitored until the end of their participation, as set forth in the protocol.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days.

4.5 Randomization Methods

4.5.1 Allocation sequence generation

A computer process will be used to generate allocation sequences in a 1:1. Any evidence suggesting increased harm in patients presenting with a contemplated biomarker will lead to the termination of recruitment of patients presenting with this biomarker and will qualify the corresponding biomarker for identifying patients who should not be treated by hydrocortisone plus fludrocortisone (see section 9).
A randomization list will be generated beforehand by a computer program and verified according to the procedures of the sponsor, independently from the physicians who will recruit patients.

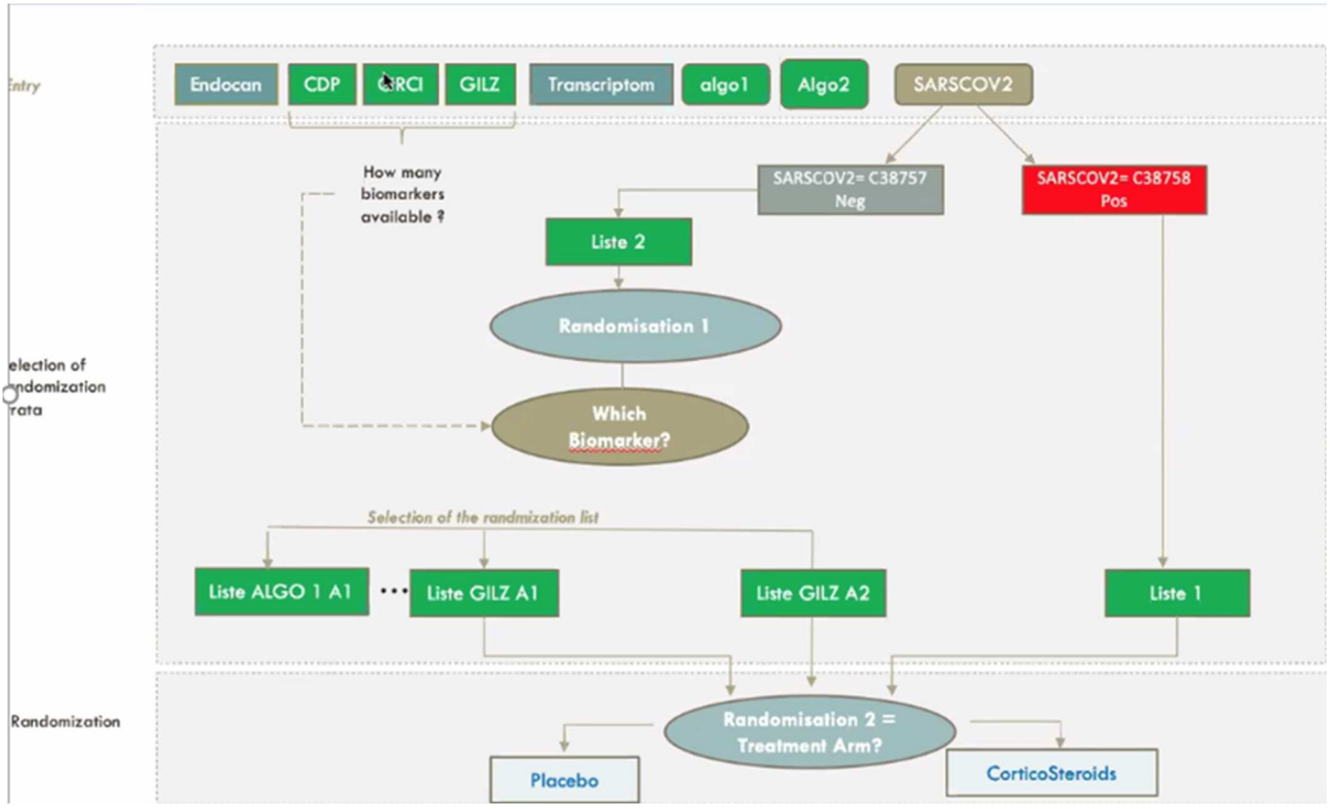
4.5.2 Stratification:

Randomization will be stratified on the following biomarkers:

.

1. CIRCI
2. Endocan
3. GILZ
4. CPD
5. Transcriptomic SRS2
6. Endotype B
7. COVID-19
8. Influenza
9. Other respiratory viruses

The full statistical analysis plan will be published before the first interim analyse.



According to the adaptive design of the umbrella trial, the number of biomarker strata is not fixed and will vary with 1) information gained from actual study participants on added-value of a specific biomarker, 2) from new biomarker released by RECORDS WP3-6, 3° from new relevant biomarker released in the literature that will be screened n a trimester basis throughout the study period. These novel biomarkers may include new clinical algorithm or phenotypes, new omic-derived signature, new biological biomarker issued from blood, urine or exhaled air.

4.5.3 Implementation

Randomization will be performed after the inclusion visit by ICU physicians, less than 24 hours after receiving the results of the biomarker.
Randomization will be centralized and performed with an internet-centralized service running 24/7 using the CleanWeb software, also used for the electronic Case Report Form (eCRF) (cf. infra).

4.6 BLINDING

Intensivists, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, and the data analyst will be blinded to the treatment allocation.

Only the pharmacist, from the General Agency of Equipments and Health Products of The Paris Public Hospital Assistance (AGEPS - APHP) will be unblinded. Treatments will be available in the pharmacies of the participating centers 24 hours a day, 7 days a week. Blinding will not be compromised because treatment boxes will be numbered, and randomization will assign a kit number present in the center.

4.7 UNBLINDING PROCEDURES

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

In practice, unblinding will be requested for any reason considered essential by the investigating physician by calling upon:

- In situations requiring unblinding in an emergency : (in case of suspected unexpected Serious Adverse Event (SAE), in the situation where the clinical condition of the patient warrants knowing whether or not he/she received hydrocortisone or fludrocortisone) at the poison control centre at Fernand Widal Hospital, Telephone: +33 (0)1 40 05 48 48.

- Apart from an emergency situation at the DRCI (Clinical Research and Innovation Department) to the DRCI project advisor whose contact informations are listed on the protocol cover page

5 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative*.

Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

The study will be conducted in two phases: an observational phase and an interventional phase.

5.1 RUN-IN observational period

The observational phase (Run in period) lasts at least 6 months. Its aim is to collect as much information as possible on biomarkers likely to influence responses to corticosteroids under the usual conditions of care and develop reference values for the biomarkers. These values will later be used during the second phase (interventional phase) to set up diagnostic tests in order to rapidly identify patients with sepsis who may be sensitive or resistant to corticoids

During the first stage, run-in observational period, all participants will receive as a standard of care, open-labeled, commercialized hydrocortisone and fludrocortisone, or dexamethasone or methylprednisolone, at equivalent doses, or no corticosteroids as left at physician discretion. Hydrocortisone will be given as a 50mg intravenous bolus every 6 hours (equivalent to 6 to 8 mg once daily of dexamethasone, equivalent o 40 mg per day of continuous infusion of methylprednisolone) for seven days and fludrocortisone will be given orally/enteraly as a 50μg tablet once a day (in the morning) for seven days.
All consecutive eligible patients should be approached for participation in the run-in observational part of the study by the clinical investigators or person qualified to carry out the research. The clinical investigator will inform the eligible person of this study then collect the consent of this person to use his/her clinical data and biological samples routinely collected for the present research. If the patient is unable to confirm or not his/her consent within the time window allowed by the protocol, his or her authorized persons (members family, curator, guardianship, trusted person) may be approached in person. The local research team could also enroll eligible patients.

5.2 Screening visit for the Interventional trial

All consecutive eligible patients should be approached for participation in the trial by the clinical investigators or person qualified to carry out the research. The clinical investigator will inform the eligible person then collect the free and written consent of the person undergoing to the research. If the patient is unable to provide consent within the time window allowed by the protocol, his or her authorized persons (members family, curator, guardianship, trusted person) may be approached in person. The local research team could also enroll eligible patients and obtain consent subsequently as per French national regulation under a deferred consent model.

To obtain informed consent, study personnel should follow the following steps:

- Present information on the study in a simple and understandable manner;
- Answer questions in a simple and understandable manner;
- Allow the potential participant/authorized persons an opportunity to reflect and discuss study participation with their family, friends, or family physician if desired;
- Confirm that the participant/authorized persons understands the risks and benefits of participating in the study and that their participation is voluntary;
- Complete and obtain signatures for informed consent form and obtain contact information from the participant/authorized persons.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
Patient if able to understand and consent: "consentement patient" If patient not able to consent: Family member, close relative if present at the time of inclusion "consentement proche" or when they become present "consentement proche poursuite" - If the patient is under guardianship: the guardian' consent is required : "consentement tutelle" - If the patient is under curatorship: the curator must be informed of the study. The patient signs a consent form with the presence of the curator	the principal investigator or collaborating physician declared and trained in the study (specify the specialist field)	• At the time of inclusion for patient if able to understand and consent • If patient not able to consent: family member / close relative □f patient not able t After inclusion for patient unable to be informed at the time of inclusion and/or family member/ close relative as soon as possible if patient is unable to be informed	• At the time of randomization for family member / close relative if one is present • After randomization as soon as possible for family member / close relative and/or patient as soon as his status allows

"consentement curatelle". Patient as soon as his status allows if he was not able toconsent on entry; “consentement de poursuite”			

5.3 Baseline visit and randomisation visit

- Verification of inclusion and exclusion criteria
- patient demographics, source of infection, severity of illness (SAPS II and SOFA scores) (Le Gall 1993 Vincent), pre-existing comorbidities as defined in the Charlson comorbidity index (addendum 15.4.2) (Charlson 1994), Clinical Frailty Scale (addendum 15.43) (Rockwood 2005; Bagshaw 2014; Muscedere 2017).
- Core temperature, vital signs, central hemodynamic data (if available)
- Standard laboratory data including serum and urinary electrolytes, creatinine, urea, cholesterol ,triglycerides and glucose levels, arterial lactate levels, arterial oxygen tension and hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin and hematocrit levels, INR, platelets count, total bilirubin levels.
- Microbiolology and virology, i.e. blood and any potential source of infection will be sampled for bacterial culture, nasopharyngeal, bronchial, or broncho-alveolar lavage fluid will be sampled for testing byPCR for SARS-CoV-2 and any other respiratory virus
- Synacthen test, i.e. blood sample for cortisol measurement immediately before and 30 and 60 minutes after 250μg intravenous bolus of corticotrophin.
- Whole blood samples will be collected for measurements of biomarkers described in WP3 and WP4. These blood samples will be managed within WP2.
- Interventions: mechanical ventilation, renal replacement, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials),

5.4 Follow-up visits

The patients included will be further followed for up to 180 days after randomization. Clinical and biological data will be assessed as described in table 4.1.19

Daily data until ICU discharge or 90 days (whichever comes first):

a. Vital status
b. protocol adherence (receipt of every planned dose until completion of 7 days treatment protocol),
c. co-interventions (administration of mechanical ventilation, renal replacement, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials),
d. core temperature (lowest and highest of the day), vital signs (lowest and highest values for heart rate, systolic and diastolic blood pressure) and whenever needed central hemodynamic data (one per day),
   standard laboratory data including serum and urinary electrolytes, creatinine, urea, cholesterol, triglycerides and glucose levels, arterial lactate levels, arterial oxygen tension and hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin and hematocrit levels, INR, platelets count, total bilirubin levels.

e. Sampling for microbiology or virology will be collected at Day 1, and 7, and additional sampling will be left at physicians' discretion
f. Whole blood samples will be collected at Day 1 and Day 7 for measurements of biomarkers described in WP3 and WP4. These blood samples will be managed within WP2.

5.5 Last study visit

At 6 months, follow-up will be achieved by telephone by the Coordinating Centre.

At 90- and 180-day data:

a. Vital status
b. Location: still ICU (or date discharge), hospital ward (or date discharge), rehabilitation centre, long-term facility, home (date discharge to home)
c. co-interventions: mechanical ventilation (or date weaned off), renal replacement (or date weaned off), vasopressors (or date weaned off)
d. core temperature (lowest and highest of the day), vital signs (lowest and highest values for heart rate, systolic and diastolic blood pressure) – if still at hospital
e. Glasgow coma scale Cognitive function
f. MDRS score
g. HRQoL, promis

5.6 Early termination visit

Patients are allowed to withdraw their participation in the research at any time and for any reason.
Patients included in the research (unable to consent or included by a relative) can refuse to continue their
participation after recovery.
The investigator can temporarily or permanently withdraw a participant from the study for any safety reason
or if it is in the participant's best interests.

If a participant wishes to withdraw their consent from the study, we will use the following strategies to minimize the impact on the validity of the trial meanwhile respecting the participant's right to withdraw. We will seek a better understanding of the patient's wishes and offer the following alternatives to complete withdrawal:

1) Discontinue in-person follow-up but allow telephone follow-up;
2) Discontinue in person and by telephone follow-up but allow access to medical records and to use personal data to be able to get life status from the national centre of epidemiology of deaths (Centre d'épidémiologie sur les causes de décés - Cépidc) via the SNDS (Système National des Données de Santé).

In any case, all the data that would have been collected before the patient's consent withdrawal will be kept in.

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

- Duration of enrolment period: 48 months
- Duration of participation for each participant: 6 months
    - Treatment period:7 days

- Duration of follow-up period:6 months

– Total study duration: 54 months
– Randomization (Interventional phase): will be performed after the inclusion visit, less than 24 hours after receiving the results of the biomarker.
– Follow-up duration and procedures for the participant in the event of premature discontinuation

5.8 Table or diagram summarising the chronology of the study

	Days													6 months
	0	**1**	**2**	**3**	**4**	**5-6**	**7**	**8-9**	**10**	**11-13**	**14**	**28**	**90**	
Verification of inclusion and exclusion criteria	X													
Informed consent	x													
Source of infection		x												
Severity of illness (SAPS II score)		x												
Sepsis data		x												
Pre-existing comorbidities (Charlson comorbidity index, Clinical Frailty Score)		x												
Randomization* (Interventional phase)		x												
Dispensation of treatments		X	X	X	X	X	X							
Biological samples<	X	X	x	x	x	x	x	x	x	x	x	x		
Additional Biological samples (biomarqueurs)	X	X[a]					X							
Protocol adherence[b]		x	x	x	x	x	x							
Co-interventions[c]		x	x	x	x	x	x	x	x	x	x	x	x	
Death or persistent organ dysfunction[d]		x	x	x	x	x	x	x	x	x	x	x	x	x
Vasopressor dependency		x	x	x	x	x	x	x	x	x	x	x	x	
Organ function including renal function (SOFA score)*	X	x	x	x	x		x		x		x	x		
HRQoL (EQ-5D-5L)[e], Promis		x										x	x	x
Serious adverse events*		x	X	X	X	x	x	x	x	x	x	x	x	X

[a]*Must be collected before the first dose of investigational product. Samples include blood, urine, cells, exhaled air*

[b]*Receipt of every planned dose according to schedule until completion of 7-day treatment protocol, samples collected per protocol instructions, biomarkers collected before the first dose of investigational product.*
[c]*Administration of mechanical ventilation, renal replacement, vasopressors, vitamin C, thiamine, intravenous fluids, blood products, sedatives, and antimicrobials. Daily data until ICU discharge or 28 days (whichever comes first).*
[d]*Dependency on mechanical ventilation, renal replacement, or vasopressors.*
eEQ5D to be filled at 3 and 6 months

** Interventional trial*

5.9 Distinction between standard care and study

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

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Verification of inclusion and exclusion criteria		X
Informed consent		X
Source of infection	X	....
Severity of illness (SAPS II score)	X	
Sepsis data	X	
Pre-existing comorbidities (Charlson comorbidity index, Clinical Frailty Score)	X	X
Randomization		X
Dispensation of treatments	X	X
Biological samples	X	X
Additional Biological samples		X
Protocol adherence[b]		X
Death or persistent organ dysfunction[d]		X
Vasopressor dependency	X	X
Organ function including renal function (SOFA score)	X	X
HRQoL (EQ-5D-5L)		X
Serious adverse events		X

5.10 Biological samples collection

Samples (serum,DNA,urine, ...) taken as part of the study will be stored in a biological sample collection.

During the study the sample collection(s) will be stored at the laboratory of Centre de Ressources Biologiques (CRB) Paris Saclay, under the supervision of Pr Jean- François Emile / Dr Anne Laure Roux***)*** for a period of 30 years **.** Relevance of the collection/purpose ***(see table below)***

At the end of the study, the samples will be stored.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition **sepsis** /in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

The sample collection will be declared to the ministry of research [and to the director of the competent regional healthcare authority - **amend as necessary** if the entity is a health establishment (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

Type of sample	Quantity	Storage location (name and entity)	Supervisor of the sample collection (name and entity)	Purpose of the sample collection	Storage duration	End use/Future (e.g. destruction)
Serum Tubes	3X3.5 mlX3 (Day 0, Day1 and Day7)	GH PSO	Pr Jean-François Emile / Mme Anne Laure Roux Centre de Ressources Biologiques (CRB) Paris Saclay	biomarkers	30 years	destruction
EDTA tubes	2X 6ml X3 (Day 0, Day1 and Day7)	GH PSO	Pr Jean-François Emile / Mme Anne Laure Roux Centre de Ressources Biologiques (CRB) Paris Saclay	bio markers	30 years	destruction
Paxe gene Blood	1X 10 ml X3 (Day 0, Day1 and Day7)	GH PSO	Pr Jean-François Emile / Mme Anne Laure Roux Centre de Ressources Biologiques (CRB) Paris Saclay	biomarkers	30 years	destruction
Mono vette Urine	1X 10 mlX3 (Day 0, Day1 and Day7)	GH PSO	Pr Jean-François Emile / Mme Anne Laure Roux Centre de Ressources Biologiques (CRB) Paris Saclay	biomarkers	30 years	destruction

5.11 The investigational medicinal products

5.11.1 Description of the drugs :

- Hydrocortisone hemisuccinate / placebo:

Vials with 100 mg hydrocortisone or placebo lyophilisate for IV injection; provided by SERB laboratory, 40 Avenue George V, 75008 Paris.
Store at room temperature.
Water for injection needed for the reconstitution for IV injection of hydrocortisone/placebo will not be specifically provided by the Sponsor but taken from hospital stocks (all available presentations) and reimbursed as additional costs

- Fludrocortisone / placebo:

Tablets of 50 µg or placebo; provided by HAC Pharma laboratory, 43 avenue de la Côte de Nacre, 14052 Caen Cedex 4.
Store at room temperature

5.11.2 Presentation of patient boxes :

Treatments will be presented in numbered boxes, labelled for this study according to the Good Manufacturing Practices under the responsibility of the Clinical Trial Department of AGEPS (Agence Générale des Equipements et Produits de Santé).

Each numbered box will contain all corticosteroids or placebo necessary for a full treatment for each patient, identified by a specific number:

- 30 vials of hydrocortisone 100mg / placebo (2 extra vials)
- 1 blister of 10 tablets of fludrocortisone 50 µg / placebo (3 extra tablets)

5.11.3 SUPPLY OF THE INVESTIGATIONAL CENTERS

The shipments to the hospital pharmacies will be insured by the the Clinical Trial Department of AGEPS.

Supply:
Numbered boxes will be sent after the opening visit.

Re supply:
Re-supplies of patient boxes will be ordered via the eCRF : boxes will be automatically sent to the centers' pharmacies according to their remaining stock.
The hospital pharmacist (with respect to domestic procedures) will confirm receipt in writing of all batches of the study medications and maintain an accurate accounting of them.

Storage:
Treatments have to be stored in a secured local.

Dispensing:

Pharmacies will dispense boxes to the care unit on the basis of a specific prescription edited by the investigator from the eCRF. The traceability will be insure with the peel-off label present on each and affixed on the prescription.

Dispensing corticosteroids/placebo kits is performed only once.In case of anomaly (broken vial), a new prescription will be edited via the eCRF, and another box may be dispensed.

Accountability and destruction:
These will be organized by the CRA through the study. After completion of the study, all drugs boxes (unused, returned…) must be returned to CTD-AGEPS for a central destruction.

5.11.4 POSOLOGY AND DRUGS ADMINISTRATION

Initiation of treatments:

Treatment should be started immediately after randomization (day 0 of the study).

Posology:

- Hydrocortisone hemisuccinate /placebo will be given as 50 mg intravenous bolus every 6 hours
- Fludrocortisone /placebo* will be given as a 50 µg tablet via a nasogastric tube once per day in the morning

* Patients with COVID-19 will receive only experimental fludrocortisone or its placebo AND NOT hydrocortisone or its placebo as they will receive dexamethasone as the standard of care.

Duration of treatments:
Study drugs will be given until the patient will be discharge from the ICU for a maximal treatment duration of 7 days for steroids. Study drugs will be stopped without tapering off.

Reconstitution for IV injection of hydrocortisone/placebo:
Hydrocortisone hemisuccinate lyophilisate will be reconstituted prior to use with 2 mL water for injection. The solvent must be injected gently into the vial. Reconstitution and dilution should be performed in accordance with Good Clinical Practices guidelines, particularly with respect to asepsis and to Hydrocortisone SmPC. Hydrocortisone must not be used if the reconstituted solution has a cloudy appearance or contains floccular or particulate matter. The SmPC instructions for use, handling and disposal should be strictly followed.
The volume injected will be 1 mL, containing 50 mg of Hydrocortisone.

"*Administration of fludrocortisone/placebo*

A 50 *µ*g fludrocortisone/Placebo tablet is administered, enterally, once a day. For patients with a nasogastric tube, the entire tablet will be introduced into the nozzle of the tube. The tube will be flushed with 50 mL of water (the 10 first mL have to be injected slowly) and clamped for at least 30 minutes after tablet administration."

5.12 Co-Interventions

We propose a pragmatic design whereby all co-interventions will be left to the discretion of the treating physician, who will be blinded to treatment assignment. However, we will carefully record use of relevant co-interventions. Unblinded administration of intravenous corticosteroids will constitute a protocol violation, except for patients with COVID-19.
Patients with COVID-19 will receive dexamethasone once daily at a dose of 6 mg for 10 days, as their standard of care

5.12.1 Unauthorized treatments

- Hydrocortisone and other corticosteroids whatever the dose and the route (except local administration, nebulization not being considered as a local administration) are not allowed, except dexamethasone 6mg per day for 10 days in patients with COVID-19. If an unavoidable indication appears during patient stay (e.g. autoimmune disease) 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 corticosteroids 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.

5.12.2 Authorized treatments

All other treatments are allowed according to best practice guidelines whenever available (Rhodes 2017). These treatments ay include for example, mechanical ventilation, renal replacement, vasopressor therapy, thiamine, nutrition therapies including multivitamins, intravenous fluids, blood products, sedatives, and antimicrobials. We will carefuly record the use of these treatments to detect and report any imbalances between the treatment groups.
Patients with COVID-19 will receive open-label dexamethasone at a dose of 6 mg once daily for 10 days (RECOVERY 2020; Sterne 2020).

5.13 Methods for monitoring compliance with the treatment

Study drugs will be administered to patients in the intensive care unit setting for 7 days and recorded with the registered monitoring form of administration. This form will be used to track the administration of study treatments and will be kept in the patient chart. This track log will be monitored by the study CRA.

5.14 Management of Potential Risks to Participants

The safety profile for hydrocortisone and fludrocortisone is remarkably favourable (Annane 2018; Venkatesh 2019). A potential risk is the acquisition of neuromuscular weakness which may more likely seen when corticosteroids are combined with neuromuscular blocking drugs. We will limit the use of curares during the study according to best practice guideliens (Rhodes 2017), and neuromuscular function/strength will be monitor and will be recorded as an outcome in this trial.

Another potential risk, is corticosteroids induced diabetes mellitus. This complication is usally seen with much higher dose and more prolonged exposure to corticosteroids than it will be in this trial. Nontheless, according current best practice guidelines for the management of sepsis (Rhodes et al SSC), blood glucose levels will be kept below 180mg/dl by intravenous insulin therapy whenever needed.

Patients treated in ICU are already monitored very closely. Any serious adverse event (SAE) will be managed immediately by the treating team. Unexpected events will be reported to the research team within 24 hours (see 6.6).

5.14 Outcome Measures

5.14.1 Primary Outcome

The primary outcome will be 90-Day organ dysfunction, ventilation and vasopressors free survival after randomization, which is a composite of day 90 mortality and survival free days off vasopressors and mechanical ventilation, and with SOFA score >6 (Laterre 2019). Such composite outcomes are increasingly used in ICU trials as reliable patient-centered outcomes (Kalkman 2015; Mehta 2017; Semler 2018).

Data on the vital status at day 90 after randomisation will be collected from the medical files (including electronic medical files for the entire hospital) and phone calls to patients and their designated contact persons. The primary endpoint is a binary variable. Patients will be classed as positive outcome if they are alive at day 90 and free of vasopressor therapy, mechanical ventilation and organ dysfunction. Patients

will be classed as negative outcome if they either died in the first 90 days after randomisation or if they remained vasopressor or mechanical ventilation dependent or with a SOFA score >6 beyond 28-days.
.

5.14.2 Secondary Outcomes

The secondary outcomes will include:

1) Mortality at 7, 14, 28 day and 6 months.
2) Vasopressor free days: defined as the number of days with permanent hemodynamic stability in the absence of any vasopressor agent, norepinephrine, phenylephrine, epinephrine, dopamine, vasopressine or its analogs, and soever. When a patient will die on vasopressor therapy, the corresponding vasopressor free day will be 0.
3) Mechanical ventilation free days: defined as the number of days with permanent appropriate oxygenation while the patients is extubated and breathing spontaneously, i.e. no need for non invasive ventilation, high flow oxygen or CPAP. Other uses of non-invasive ventilation (e.g., chronic night-time use for chronic obstructive pulmonary disease) are not counted. When a patient will die on mechanical ventilation or will be discharge home on mechanical ventilation, the corresponding mechanical ventilation free day will be 0.
4) Organ dysfunction free days: Organ function (including renal function) will be assessed by the SOFA score (Vincent 1996). Organ dysfunction will be defined by a SOFA score of > 6 (Annane 2018). Organ dysfunction free days are defined by the number of days with os total SOFA score of 6 or less. When a patient will die on vasopressor therapy, the corresponding vasopressor free day will be 0.
5) HRQoL in 6-month survivors assessed by the EuroQol-5D (EQ-5D). This questionnaire is a standardised measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal. It is made up for two components; health state description and evaluation. The health status is measured in terms of five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In evaluation part, the respondents evaluate their overall health status using the visual analogue scale. See Figure 4.
6) Proportion of patients with a decision to withhold and/or withdraw active treatments
7) ICU and hospital length of stay
8) Rate of re-admission to the ICU during the 180 days after randomization
9) Safety endpoints:
   - Proportion of patients affected by any serious adverse events associated with corticosteroids, among the following: hospital-acquired infections, hyperglycemia, hypernatremia, neurological disorders (coma, stroke or muscle weakness, as defined below) during the 90 days after randomization
   - Coma will be defined as a Glasgow coma score < 8
   - Neurologic sequelae will be assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficit with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficit.
   - Proportion of patients affected by hospital-acquired infections (CTINILS. Définition des infections associées aux soins. 2007)
   - Number of episodes of hyperglycemia (blood glucose levels >150mg/dl) during ICU stay (or up to day 90, whichever occurs first)
   - Number of episodes of hypernatremia (serum sodium > 145 mmol/L) during ICU stay (or up to day 90, whichever occurs first)
   - Glasgow coma scale at ICU and hospital discharge (see annex).
   - Number of patients with an episode of stroke (medical diagnosis as registered in the medical file) during ICU stay (or up to day 90, whichever occurs first)
   - Gastroduodenal bleeding requiring transfusion or hemostatic treatment during ICU stay (or up to day 90, whichever occurs first)

5.15 Data Collection and Participant Follow-up

Potential participants will be referred to the research team by intensivists and other ICU staff. The research team will confirm eligibility and the site principal investigator and co-investigators will confirm whether the patient or others authorized persons may be approached for consent. If that is the case, the research team will obtain consent from the patient or others authorized persons or will enroll and obtain consent subsequently as a deferred consent model

Daily data will be collected from day 1 until day 90 (or at the time of ICU discharge). At 6 months, follow-up will be achieved by telephone by the Coordinating Centre. Table 5.1.8 describes requirements and procedures at each follow-up time point. All study outcomes (as defined in sections 8.1 and 8.2) will be documented on the electronic CRFs (eCRF).

Time points:

1) Baseline data:
    a. patient demographics, source of infection, severity of illness (SAPS II and SOFA scores) (Le Gall 1993), pre-existing comorbidities as defined in the Charlson comorbidity index (Table 3) (Charlson 1994), Clinical Frailty Scale (Table 4) (Rockwood 2005; Bagshaw 2014; Muscedere 2017).
    b. Core temperature, vital signs, central hemodynamic data (if available)
    c. Standard laboratory data including serum and urinary electrolytes, creatinine, urea, *cholesterol ,triglycerides* and glucose levels, arterial lactate levels, arterial oxygen tension and hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin and hematocrit levels, INR, platelets count, total bilirubin levels.
    d. Microbiology and virology, blood and any suspected soure of infection will be sampled, nasopharyngeal, bronchial or broncho-alveolar lavage fluids will be tested by PCR for SARS-CoV-2 and other respiratory viruses.
    e. Synacthen test, i.e. blood sample for cortisol measurement immediately before and 30 and 60 minutes after 250μg intravenous bolus of corticotrophin.
    f. Whole blood samples will be collected for measurements of biomarkers described in WP3 and WP4. These blood samples will be managed within WP2.
    g. Interventions: mechanical ventilation, renal replacement, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials),

2) Daily data until ICU discharge or 90 days (whichever comes first):
    a. Vital status
    b. protocol adherence (receipt of every planned dose until completion of 7 days treatment protocol),
    c. co-interventions (administration of mechanical ventilation, renal replacement, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials),
    d. core temperature (lowest and highest of the day), vital signs (lowest and highest values for heart rate, systolic and diastolic blood pressure) and whenever needed central hemodynamic data (one per day),
    e. standard laboratory data including serum and urinary electrolytes, creatinine, urea, cholesterol , triglycerides and glucose levels, arterial lactate levels, arterial oxygen tension and hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin and hematocrit levels, INR, platelets count, total bilirubin levels.

f. Sampling for microbiology and virology will be done at Day 1, Day 3 and Day 7, additional samples will be left at hysicians' discretion
g. Whole blood samples will be collected at Day 1 and Day 7 for measurements of biomarkers described in WP3 and WP4. These blood samples will be managed within WP2.

3) At 90- and 180-day data:
   a. Vital status
   b. Location: still ICU (or date discharge), hospital ward (or date discharge), rehabilitation centre, long-term facility, home (date discharge to home)
   c. co-interventions: mechanical ventilation (or date weaned off), renal replacement (or date weaned off), vasopressors (or date weaned off)
   d. core temperature (lowest and highest of the day), vital signs (lowest and highest values for heart rate, systolic and diastolic blood pressure) – if still at hospital
   e. Glasgow coma scale
   f. Cognitive function
   g. MDRS score
   h. HRQoL

To minimize patient discomfort and bedside teams' workload, study sample collection will coincide as much as possible with the routine drawing of blood ordered by the treating teams. Also, for the convenience of the patient, study samples of day 0, day 1 and day 7 may be collected at the same time of clinically requested samples happening during the same day. The study samples will be destroyed thereafter if the patient or his/her authorized persons does not consent to participate.

SOFA scores will be calculated from tests ordered locally. In case of missing data (i.e. if the necessary test is not done at certain study time points), SOFA scores will be imputed. All imputations will be pre-specified in the statistical analysis plan before unblinding the trial.

Clinical (non-biomarker) data in this trial will be obtained from the patients' medical records. Local research teams will be responsible for data collection while the patients are still hospitalized.

In contrast, telephone follow-up at 90 day and at 6 months will be centralized and conducted by the URC Paris Saclay Ouest to 1) ensure uniform use of the follow-up questionnaires; and 2) reduce burden on local research teams.

5.16 Cohort Retention

Once a patient is enrolled in the trial, the clinical site will make every reasonable effort to follow the participant for the entire duration of the study period. Loss to follow up is rare in critical care trials, especially for outcomes measured at day 90. To minimize loss to follow-up at 6 months, consent forms will encompass permission to collect alternate contacts information. If necessary, the URC HUPIFO team will request the assistance of the local research team who will have access to the participant medical records, and potentially information contact of the patient's treating general practicioner notably to document survival of the patient.

Participants may discontinue their participation to the RECORDS Trial at any time. If a participant wishes to withdraw their consent from the study, we will use the following strategies to minimize the impact on the validity of the trial meanwhile respecting the participant's right to withdraw. We will seek a better understanding of the patient's wishes and offer the following alternatives to complete withdrawal:

1) Discontinue in-person follow-up but allow telephone follow-up;

2) Discontinue in person and by telephone follow-up but allow access to medical records and to use personal data to be able to get life status from the national centre of epidemiology of deaths (Centre

d'épidémiologie sur les causes de décés - Cépidc) via the SNDS (Système National des Données de Santé).

In any case, all the data that would have been collected before the patient's consent withdrawal will be kept in.

We will adhere to the intention-to-treat principle and data from patients will be analyzed in the group to which they will have been allocated irrespective of protocol adherence. Reasons for protocol deviations, should they arise, will be recorded. In the special case of participants mistakenly randomized, we will only allow post-randomisation exclusions if: 1) the information about ineligibility was available at randomization; 2) two members of the Steering Committee agree that the participant was mistakenly randomized; 3) participants did not receive the intervention; and 4) participants remain blinded to their allocation.[30,31]

6 DATA MANAGEMENT

Multiple measures are in place for data quality control. These measures include: 1) on-site training of research and clinical personnel; 2) standard operating procedures to guide storage and administration of the study drug as well as processing, storage of blood samples; 3) ongoing assessment of quality metrics and periodic feedback to the clinical sites on performance with benchmarking from other sites; 4) site monitoring visits (remotely or in person); 5) ongoing review of missing data and outliers; and 6) rapid dissemination of responses to frequently asked questions via the international study website and monthly newsletter. Coordinating Centre personnel and the Principal Investigators will be available 24/7 to answer study-related questions.

6.1 DATA COLLECTION PROCEDURES AND ELECTRONIC CASE REPORT FORM

Potential participants will be referred to the research team by intensivists and other ICU staff. The research team will confirm eligibility and the site principal investigator and co-investigators will confirm whether the patient or other authorized persons may be approached for consent. If that is the case, the research team will obtain consent from the patient or other authorized persons or will enroll and obtain consent subsequently as per local REB recommendations under a deferred consent model.

Daily data will be collected from day 1 until day 90 (or at the time of ICU discharge). At 3 and 6 months, follow-up will be achieved by telephone by the Coordinating Centre. All study outcomes will be documented on the electronic CRFs (eCRF).

Each patient is assigned a unique ID that is used to index the CRF and the other study documents.

An e-CRF will be developed by URC Paris Saclay Ouest using dedicated software (CleanWeb), to verify data and facilitate follow-up. It will capture data on the site by investigators or their assistants, as well as online randomization of patients.

Access to the e-CRF via the Internet will be secured with a username and password, and the data flow will be encrypted using the https protocol. The data will be collected and recorded permanently and prospectively.

At the end of the study, after the processing of the requests, the database will be frozen and transmitted to the statistics, according to the procedures established by the promoter. Clinical data will be captured in real time in the CRF by the URC's TEC.

6.2 IDENTIFICATION OF DATA RECORDED DIRECTLY IN THE CRFS WHICH WILL BE CONSIDERED AS SOURCE DATA

- Baseline data: patient demographics, Synacthen® test, severity of illness (SAPSII and SOFA score), pre-existing comorbidities as defined in the Charlson comorbidity index, vital signs, core temperature, interventions, standard laboratory test, synacthen test
- Daily data until ICU discharge or 90 days (whichever comes first): protocol adherence (receipt of every planned dose until completion of 7 days treatment protocol), vital status, core temperature, vital signs, co-interventions (administration of mechanical ventilation, renal replacement, vasopressors, unblinded

corticosteroids, thiamine, vitamin C, nutrition, intravenous fluids, blood products, sedatives, stress ulcer prophylaxis, anticoagulants, and antimicrobials), standard laboratory tests.
- 90-day and 180-day data: vital status

6.3 RIGHT TO ACCESS DATA AND SOURCE DOCUMENTS

6.3.1 Data access

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

6.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

In the context of the study, the types of source document will be the medical file, laboratory signed data,, the imaging recordings,

6.3.3 Data confidentiality

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

6.4 DATA PROCESSING AND STORAGE OF RESEARCH DOCUMENTS AND DATA

The e-CRF should contain only the data necessary for analysis for publication. All data relating to the subject and necessary for its follow-up during and outside the research, will be collected in his medical file.
In this research the identity of patient: name (marital name, maiden name) surname, date and place of birth is required to get life status from the SNDS (Système National des Données de Santé)

Furthermore, it should be noted that the self-questionnaires will be completed directly by the patients on the ePRO software. To do this the patient's e-mail address and phone number will be collected. The investigators enter the patient's email address into the ePRO software. Patients then receive an automatic email or SMS with access codes so that they can complete the questionnaires online. This data (email address) is permanently deleted when the status of the study is set to "Study completed".

Personal data is stored encrypted in a separate database from the study database. The link between these 2 databases is based on the system IDs of the entities.
The algorithm used is the PBEWITHMD5ANDDES. The key is 64 bits but only 56 are actually used.
The sponsor will obtain the authorization of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research

6.4.1 DATA OWNERSHIP

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

6.4.2 DATA DISCREPANCY INQUIRIES

Once data are submitted, errors will be detected by the program system to detect missing data or errors. The data managers from the URC PIFO, with the support from the Coordinating Centre will review and validate each data field for errors and inconsistencies. Clinical site personnel will be notified of these errors through regular quality control reports, which include the following:

1) Listing of participants entered into the trial at their clinical site.
2) Listing of participants who have completed follow-up at their clinical sites.
3) Outstanding data queries and data clarification requests.
4) Listing of missing data.
5) Listing of participants with overdue 6-month follow-up visits.
6) Protocol adherence to study drug administration.

Clinical site personnel will be required to respond promptly to each query on the quality control report. To respond to queries study personnel should check the original forms for inconsistency and check other sources of participant records to determine the correction. Clinical site personnel will then modify the data in the e-CRF system to reflect the correction and resubmit data to URC PIFO to resolve the query.

6.4.3 SECURITY AND BACK-UP OF DATA

All study documents and specimens must be kept secure in locked cabinets or other enclosures that are accessible only to study personnel. All electronic data must be password-protected and accessible only to study personnel. The URC-PIFO will be responsible for backing up all submitted data within the EDC system.

7 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

7.1 DESCRIPTION OF SAFETY ENDPOINTS ASSESSMENT PARAMETERS

The proportion of patients affected by any serious adverse events associated with corticosteroids, among the following: hospital-acquired infections, hyperglycemia, hypernatremia, neurological disorders (coma, stroke or muscle weakness, as defined below) during the 90 days after randomization

7.2 ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE SAFETY ENDPOINTS

- Coma will be defined as a Glasgow coma score < 8
- Neurologic sequelae will be assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficit with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficit.
- Proportion of patients affected by hospital-acquired infections (CTINILS. Définition des infections associées aux soins. 2007)
- Number of episodes of hyperglycemia (blood glucose levels >150mg/dl) during ICU stay (or up to day 90, whichever occurs first)
- Number of episodes of hypernatremia (serum sodium > 145 mmol/L) during ICU stay (or up to day 90, whichever occurs first)
- Glasgow coma scale at ICU and hospital discharge (see annex).
- Number of patients with an episode of stroke (medical diagnosis as registered in the medical file) during ICU stay (or up to day 90, whichever occurs first)
- Gastroduodenal bleeding requiring transfusion or hemostatic treatment during ICU stay (or up to day 90, whichever occurs first)

7.3 RECORDING AND REPORTING ADVERSE EVENTS

7.3.1 Definitions

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

- **Adverse event**

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

- **Adverse reaction**

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

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

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

- **Serious adverse event or reaction**

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

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

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

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

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor , as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

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

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

7.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events by using the Common Terminology Criteria for Adverse Events

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product.

To the extent that the information contained in the marketing authorizations is likely to change, it is necessary to ensure at the time of the prescription of the drugs compliance including contraindications,

warnings and precautions of use, drug interactions. Refer to the information available on the Public Drug Database, accessible via the Internet at the following address : http://base-donnees-publiqu.medicament.sgouv.fr/ .

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

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

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

Table: WHO-UMC causality categories (excerpt)

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

*All points should be reasonably complied with
**Or study procedures

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

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

A serious adverse event is any untoward medical occurrence that:

1- results in death 2- is life-threatening to the participant enrolled in the study 3- requires hospitalisation or prolongation of existing hospitalisation 4- results in persistent or significant disability/incapacity 5- is a congenital anomaly/birth defect

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

Adverse events deemed "medically significant" by the investigator even if they would not be classified as serious according to the definition here-above.

- Infections grades 4 (Life-threatening consequences; urgent intervention indicated) and 5 (death) according to CTCAE as well as all superinfections grade ≥3 and viral reactivation grade ≥ 3
- For COVID-19 patients, any worsening of SARS-CoV 2 infection grade ≥ 3 should be notified to the sponsor without delay.
- Bleeding in the gastrointestinal tract defined by clinical evidence of active bleeding and need for blood transfusion OR hemostatic endoscopic or surgical procedures
- Hyperglycemia grades 3 (insulin therapy initiated), 4 (Life-threatening consequences; urgent intervention indicated) and 5 (death) according to CTCAE
- Hypernatremia grades 4 (>160 mmol/L; life-threatening consequences) and 5 (death),
- Coma,
- Stroke
- Muscle weakness grades 3 (distal motor deficit), 4 (mild-to-moderate proximal motor deficit), and 5 (severe proximal motor deficit) according to MDRS scale.

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

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

Expected SAEs that were prespecified as trial outcomes will not be reported as SAEs and are only recorded in the case report forms.

- **Observational phase**: All AE and SAE will be collected in the case report forms and will not require notification to the sponsor. These can be analyzed at the request of the DSMB committe.
- **Interventional phase**: All of the SAE listed below will be collected in the case report form and will not require notification to the sponsor
    - *Normal and natural course of the condition*:
        - *planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant's condition compared to baseline],*
        - *hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition,*
        - *emergency hospitalisation at inclusion or prolongation of hospitalisation after inclusion for monitoring the condition under investigation*

    - *Death occurred after 90 days*

The primary objective of the study is to compare the effect hydrocortisone plus fludrocortisone vs. placebo on a composite of death or persistent organ dysfunction – defined as continued dependency on mechanical ventilation, new renal replacement therapy, or vasopressors – assessed at 90 days on intensive care unit (ICU) adults and having different biological profiles for immune responses and corticosteroids bioactivity

deaths after 90 days do not need to be notified to the sponsor without delay but will be recorded in the case report forms.
An e-CRF extraction of death will be realized every year on the occasion of the preparation of the annual safety report (DSUR). This extraction will be realized by the clinical research unit and transmitted to vigilance department at expertisecsi.drc@aphp.fr.

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

- All serious adverse effects of grade 3 or less according to CTCAE and reported in the section "*Effets indésirables*" of the SPCs of the investigationals medicinals products

- All adverses events of grade 3 or less according to CTCAE related to biological test and blood sample.

- *Special circumstances*
  - *Hospitalisation for a pre-existing illness or condition*
  - *Hospitalisation for a medical or surgical treatment scheduled prior to the study*
  - *Admission for social or administrative reasons*

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

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

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

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins treatment with an investigational medicinal product (interventional period)
- throughout the whole follow-up period required for the trial
- until 90 days after the end of the participant's treatment with the investigational medicinal product.
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication)

7.3.2.5 Procedures and deadlines for notifying the sponsor

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

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

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department of the Clinical Research and Innovation Delegation (DRCI) within the APHP or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents

must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

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

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

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

7.3.3 Role of the sponsor

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

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classified as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics is considered unexpected.

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

- For serious adverse events likely to be related to the investigational medicinal products: refer to the SmPC for HYDROCORTISONE UPJOHN 100 mg**"** laboratory origin : Serb and to the SmPC for **"**FLUCORTAC 50 µg" laboratory origin : H.A.C. Pharma.
- To the extent that the information contained in the marketing authorizations is likely to change, it is necessary to ensure at the time of the prescription of the drugs compliance including contraindications, warnings and precautions of use, drug interactions. Refer to the information available on the Public Drug Database, accessible via the Internet at the following address : http://base-donnees-publiqu.medicament.sgouv.fr/ .

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

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

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

7.3.3.1 Blindness

After unblinding by the sponsor and if the patient is receiving the product under investigation: the case will be reported without delay as a suspected unexpected serious adverse reaction. If the patient is receiving the comparator product: the sponsor will reassess the unexpected nature of the adverse reaction based on the reference document for the comparator product identified in the protocol.
In exceptional situations, if the study involves a condition with a high mortality and/or morbidity rate, and if the ANSM grants permission at the request of the sponsor as part of the clinical trial authorisation application, the methods for unblinding and for reporting suspected unexpected serious adverse reactions can be modified. These methods will then be defined thoroughly in the study protocol.

7.3.3.2 Analysis and declaration of other safety data

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

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

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

7.3.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

7.3.4 Data Safety Monitoring Board (DSMB)

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

The DSMB members are:

- Pr. Eric CAUMES, service des Maladies Infectieuses et Tropicales, hôpital Pitié Salpétrière.
- Pr Anne-Claude CREMIEUX, service des Maladies Infectieuses et Tropicales, hôpital Saint-Louis – APHP.
- Pr Christian THUILLEZ, pharmacologue,Haute Autorité de Santé (fin de fonction fin juin 2020).
- Pr Jean-Daniel.CHICHE , réanimateur, Chef de service de médecine intensive adutlte au Centre Hospitalier Universitaire Vaudois (CHUV), Suisse

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

7.3.5 Discontinuation of the Study

In the event of a premature discontinuation of the clinical trial (e.g. sponsor decision to discontinue the trial due to safety concerns, alternative therapy newly available that may benefit research subjects), a notification will be sent to ANSM and the CPP no later than 15 days after the date of the discontinuation. A discontinuation procedure will be made available when necessary (Figure 5).

7.3.6 Dissemination Policy

Dissemination will be done via an integrated knowledge translation strategy.

Plans for end-of-study dissemination include presentations at major international conferences, publications in high-impact journals and, building on experience with social media developed during previous trials, dissemination of our results via social media platforms and discussion forums managed by partner organizations.

8 STUDY COMMITTEES

8.1 EXECUTIVE COMMITTEE

The Executive Committee is comprised of Djillali Annane, Sylvie Chevret, Lamiae Grimaldi, Bruno François. The Executive Committee is responsible for day-to-day management of the RECORDS trial.

8.2 STEERING COMMITTEE

The Steering Committee consists of intensivists, statisticians, research methodologists, and stakeholders (including patient representatives) and will meet by quarterly teleconference. The Steering Committee will provide guidance and direction to the overall trial.

8.3 DATA SAFETY MONITORING BOARD COMMITTEE

There is need to establish a DSMB committee for this trial as the drugs used in this trial are corticosteroids, , which is also on line with the trial categorisation as Risk B via the APHP logistic score.

9 STATISTICAL ANALYSIS

9.1 SAMPLE SIZE DETERMINATION

We will enroll a total of at most 1800 patients. Sites are expected to enroll at least 1or 2 patients per month.

Adaptive outcomes

The goal is to develop an adaptive clinical trial design which evaluates the therapeutic intervention of targeted therapy, identifies subset of subjects who respond better to the experimental therapy.
Sequential analyses will use the number of vasopressor-free days at day 28 as the measure of efficacy, and the occurrence of severe adverse events within the first 28 days as the measure of toxicity. According to the literature (the APPROCCHS trial), the number of vasopressor-free days at day 28 in the hydrocortisone+fludrocortisone group was 17.1±10.8 versus 15.0 ± 11.1 in the placebo group. Thus, a sample of 176x2=352 patients achieves 80.04 % power to reject the null hypothesis of equal means when the mean difference between arms is 3 days with SD of 10 days, and with a significant level (alpha) of 0.05 using a two-sample t-test. For interactions to be detected with the same power as the overall effect, sample sizes should be inflated (Brookes 2004); estimated here at a multiple of fourfold; therefore, to handle potential dropouts, a sample of 1800 patients was considered to be enrolled.
Note that Bayesian inference will be used for sequential analyses, so that no inflation of type I error rate is to be corrected.

Primary outcome

To detect a 10% absolute risk reduction (from 45% to 35%) in the day 90 mortality, a sample size of 373 evaluable patients per arm (thus a total of 746 patients) is required to reach a 80% power. The planned sample of 1800 patients will achieve a 99.16%
power to reject the null hypothesis of equal mortality when the difference between arms is 10% overall, and with a 5% alpha level.
Sample sizes were computed using PASS 15 software (2017).
The power to detect this difference within each group of analysis will depend on the prevalence of each biomarker of interest.

9.2 STATISTICAL METHODS

9.2.1 Adaptive Bayesian analyses

Clinical trial methodology needs to adapt to personalized medicine by including more frequent interim analyses of accumulating data, or by making greater use of those biomarkers information (Saad 2017; Janiaud 2019). An adaptive design is a clinical trial design that allows adaptations or modifications to aspects of the trial after its initiation without undermining the validity of the trial.
Therefore, the aim of the sequential analyses will be to detect treatment-by-biomarker interactions, that is, whether the treatment effect may be different according to biomarkers, that may potentially stop the recruitment of patients presenting with certain levels of that biomarker if there is any evidence that it interacts negatively with the outcome. Treatment effect will be assessed on two main outcome measures, namely a tolerance measure (to detect potential deleterious effects of treatment in some subsets) and an early surrogate efficacy measure (to detect a potential futility to continue treatment evaluation in some cohorts). As described above (section 4.8.2), the tolerance measure will be the occurrence within the first

7, 14 and 28 days of any grade 3 or over adverse events such as hospital-acquired infections, hyperglycemia, hypernatremia, neurological disorders, and the efficacy measure will be the number of vasopressor-free days within the first 28 days.

Search for treatment-by-cohort interactions will be based on each endpoint, and each cohort, separately. Let A and B denote the 2 treatment arms. The treatment effect, θ, of A over B will be considered as the parameter of interest.
Let consider a set of K biomarkers available at baseline, with $x_i = (x_{1i}, \dots, x_{Ki})$ the set of biomarkers for subject *i*, and $Y_{ij} = 1$ the outcome of subject i in arm j.

We will use a Bayesian inference. This is in line with the growing literature to propose Bayesian approaches in randomized clinical trial (), including to identify subpopulations with enhanced treatment effects (Simon 2018). Moreover, it allows to go further than the "statistically significant" findings based on p-values (Wasserstein 2019; Amrhein 2019). Last, Unlike in the frequentist evaluation of the influence condition, the Bayesian evaluation of the influence condition has the advantage of separating the parameters of clinical relevance and risk tolerance (Millen 2014), as detailed below.
Search for treatment-by-cohort interactions will be based on each biomarker and outcome, separately. Treatment-by-covariate interaction will be measured by a Bayesian criterion proposed by Millen (2014), based on the posterior probability of the 'interaction condition' defined in terms of the subpopulation effect sizes estimates:

$$P\left(\hat{\theta}_+ / \hat{\theta}_- \geq \lambda_1 \,|X\right) \geq \gamma_1,$$

where X is the observed data, $\hat{\theta}_+$ is the treatment effect on the efficacy outcome in one subset and $\hat{\theta}_-$ in the remaining subpopulation, λ_1 is a threshold of clinically meaningful effect, close to that proposed by Morita (2014), and γ_1 represents the information threshold for decision-making. Inversely, it will apply to the tolerance outcome, based on

$$P(\hat{\tau}_+ / \hat{\tau}_- \geq \lambda_2 \,|X) \geq \gamma_2,$$

where $\hat{\tau}_+$ is the treatment effect on adverse event in one subset and $\hat{\tau}_-$ in the remaining subpopulation, λ_2 is a threshold of clinically deleterious effect, and γ_2 represents the information threshold for decision-making.
The estimates $\hat{\theta}_j$ or $\hat{\tau}_j$ will be defined according to the type of the endpoint, either continuous, with $\hat{\theta}_j = \frac{\hat{\mu}_{Aj} - \hat{\mu}_{Bj}}{\hat{\sigma}_i}$, is the effect size defined within each subgroup as the mean treatment difference divided by the common standard deviation, or binary $\hat{\tau}_j = \frac{\hat{p}_{Aj} - \hat{p}_{Bj}}{\sqrt{\bar{p}_j(1-\bar{p}_j)}}$ where $\bar{p}_j$ is the estimated average adverse event rate.
Noninformative prior distribution will be considered.

9.2.2 Reduction of Bias

Risk of selection bias will be reduced by concealed randomization using variable and undisclosed blocks. Physicians, nurses, patients and family members, all research personnel, and outcome assessors and adjudicators will be blinded. Accordingly, decisions to discontinue life-sustaining therapies and other outcomes that require subjective assessments (e.g. HRQoL) will not be affected by individually held beliefs regarding the effects of corticosteroids.

10 Quality Control and ASSURANCE

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

10.1 GENERAL ORGANISATION

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

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

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

10.1.1 Strategy for centre opening

The opening strategy of the centers will be determined before the start of the research.

10.1.2 Scope of centre monitoring

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

10.2 QUALITY CONTROL

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

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

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

10.3 CASE REPORT FORMS

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

10.4 MANAGEMENT OF NON-COMPLIANCES

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

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

10.5 AUDITS/INSPECTIONS

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

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

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

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

10.6 PRINCIPAL INVESTIGATOR'S COMMITMENT TO ASSUME RESPONSIBILITY

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

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

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

11 ETHICAL AND LEGAL CONSIDERATIONS

11.1 METHODS FOR INFORMING RESEARCH PARTICIPANT AND OBTAINING THEIR CONSENT

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

All consecutive eligible patients should be approached for participation in the trial by the clinical investigators or person qualified to carry out the research. The clinical investigator will inform the eligible person then collect the free and written consent of the person undergoing to the research. If the patient is unable to provide consent within the time window allowed by the protocol, his or her authorized person (member family, curator, guardianship, trusted person) may be approached in person. The local research team could also enroll eligible patients and obtain consent subsequently as per French national regulation under a deferred consent model.

To obtain informed consent, study personnel should follow the following steps:

- Present information on the study in a simple and understandable manner;
- Answer questions in a simple and understandable manner;
- Allow the potential participant/authorized persons an opportunity to reflect and discuss study participation with their family, friends, or family physician if desired;
- Confirm that the participant/authorized persons understands the risks and benefits of participating in the study and that their participation is voluntary;
- Complete and obtain signatures for informed consent form and obtain contact information from the participant/authorized persons.

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

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

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent or consent from his or her authorized person as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

11.2 PROHIBITION FROM PARTICIPATING IN ANOTHER CLINICAL STUDY

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies. Whilst participating on this research study, participants could be included only one time in the study

11.3 AUTHORISATION FOR THE RESEARCH LOCATION

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

11.4 LEGAL OBLIGATIONS

11.4.1 Role of the sponsor

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

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

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

11.4.3 Request for approval from the ANSM

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

11.4.4 Procedures relating to data protection regulations

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

This research is not governed by the CNIL "Reference Method" (MR-001) because the inclusion of patients can be done in an emergency situation without obtaining consent at the time of inclusion. In addition, and in order to recover the vital status of the patients, the collection of the name (and marital name for women), first name, date and place of birth of the patients is required to query the national database SNDS (Système National des Données de Santé) in which the vital status (living or dead) of an individual will be retrieved by queryingthe national centre of the epidemiology of deaths (Centre d'épidémiologie sur les causes de décés - Cépidc).
The sponsor will obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research

11.4.5 Amendments to the research

Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to participants (e.g. changes to the study objectives, inclusion/exclusion criteria, study design, sample size, or study procedures) will require a formal amendment to the protocole.

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

11.4.6 Final study report

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

11.4.7 Archiving

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

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list):
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - the ANSM authorisations and CPP (Research Ethics Committee) decisions
    - any correspondence
    - the enrolment list or register
    - the appendices specific to the research
    - final study report
- The data collection documents

12 Funding and Insurance

12.1 FUNDING SOURCES

This study is supported by a grant from ANR (French Ministry of Higher Education, Research and Innovation): RHU 2019 "ANR-18-RHUS-00XX" (Recherche hospital-universitaire en santé).

12.2 INSURANCE

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

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

13 Publication rules

13.1 MENTION OF AP-HP AFFILIATION FOR PROJECTS SPONSORED BY AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- Each of these affiliations must be identified by an address separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

For any publication, the APHP will be mentioned in the affiliation of the authors.

13.2 MENTION OF THE SPONSOR AP-HP (DRCI) IN THE ACKNOWLEDGEMENTS OF THE TEXT

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

13.3 MENTION OF THE FINANCIAL BACKER IN THE ACKNOWLEDGEMENTS OF THE TEXT

- "The study was funded by a grant from ANR- RHU 2019 (French Ministry of Higher Education, Research and Innovation)"

This study has been registered on the website http://clinicaltrials.gov/ under number : NCT04280497

14 Bibliography

ACCP/SCCM 1992
ACCP/SCCM Consensus Conference Panel. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Critical Care Medicine 1992;20(6):864-74. [PubMed: 1597042]
Allen 2018
Allen JM, Feild C, Shoulders BR, Voils SA. Recent updates in the pharmacological management of sepsis and septic shock: a systematic review focused on fluid resuscitation, vasopressors, and corticosteroids. Annals of pharmacotherapy 2018;53:385-95. [DOI: 10.1177/1060028018812940; PubMed: 30404539]
Angus 2013
Angus DC, van der Poll T. Severe sepsis and septic shock. New England Journal of Medicine 2013;369(21):840-51. [PubMed: 23984731]
Annane 2000
Annane D, Sébille V, Troché G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283(8):1038-45. [PubMed: 10697064]
Annane 2003
Annane D, Aegerter P, Jars-Guincestre MC, Guidet B; CUB-Rea Network. Current epidemiology of septic shock: the CUB-Réa Network. American Journal of Respiratory and Critical Care Medicine 2003;168(2):165-72. [PubMed: 12851245]
Annane 2005
Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet 2005;365(9453):63-78. [PubMed: 15639681]
Annane 2009
Annane D. Improving clinical trials in the critically ill: unique challenge: sepsis. Critical Care Medicine 2009;37 Suppl(1 Suppl):117-28. [PubMed: 19104211]
Annane 2017a
Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Medicine 2017;43(12):1781-92. [PubMed: 28940017]
Annane 2017b
Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Medicine 2017;43(12):1751-63. [PubMed: 28940011]
Annane 2018
Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. New England Journal of Medicine 2018;378(9):809-18. [PubMed: 29490185]
Antcliffe 2018
Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, et al. Transcriptomic Signatures in Sepsis and a Differential Response to Steroids: From the VANISH Randomized Trial. Am J Respir Crit Care Med. 2018 Oct 26. doi: 10.1164/rccm.201807-1419OC.
Amrhein 2019
Amrhein V, Greenland S, McShane B. retire statistical significance. Nature 2019;567:305-307.
Bagshaw 2014
Bagshaw, S. M. et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ 2014; 186, E95-102, doi:10.1503/cmaj.130639.
Barczyk 2010
Barczyk K, Ehrchen J, Tenbrock K, Ahlmann M, Kneidl J, Viemann D, et al. Glucocorticoids promote survival of anti-inflammatory macrophages via stimulation of adenosine receptor A3. Blood 2010;116(3):446-55. [PubMed: 20460503]
Barnes 1995
Barnes PJ, Greening AP, Crompton GK. Glucocorticoid resistance in asthma. American Journal of Respiratory and Critical Care Medicine 1995;152 Suppl(6 Pt 2):125-40. [PubMed: 7489120]
Boonen 2013
Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, et al. Reduced cortisol metabolism during critical illness. New England Journal of Medicine 2013;388(16):1477-88. [PubMed: 23506003]
Briegel 1994
Briegel J, Kellermann W, Forst H, Haller M, Bittl M, Hoffmann GE, et al. Low-dose hydrocortisone infusion attenuates the systemic inflammatory response syndrome. The Phospholipase A2 Study Group. Clinical Investigation 1994;72(10):782-7. [PubMed: 7865982]
Brookes 2004
Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004 Mar;57(3):229-36.
Bruno 2012
Bruno JJ, Dee BM, Anderegg BA, HernandezM, Pravinkumar SE.. US practitioner opinions and prescribing practices regarding corticosteroid therapy for severe sepsis and septic shock. Journal of Critical Care 2012;27(4):351-61. [PubMed: 22341726]
Cai 2008
Cai L, Ji A, de Beer FC, Tannock LR, van der Westhuyzen DR. SR-BI protects against endotoxemia in mice through its roles in glucocorticoid production and hepatic clearance. Journal of Clinical Investigation 2008;118(1):364–75. [PubMed: 18064300]
Cain 2017
Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nature Reviews. Immunology 2017;17(4):233-47. [PubMed: 28192415]
Charlson 1994
Charlson, M., Szatrowski, T. P., Peterson, J. & Gold, J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47, 1245-1251.

Chow 2008
Chow, S.C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC. Boca Raton, Florida.
Chrousos 1995

Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. New England Journal of Medicine 1995;322(20):1351-62. [PubMed: 7715646]
Cooper 2003
Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. New England Journal of Medicine 2003;348(8):727-34. [PubMed: 12594318]
Cronin 1995
Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MAD, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Critical Care Medicine 1995;23(8):1430-9. [PubMed: 7634816]
Crouser 2017
Crouser ED, et al. Improved Early Detection of Sepsis in ED With a Novel Monocyte Distribution Width Biomarker. Chest. 2017;152:518‐526
Davenport 2018
Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, Rautanen A, Gordon AC, Garrard C, Hill AVS, Hinds CJ, Knight JC. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med 2016;4: 259–71.
de Kruif 2007
de Kruif MD, Lemaire LC, Giebelen IA, van Zoelen MA, Pater JM, van den Pangaart PS, et al. Prednisolone dose-dependently influences inflammation and coagulation during human endotoxemia. Journal of Immunology 2007;178(3):1845-51. [PubMed: 17237435]
De Freitas Caires 2018
De Freitas Caires N, et al. Endocan, sepsis, pneumonia, and acute respiratory distress syndrome. Crit Care. 2018;22(1):280
Devereaux 2001
Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM, et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA 2001;285(15):2000-3. [PubMed: 11308438]
D'Agostino 1988
D'Agostino RB, Chase W, Belanger A.The Appropriateness of Some Common Procedures for Testing the Equality of Two Independent Binomial Populations', The American Statistician,1988:198-202.
di Villa Bianca 2003
Villa Bianca RE, Lippolis L, Autore G, Popolo A, Marzocco S, Sorrentino L, et al. Dexamethasone improves vascular hyporeactivity induced by LPS in vivo by modulating ATP-sensitive potassium channel activity. British Journal of Pharmacology 2003;140(1):91–6. [PubMed: 12967938]
Duma 2004
Duma D, Silva-Santos JE, Assreuy J. Inhibition of glucocorticoid receptor binding by nitric oxide in endotoxemic rats. Critical Care Medicine 2004;32(11):2304–10. [PubMed: 15640646]
Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34. [PubMed: 9310563]
Ellouze 2019
Ellouze M, et al. The targeted overexpression of GILZ in macrophages limits systemic inflammation while increasing bacterial clearance in sepsis, submitted. Submitted.
Erschen 2007
Ehrchen J, Steinmüller L, Barczyk K, Tenbrock K, Nacken W, Eisenacher M, et al. Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. Blood 2007;109(3):1265-74. [PubMed: 17018861]
Fabian 1982
Fabian TC, Patterson R. Steroid therapy in septic shock. Survival studies in a laboratory model. American Surgeon 1982;48(12):614-7. [PubMed: 6760756]
Fang 2018
Fang F, Zhang Y, Tang J, Lunsford LD, Li T, Tang R, et al. Association of corticosteroid treatment with outcomes in adult patients with sepsis: a systematic review and meta-analysis. JAMA Internal Medicine 2019;179(2):213-23. [DOI: 10.1001/jamainternmed.2018.5849; PubMed: 30575845]
Fleiss 2003
Fleiss J L, Levin B,Paik MC. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.
Galigniana 1999
Galigniana MD, Piwien-Pilipuk G, Assreuy J. Inhibition of glucocorticoid receptor binding by nitric oxide. Molecular Pharmacology 1999;55(2):317–23. [PubMed: 9927624]
Gaudet 2017
Gaudet A, Chenevier-Gobeaux C, Parmentier E, Delobel J-E, Dubucquoi S, Mathieu D, et al. Endocan is a stable circulating molecule in ICU patients. Clin Biochem. 2017.
Gaudet 2018
Gaudet A, et al. Low endocan levels are predictive of Acute Respiratory Distress Syndrome in severe sepsis and septic shock. J Crit Care. 2018;47:121‐126.
Goodwin 2013
Goodwin JE, Feng Y, Velazquez H, Sessa WC. Endothelial glucocorticoid receptor is required for protection against sepsis. Proceeding of the National Academy of Science 2013;110(1):306–11. [PubMed: 23248291]
Heller 2003
Heller AR, Heller SC, Borkenstein A, Stehr SN, Koch T. Modulation of host defence by hydrocortisone in stress doses during endotoxaemia. Intensive Care Medicine 2003;29(9):1456-63. [PubMed: 12879235]
Heming 2018
Heming N, Sivanandamoorthy S, Meng P, Bounab R, Annane D. Immune effects of corticosteroids in sepsis. Frontiers in Immunology 2018;9:1736. [DOI: 10.3389/fimmu.2018.01736; PubMed: 30105022]
Hotta 1986
Hotta M, Baird A. Differential effects of transforming growth factor type beta on the growth and function of adrenocortical cells in vitro. Proceedings of the National Academy of Sciences of the United States of America 1986;83(20):7795-9. [PubMed: 3020557]
Huang 1987
Huang ZH, Gao H, Xu RB. Study on glucocorticoid receptors during intestinal ischemia shock and septic shock. Circulatory Shock 1987;23(1):27-36. [PubMed: 3690811]
Jaattela 1991

Jaattela M, Ilvesmaki V, Voutilainen R, Stenman UH, Saksela E. Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. Endocrinology 1991;128(1):623-9. [PubMed: 1702707]
Janiaud 2019
Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. Cancer Treat Rev. 2019;73:20-30
Kadri 2017
Kadri SS, Rhee C, Strich JR, Morales MK, Hohmann S, Menchaca J, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. Chest 2017;151(2):278-28. [PubMed: 27452768]
Kalkman 2015
Kalkman CJ, Kappen TH: Patient-centered endpoints for perioperative outcomes research. Anesthesiology 2015; 122:481–483
Kalil 2011
Kalil AC, Sun J. Low-dose steroids for septic shock and severe sepsis: the use of Bayesian statistics to resolve clinical trial controversies. Intensive Care Medicine 2011;37(3):420–9. [PubMed: 21243334]
Kanczkowski 2013
Kanczkowski W, Alexaki VI, Tran N, Großklaus S, Zacharowski K, Martinez A, et al. Hypothalamo-pituitary and immune-dependent adrenal regulation during systemic inflammation. Proceedings of the National Academy of Science 2013;110(36):14801–6. [PubMed: 23959899]
Katsenos 2014
Katsenos CS, Antonopoulou AN, Apostolidou EN, Ioakeimidou A, Kalpakou GT, Papanikolaou MN, et al; on behalf of the Hellenic Sepsis Study Group. Early administration of hydrocortisone replacement after the advent of septic shock: impact on survival and immune response. Critical Care Medicine 2014;42(7):1651-7. [PubMed: 24674923]
Kellum 2007
Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Archives of Internal Medicine 2007;167(15):1655-63. [PubMed: 17698689]
Lachin 2000
Lachin JM. 2000. Biostatistical Methods. John Wiley & Sons. New York.
Lamontagne 2018
Lamontagne F, Rochwerg B, Lytvyn L, Guyatt GH, Møller MH, Annane D, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ 2018;362:k3284. [PubMed: 30097460]
Laterre 2019
Laterre PF et al. Selepressin for the treatment of septic shock: an adaptive randomized clinical trial JAMA. 2019
Lefering 1995
Lefering R, Neugebauer EAM. Steroid controversy in sepsis and septic shock: a meta-analysis. Critical Care Medicine 1995;23(7):1294-303. [PubMed: 7600840]
Le Gall 1993
Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score
(SAPS II) based on a European/North American multicenter study. JAMA 1993;
270:2957–2963
Lipiner 2007
Lipiner D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, et al. Adrenal function in sepsis: the retrospective CORTICUS cohort study. Critical Care Medicine 2007;35(4):1012-8. [PubMed: 17334243]
Lowenberg 2005
Lowenberg M, Tuynman J, Bilderbeek J, Gaber T, Buttgereit F, van Deventer S, et al. Rapid immunosuppressive effects of glucocorticoids mediated through Lck and Fyn. Blood 2005;106(5):1703-10. [PubMed: 15899916]
Machin 1997
Machin D, Campbell M, Fayers P, Pinol A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, Mass.
Marik 2008
Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Critical Care Medicine 2008;36(6):1937–49. [PubMed: 18496365]
Meduri 1998
Meduri GU, Chrousos GP. Duration of glucocorticoid treatment and outcome in sepsis: is the right drug used the wrong way? Chest 1998;114(2):355-60. [PubMed: 9726712]
Melby 1958
Melby JC, Spink WW. Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. Journal of Clinical Investigation 1958;37(12):1791-8. [PubMed: 13611047]
Menon 2013
Menon K, McNally D, Choong K, Sampson M. A systematic review and meta-analysis on the effect of steroids in pediatric shock. Pediatric Critical Care Medicine 2013;14(5):474-80. [PubMed: 23867428]
Mehta 2017
Mehta RH, Leimberger JD, van Diepen S, et al.: Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. N Engl J Med 2017; 376:2032–2042
Millen 2014
Millen BA, Dmitrienko A, Song G. Bayesian assessment of the influence and interaction conditions in multipopulation tailoring clinical trials. J Biopharm Stat. 2014;24(1):94-109.
Molijn 1995
Molijn GJ, Koper JW, van Uffelen CJ, de Jong FH, Brinkmann AO, Bruining HA, et al. Temperature-induced down-regulation of the glucocorticoid receptor in peripheral blood mononuclear leucocyte in patients with sepsis or septic shock. Clinical Endocrinology 1995;43(2):197-203. [PubMed: 7554315]
Moran 2010
Moran JL, Graham PL, Rockliff S, Bersten AD. Updating the evidence for the role of corticosteroids in severe sepsis and septic shock: a Bayesian meta-analytic perspective. Critical Care 2010;14(4):R134. [PubMed: 20626892]
Morita 2014

Morita S, Yamamoto H, Sugitani Y. Biomarker-based Bayesian randomized phase II clinical trial design to identify a sensitive patient subpopulation. Stat Med. 2014; 33:4008–4018

Muscedere 2017
Muscedere, J. et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med 2017; 43, 1105-1122, doi:10.1007/s00134-017-4867-0.
Ni 2018
Ni YN, Liu YM, Wang YW, Liang BM, Liang ZA. Can corticosteroids reduce the mortality of patients with severe sepsis? A systematic review and meta-analysis. American Journal of Emergency Medicine 2018;S0735-6757:30953-7. [PubMed: 30522935]
Nishida 2018
Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016). Acute Medicine and Surgery 2018;5:3-89. [PubMed: 29445505]
Norman 2004
Norman AW, Mizwicki MT, Norman DP. Steroid-hormone rapid actions, membrane receptors, and a conformational ensemble model. Nature Reviews. Drug Discovery 2004;3(1):27-41. [PubMed: 14708019]
Park 2012
Park HY, Suh GY, Song JU, Yoo H, Jo IJ, Shin TG, et al. Early initiation of low-dose corticosteroid therapy in the management of septic shock: a retrospective observational study. Critical Care 2012;16(1):R3. [PubMed: 22226237]
Parrillo 1993
Parrillo JE. Pathogenic mechanisms of septic shock. New England Journal of Medicine 1993;328(20):1471-7. [PubMed: 8479467]
PASS 2017
PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.
Peters 2008
Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. Journal of Clinical Epidemiology 2008;61(10):991-6. [PubMed: 18538991]
Polito 2011
Polito A, Sonneville R, Guidoux C, Barrett L, Viltart O, Mattot V, et al. Changes in CRH and ACTH synthesis during experimental and human septic shock. PLoS One 2011;6(11):e25905. [PubMed: 22073145]
Ranieri 2012
Ranieri, V.M. et al. Acute respiratory distress syndrome: the Berlin Definition. ARDS Definition Task Force. JAMA 2012; 307, 2526-33, doi: 10.1001/jama.2012.5669
RECOVERY 2020
The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.
Rhee 2017
Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al; CDC Prevention Epicenter Program.. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA 2017;318(13):1241-9. [PubMed: 28903154]
Rhen 2005
Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids: new mechanisms for old drugs. New England Journal of Medicine 2005;353(16):1711-23. [PubMed: 16236742]
Rhodes 2017
Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Medicine 2017;43(3):304-77. [PubMed: 28101605]
Rochwerg 2018
Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. Critical Care Medicine 2018;46(9):1411-20. [PubMed: 29979221]
Rockwood 2005
Rockwood, K. et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 173, 489-495, doi:10.1503/cmaj.050051 (2005).
Ronald 2019
Ronald L. Wasserstein, Allen L. Schirm & Nicole A. Lazar. Moving to a World Beyond “p < 0.05”, The American Statistician 2019, 73:sup1, 1-19
Ronchetti 2015
Ronchetti S, et al. GILZ as a Mediator of the Anti-Inflammatory Effects of Glucocorticoids. Front Endocrinol (Lausanne). 2015;6:170.
Rothwell 1991
Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991;337(8741):582-3. [PubMed: 1671944]
Ryan 2013
Ryan TP 2013. Sample Size Determination and Power. John Wiley & Sons. Hoboken, New Jersey.
Rygard 2018
Rygård SL, Butler E, Granholm A, Møller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Medicine 2018;44(7):1003-16. [PubMed: 29761216]
Saad 2017
Saad ED, Paoletti X, Burzykowski T, Buyse M. Precision medicine needs randomized clinical trials. Nat Rev Clin Oncol. 2017;14(5):317-323.
Semler 2018
Semler MW, Self WH, Wanderer JP, et al.: Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018; 378:829–839
Sharshar 2003
Sharshar T, Gray F, Lorin de la Grandmaison G, Hopkinson NS, Ross E, Dorandeu A, et al. Apoptosis of neurons in cardiovascular autonomic centres triggered by inducible nitric oxide synthase after death from septic shock. Lancet 2003;362(9398):1799-805. [PubMed: 14654318]
Sherwin 2012
Sherwin RL, Garcia AJ, Bilkovski R. Do low-dose corticosteroids improve mortality or shock reversal in patients with septic shock? A systematic review and position statement prepared for the American Academy of Emergency Medicine. Journal of Emergency Medicine 2012;43(1):7-12. [PubMed: 22221983]
Simon 2018
Simon N, Simon R. Using Bayesian modeling in frequentist adaptive enrichment designs. Biostatistics 2018;19(1):27-41.
Singer 2016

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-10. [PubMed: 26903338]
Stata 2015
Stata Statistical Software: Release 14 [Computer program]. StataCorp. 2015. College Station, TX: StataCorp LP, 2015.
Sterne 2020
Sterne JA , Murthy S, Diaz J, Slutsky AS, Villar J, Angus DC, Annane D, et al. Systemic Corticosteroids for Critically Ill Patients with COVID-19: A Prospective Meta-analysis of Randomized Clinical Trials. JAMA 2020 (in press).

Tavaré 2017
Tavaré A, O'Flynn N. Recognition, diagnosis, and early managementof sepsis: NICE guideline. British Journal of General Practice 2017;67(657):185-6. [PubMed: 28360070]
Tsao 2004
Tsao CM, Ho ST, Chen A, Wang JJ, Li CY, Tsai SK, et al. Low-dose dexamethasone ameliorates circulatory failure and renal dysfunction in conscious rats with endotoxemia. Shock 2004;21(5):484-91. [PubMed: 15087827]
Vachharajani 2006
Vachharajani V, Vital S, Russell J, Scott LK, Granger DN. Glucocorticoids inhibit the cerebral microvascular dysfunction associated with sepsis in obese mice. Microcirculation 2006;13(6):477-87. [PubMed: 16864414]
van der Poll 2017
van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nature Reviews. Immunology 2017;17(7):407-20. [PubMed: 28436424]
Varga 2008
Varga G, Ehrchen J, Tsianakas A, Tenbrock K, Rattenholl A, Seeliger S, et al. Glucocorticoids induce an activated, anti-inflammatory monocyte subset in mice that resembles myeloid-derived suppressor cells. Journal of Leukocyte Biology 2008;84(3):644-50. [PubMed: 18611985]
Venkatesh 2018
Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. New England Journal of Medicine 2018;378:797–808. [DOI: 10.1056/NEJMoa1705835; PubMed: 29347874]
Vincent 1996
Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Medicine 1996;22(7):707-10. [PubMed: 8844239]
Vincent 2013
Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet 2013;381(9868):774-5. [PubMed: 23472921]
WHO 2018
WHO. Improving prevention, diagnosis and clinical management of sepsis..
https://www.who.int/servicedeliverysafety/areas/sepsis/en/#.XAAf362Zqkk.mendeley. 2018 (Accessed 29 November 2018).
Wong 2011
Wong HR, Cvijanovich NZ, Allen GL, et al. Validation of a gene expression-based subclassificationstrategy for pediatric septic shock. Crit Care Med. 2011; 39(11):2511–2517. [PubMed: 21705885]
Wong 2015
Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. Am J Respir Crit Care Med. 2015;191(3):309-15.
Wong 2018
Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald JC, Checchia PA, Meyer K, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Lutfi R, Gertz S, Grunwell JR, Lindsell CJ. Endotype transitions during the acute phase of pediatric septic shock reflect changing risk and response. Crit Care Med 2018; 46(3): e242–e249. doi:10.1097/CCM.0000000000002932
Yang 2018
Yang T, Li Z, Jiang L, Xi X. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. Critical Care 2018;22(1):187. [DOI: 10.1186/s13054-018-2111-0; PubMed: 30075789]

15 List of addenda

15.1 LIST OF INVESTIGATORS

15.2 SERIOUS ADVERSE EVENTS NOTIFICATION FORM

15.3 PREGNANCY NOTIFICATION FORM

15.4 QUESTIONAIRE OR SCALE

15.4.1 Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA)

15.4.2 Charlson Comorbidity Index.

15.4.3 Clinical Frailty Scale.

15.4.4 EQ5D

15.4.5 Glascow coma scale

15.4.6 Muscular Disability Rating Scale (MDRS)

15. 4. 7 Adult cognitive function score (PROMIS)

15.5 ANNEXES

15.5.1 Annex 1 : Forest plots - Randomized controlled trials of corticosteroids for sepsis

15.5.2 Annex 2 : Unblinding of Clinical Site Personnel for Emergency Medical Management.

15.5.3 Annex 3 : SCRIPT FOR TELEPHONE INTERVIEW

15.5.4 Annex 4 : Plan for Discontinuation of the Study.

15.5.5 Annex 5 : Ventilator procedures

15.6 PATIENT CARD