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Rapid rEcognition of COrticosteRoiD resistant or sensitive Sepsis (RECORDS): study protocol for a Multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial.

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Abstract (231)

Introduction. Corticosteroids affect variably survival in sepsis trials, suggesting heterogeneity in patients' response to corticosteroids. The RECORDS trial aimed at defining endotypes associated with adults with sepsis responsiveness to corticosteroids.

Methods and analysis. RECORDS a multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial will randomly assigned to a biomarker stratum 1800 adults with community acquired pneumonia, vasopressor dependent sepsis, septic shock, or Acute Respiratory Distress Syndrome. In each stratum, patients will be randomly assigned to receive a 7-day course of hydrocortisone and fludrocortisone or their placebos. COVID-19 patients be treated with a 10-day standard course of dexamethasone and randomized to fludrocortisone or its placebo. Primary outcome will be 90-day death or persistent organ dysfunction. Large simulation study will be performed across a range of plausible scenarios to foresee power to detect a 5-10% absolute difference with corticosteroids. We will assess subset-by-treatment interaction by estimating in a Bayesian framework two quantities: (i) measure of influence, relying on the value of the estimation of corticosteroids effect in each subset, and (ii) measure of interaction.

Ethics and dissemination. The protocol was approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020. Trial results will be disseminated at scientific conferences and results will be published in peer reviewed journals.

Registration. ClinicalTrials.gov number NCT04280497.

Protocol version N°5.2 dated 15/09/2021

Key words: adults, precision medicine, community acquired pneumonia, ARDS, sepsis, endotypes, multiomics, biomarkers

Words count: 3890

Article summary

Strengths and limitations of this study

- Increasing evidence suggests heterogeneity in the response to corticosteroids among patients with sepsis, that might be unmasked by endotyping individual immune response to infection.
- So far, there are no data from randomized trial evaluating endotypes-guided corticotherapy in patients with sepsis.
- This protocol shows the methodology of an adaptive trial integrating and evaluating novel biomarkers stemming from bench-side and in silico research.
- The RECORDS trial will provide the first data from adequately powered randomized trial of the value of biomarkers, including serum levels of proteins, cellular markers, and multi-omics, and of intelligent algorithms to identify the best sepsis population to be selected for corticotherapy and those who should not be treated with corticosteroids.

Introduction

The World Health Organization (WHO) identified sepsis as a high priority condition due to its incidence (~49 million cases/year), mortality (~11 million fatalities/year) and morbidity (cognitive decline at 5 years in up to half of survivors).[1] Dysregulated immune and endogenous cortisol responses to infection are hallmarks of sepsis, requiring prompt source control, anti-infective treatment, and cardiorespiratory management. Both overwhelming systemic inflammation and impaired endogenous cortisol response to infection are improved by the administration of corticosteroids.[2] Evidence from 61 trials accounting for 12,192 patients, including both children and adults with sepsis, suggested that corticosteroids saved 1 additional life every 33 treated patients.[3] There was no evidence of any difference in corticosteroids effects on survival between children and adults (Chi2 = 0.29; df = 1; P = 0.62; I2 = 0%), between uncomplicated sepsis, septic shock, ARDS, and CAP (Chi2 = 7.60; df = 3; P = 0.06; I2 = 60.5%). International guidelines (panel including consumers) recommended administrating corticosteroids in sepsis.[4] Likewise, the WHO recommended treatment with corticosteroids for COVID-19 patients requiring respiratory support, in keeping with results from the RECOVERY trial.[5] However, survival benefits of corticosteroids varied across trials highlighting the need to identify optimal target populations for corticosteroids.[6-9] The effects of corticosteroids on survival from sepsis are independent of age, gender, disease severity, type or source of infection, or type of pathogen.[3] No reliable, routinely available diagnostic test predicts the response to corticosteroids in sepsis. Nevertheless, preliminary studies in adults[10] and children with sepsis[11] suggested that transcriptomic signatures may be associated with increased mortality in corticosteroids treated patients. Additionally, machine learning derived for individual prediction outperformed one size-fits-all decisions of hydrocortisone treatment in

septic shock.[12] Theoretically, survival benefits related to the administration of corticosteroids require (i) hyperinflammation in response to an infection and (ii) intact cellular mechanisms enabling corticosteroid bioactivity.[2] Both hyperinflammation and cellular mechanisms enabling corticosteroid bioactivity are potential biomarkers of corticosteroid sensibility or resistance.

The RECORDS trial aims at identifying biomarkers defining sepsis populations who may either benefit or be harmed by corticotherapy. Biomarkers assessed in this trial are selected through analysis of biological and clinical data previously obtained[17] and from the observational period of the current trial.

Methods and analysis

Study design and oversight

The study is divided into two distinctive stages, e.g. a run-in prospective observational cohort followed by a biomarker-guided adaptive randomized controlled trial. As per request from the French National Agency for Drug Safety, randomization is first stratified by SARS-CoV-2 status (see figure 1). Patients tested positive for SARS-CoV-2 patients are randomized in a one-step process to receive either dexamethasone and fludrocortisone or dexamethasone and fludrocortisone placebo. Patients tested negative for SARS-CoV-2 patients are randomly assigned to a biomarker/signature and then randomized for hydrocortisone (HC) and fludrocortisone (FC) or their respective placebos. Patients positive to influenza or other respiratory viruses are not mandatorily assigned to the arms corresponding to their infections (Influenza (+) or other

respiratory viruses (+)) as they are randomly assigned to any biomarker/signature arms of the two-step randomization (see figure 1).

The protocol and qualification of all investigators were approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020 and by the French National Agency for Drug Safety (ANSM, France) on April 9, 2020. Inclusion in the observational part of the trial started on April 10, 2020 in 19 centers in France. The interventional part of the trial started on June 10, 2021, in 20 centers nationwide. Recruitment is expected to be completed by December 2024.

Informed written consent of the patient is to be obtained prior to any act relating to the study. Whenever the patients are unable to consent themselves, consent of a legally authorized representative is sought (France, art. L 1122-1 CSP). The ethics committee allowed for deferred consent when no legally authorized representative is available.

A data safety and monitoring board (DSMB) including experts in intensive care and in infectious diseases, was set up before recruitment of the first patient. DSMB members have full access to the raw data of the trial and meet on a regular basis.

Data monitoring is performed by the sponsor (Assistance Publique-Hôpitaux de Paris *AP-HP, Paris Ile-de-France Ouest Clinical Trial Unit, URC HUPIFO*). The sponsor has full access to patients' charts and checks for accuracy all data recorded onto the electronic case report form (eCRF). Data management is performed by the sponsor.

The Biological Resource Centre of the Raymond Poincaré Hospital (APHP), provides centers with sample kits for biomarker measurements, collects and stores samples obtained from centers.

A central pharmacy (Agence Générale des Equipements et Produits de Santé, AGEPS) labels study drugs and ships them to participating centers. Unused drugs are destroyed by local pharmacist.

The trial is registered at ClinicalTrials.gov under number NCT04280497.

Data access: trial's investigators will have access to all trial's data and will vouch for the integrity of the data. Data will be shared within 6 months of the publication of the results of the primary analysis after trial completion. To access data third party will have to sign with the trial sponsor a data sharing agreement.

Study Participants: recruitment strategy, inclusion and exclusion criteria, conduct of the trial

Inclusion criteria

ICU patients aged ≥18 years will be eligible for inclusion into the trial if they meet all of the following criteria: 1) proven or suspected infection as the main diagnosis, 2) Community Acquired Pneumonia (CAP) related sepsis, or vasopressor-dependent sepsis, or septic shock[13] or Acute Respiratory Distress Syndrome (ARDS)[14], 3) tested for one or more trial-specific biomarkers (see figure 1), 4) affiliated to the French social security or benefiting from universal health coverage. Patients under guardianship or curatorship may be included.

Exclusion criteria

Patients will not be eligible for the trial if they meet at least one of the following criteria: 1) expected death or withdrawal of life-sustaining treatments within 48 hours, 2) previously enrolled in the study, 3) formal indication for corticosteroids according to most recent international guidelines, 4) vaccination with live virus within the past 6 months, 5) hypersensitivity to

hydrocortisone or fludrocortisone or (microsined betamethasone dipropionate) or any of their excipients (SPC), 6) pregnancy, women of childbearing potential not using contraception, 7) nursing women.

Study measurements and procedures (table 1)

Screening visit

After obtaining consent, the screening visit is performed in order to confirm inclusion and exclusion criteria and collect 1) patient demographics, 2) characteristics of infection, 3) severity of illness (SAPS II and SOFA score), 4) pre-existing comorbidities as defined by the Charlson comorbidity index, Clinical Frailty Scale, 5) core temperature and vital signs, 6) central hemodynamic data, 7) standard laboratory data including serum and urinary electrolytes, creatinine, urea, cholesterol, triglycerides and glucose levels, arterial lactate levels, arterial oxygen tension, hemoglobin oxygen saturation, arterial pH, white blood cell count, hemoglobin and hematocrit levels, INR, platelet count, total bilirubin level, microbiology and virology, results of the ACTH test, 8) measurement of biomarkers (serum endocan, monocytes expression of glucocorticoid induced leucine zipper (GILZ) and of dual specificity protein phosphatase 1 (DUSP-1), monocyte distribution width (MDW), and blood genomic, transcriptomic and metabolomic measurements, exhaled air metabolomic) 9) interventions including mechanical ventilation, renal replacement therapy, vasopressors, administration of open label corticosteroid, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials, 10) results of the skin vasoconstrictor response to glucocorticoids. The screening visit ends with the randomization of eligible patients within 24 hours of obtaining the results of intelligent algorithms and biomarkers.

Table 1: Data collection and conduct of the trial

Variables/Visits	Daily data until ICU discharge or 90 days (whichever occurs first)	Specific measures at day 1 & 7	Last study visit (90- and 180-day data)
Vital status	X		X
Location (ICU/date of discharge), hospital ward/date of discharge, rehabilitation centre, long-term facility, home/date of discharge			X
Protocol adherence (receipt of every IMP dose until treatment completion)	X		X
Co-interventions (mechanical ventilation, renal replacement therapy, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, & antimicrobials)	X		X
Core temperature (daily lowest & highest value)	X		X
Vital signs (lowest & highest values for heart rate, systolic & diastolic blood pressure)	X		X
Central hemodynamic data	X		

Standard laboratory data (serum and urinary electrolytes, creatinine, urea, cholesterol, triglycerides & glucose levels, arterial lactate levels, arterial oxygen tension& hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin & hematocrit levels, INR, platelet count, total bilirubin level)	X		
Microbiological or virological samples		X	
Other sampling left at the physicians' discretion	X		
Whole blood samples for measurements of biomarkers		X	
Glasgow coma scale Cognitive function			X
Muscular Disability Rating Scale (MDRS) score			X
Health-Related Quality of Life (HRQoL, EQ-5D-5L)[20]			X
PROMIS® (Fatigue 13a, Ability to participate in social roles and activities 8a, Physical function 8b, Emotional distress-Depression 8b, Emotional distress-Anxiety 8a, Cognitive function 8a)			X

Endotyping

Candidate biomarkers are selected from: 1) signatures described in the literature, 2) biomarkers identified from RECORDS data obtained in the observational period of the study and 3) any national and/or international guidelines (figure 2). At the onset of the trial, 13 biomarkers/signatures had been identified. In the COVID-19 stratum, patients will be randomized in a single step (figure 1) to receive dexamethasone 6mg per day for 10 days[5] combined with fludrocortisone or its placebo. The added value of a drug exhibiting a mineralocorticoid activity is worth evaluating in view of the role of the angiotensin-converting enzyme 2 receptor and endothelial dysfunction in the pathogenesis of COVID-19.[15] The Influenza virus and non-Influenza respiratory virus strata aim at filling the evidence gap related to the lack of randomized trial having assessed corticotherapy in viral pneumonia related sepsis.[16] The CIRCI (Critical Illness-Related Corticosteroid Insufficiency) stratum is defined by baseline total cortisol of 10µg/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 cosyntropin.[17] Endocan is an endothelial peptidoglycan that contributes to regulate inflammation by counteracting leukodiapesis, a key target for corticosteroids.[18] We identified serum levels of endocan below 12.8ng/ml as a marker of hyperinflammation in the run-in period of RECORDS trial. The Monocyte Distribution Width (MDW) stratum is defined by MDW >25.[19] The lymphocytes count stratum is defined by lymphocyte count below $870x10^3$/ml, according to a recent study suggesting that lymphopenia was associated with corticosteroids resistance.[19] The Transcriptomic Sepsis Response Signature (SRS) stratum is based on two distinct signatures suggesting immune suppression (SS1) and relative immune competency (SRS2).[20] Using generalized linear model based on a set of seven genes (DYRK2, CCNB1IP1, TDRD9, ZAP70, ARL14EP, MDC1, and ADGRE3), hydrocortisone may

be associated with increased mortality in SRS2 patients.[10] The endotype A/B stratum is based on transcriptomic analysis of 100 genes reflecting the adaptive immunity and glucocorticoid receptor signaling. In children with sepsis, two distinct endotypes were identified, endotype A characterized by immune suppression and a higher risk for mortality when compared to endotype B.[21] The Glucocorticoid-Induced Leucine Zipper (GILZ) and Dual Specificity Phosphatase 1 (DUSP-1) strata are defined by reduced expression of GILZ and DUSP-1 by unstimulated isolated circulating monocytes. GILZ[22] and DUSP-1 are key endogenous regulators of the immune response. Preliminary data from the observational period of RECORDS suggested an association between the spontaneous expression of GILZ and of DUSP-1 and increased mortality in serious COVID-19 (unpublished). The cutaneous vasoconstrictor response to glucocorticoids stratum is defined according to previous report in asthma.[23] Briefly, the test is performed by applying 30µg/ml betamethasone to the skin of the forearm. The degree of skin blanching is assessed after 12h of exposure with a score ranging from 0 to 4; 0 no skin blanching, 1 skin blanching is less than 50% of the area of application, 2 skin blanching is more than 50% of the area of application, 3 if blanching recovers the whole area of application, and 4 if blanching expands beyond the area of application. A score of 2 or less indicates resistance to corticosteroids. A photography of the forearm restricted to the tested skin area will be recorded. The intelligent algorithms strata include two algorithms one developed through machine learning[12] and another one using other machine learning modeling approaches (unpublished), both being embedded into the eCRF.

Follow-up

All patients are followed-up at 3 and 6 months from randomization. The details of follow-up are given in table 1.

Vital status by day 90 after randomization will be collected from the medical file and/or through phone calls with patients or their legal representative.

Outcomes

The primary outcome assessed at 90 days, is a composite of death or persistent organ dysfunction – defined as SOFA score >6 and a continued dependency on either mechanical ventilation, new renal replacement therapy, or vasopressors.[8,24] The primary endpoint is a binary variable. Patients will be classified as a success if they are alive on day 90 and free of vasopressor therapy, mechanical ventilation, renal replacement therapy, and organ dysfunction. Patients will be classified as a failure if they either died within 90 days of randomization or if they remained dependent on either vasopressor, mechanical ventilation, RRT, or exhibited a SOFA score >6.

Secondary outcomes include: 1) Mortality at 7, 14 and 28 days and 6 months; 2) Vasopressor free days: defined as the number of days with permanent hemodynamic stability in the absence of any vasopressor agent including norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin or its analogs. When a patient dies while receiving vasopressors, the number of vasopressor free days is arbitrarily set at 0; 3) Mechanical ventilation free days: defined as the number of days with permanent appropriate oxygenation while the patient is extubated and breathing spontaneously, i.e. no need for non-invasive ventilation, high flow oxygen or continuous positive airway pressure (CPAP). Other uses of non-invasive ventilation (e.g., chronic night-time use for chronic obstructive pulmonary disease) are not compatibilized. When a patient dies while receiving mechanical ventilation or is discharged home while receiving mechanical ventilation, the number of mechanical ventilation free days is arbitrarily set at 0; 4) Organ dysfunction free days: Organ

function (including renal function) will be assessed using the SOFA score.[25] Organ dysfunction will be defined by a SOFA score > 6.[8] Organ dysfunction free days is defined by the number of days with a total SOFA score of 6 or less. When a patient dies before the SOFA decreased to 6 or less, the number of organ dysfunction free days is arbitrarily set at 0; 5) 6-month HRQoL in survivors assessed using the EQ-5D-5L.[26] This standardised questionnaire was developed to provide a simple, generic measure of health for clinical and economic appraisal. It is made up of two components: health status description and health status self-assessment. Health status is assessed using five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Health status self-assessment reports on patients overall health status using a visual analogue scale; 6) Fatigue, ability to partake in social activities, physical function, emotional distress, depression, anxiety and cognitive function are assessed using the PROMIS short form questionnaire 7) Proportion of patients with a decision to withhold and/or withdraw active treatments; 8) ICU and hospital length of stay; 9) Rate of ICU re-admission up to 180 days after randomization.

Safety endpoints include: proportion of patients affected by any serious adverse event associated with corticosteroids, 1) hospital-acquired infection (CDC. Healthcare-Associated Infections (HAIs) progress report. 2020) within 90 days of randomization, 2) hyperglycemia (blood glucose level >150mg/dl) and hypernatremia (serum sodium > 145 mmol/L) during the ICU stay (or up to day 90, whichever occurs first), 3) Gastroduodenal bleeding requiring transfusion or hemostatic treatment during the ICU stay (or up to day 90, whichever occurs first), 4) neurological disorder (coma, stroke or muscle weakness, as defined below) up to 180 days from randomization. Coma is defined by a Glasgow coma score <8 in the absence of sedation. Neuromuscular sequelae are

assessed using 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.

Randomization

Timing of randomization

The period from inclusion to randomization, including the period of laboratory testing for biomarkers, should not exceed 24 hours.

Generation of the randomization list

A computer process is used to generate allocation sequences in a 1:1 ratio, independently from Healthcare staff, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, or the data analyst.

Allocation concealment

Randomization will be concealed by being centralized and performed with an internet-centralized service running 24/7 imbedded in the electronic Case Report Form (eCRF). Healthcare staff, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, and the data analyst will be blinded to treatment allocation. Only the central pharmacist, from the General Agency of Equipment and Health Products (AGEPS – APHP) will be unblinded.

Allocation of stratification

Stratification is randomly performed amongst all assessed biomarkers for each patient. The randomization algorithm runs separately while communicating with the eCRF. Data related to

biomarker results, virology results and input required for determining intelligent algorithm are sent to the randomization algorithm. The result of a single biomarker is sufficient to run the randomization algorithm. Within the randomly selected biomarker strata, the randomization algorithm then determines the assigned treatment arm: hydrocortisone and fludrocortisone versus their respective placebos. COVID-19 patients are all treated with dexamethasone and randomly assigned to receive fludrocortisone or its placebo.

Interventions

Experimental treatments

Investigational medicinal products are presented in numbered boxes, labelled for this study according to the Good Manufacturing Practices under the responsibility of AGEPS. Each numbered box contains enough corticosteroids or placebo to fully treat one patient. A drug box contains 30 vials of hydrocortisone 100mg or placebo and 1 blister of 10 tablets of fludrocortisone 50µg or placebo.

Hydrocortisone hemisuccinate (SERB, Paris) or its placebo is administered as a 50mg intravenous bolus every 6 hours for seven days. Fludrocortisone or its placebo (HAC Pharma, Caen) is administered as a 50µg tablet via a nasogastric tube once a day in the morning, for seven days. COVID-19 patients are to be treated with open label dexamethasone (6mg) once a day over 10 days and 50µg fludrocortisone or its placebo (HAC Pharma, Caen) via a nasogastric tube, once a day in the morning, for seven days.

Allowed co-interventions

Treatments are allowed according to best practice guidelines.[27] These treatments may include, mechanical ventilation, renal replacement therapy, vasopressor therapy, thiamine, nutrition therapies including multivitamins, intravenous fluids, blood products, sedatives, and antimicrobials. We will carefully record the use of these treatments.

Forbidden interventions

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 occurs after randomization (e.g. autoimmune disease), the patient should be treated. In this case, study treatments are to be suspended to avoid the administration of unnecessarily high-dose of hydrocortisone. However, short-duration administration of open-labelled corticosteroids is allowed for prevention of post-extubation laryngeal edema.

Continuous infusion of neuromuscular blocking agents is to be avoided. Whenever neuromuscular blocking drugs are mandatory (e.g. for severe ARDS), it should be interrupted every 12 hours to avoid prolonging the treatment longer than necessary.

Statistical analysis

A full statistical analysis plan will be reported in a separate paper.

Sample size

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. In a recent study,[8] the number of vasopressor-free days at day 28 with

hydrocortisone+fludrocortisone was 17.1±10.8 versus 15.0 ± 11.1 in placebos. 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[28]; estimated here at a multiple of fourfold; therefore, to handle potential dropouts, a sample was estimated at 1800 patients. Bayesian inference will be used for sequential analyses.

To detect a 10% absolute risk reduction from 45% to 35% in 90-day all-cause mortality,[8] a sample size of 373 evaluable patients per arm (thus a total of 746 patients) is required to reach 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.

Performance of the Bayesian design

To restrict inclusion to patients most likely to benefit from corticosteroids during trial accrual, an enrichment design will be used, based on treatment-by-subset interaction. Two main objectives will be considered: (1) To estimate corticosteroid marginal effect; and (2) To test for heterogeneity across subsets. We previously reported that this strategy successfully selected patients sensitive to treatment and discarded the less sensitive ones.[29] Performance of design will be challenged using a large simulation study performed across a range of plausible scenarios to foresee power to detect

a 5-10% absolute difference with corticosteroids, considering a fixed sample size of 1800 patients, several sizes of each subset, under several scenarios of treatment effect and interaction.

Data analysis

All patients, whatever their biomarker status will be randomized across the two treatment groups. Statistical analysis will be conducted using "biomarker-by-treatment interaction" with separate tests, given the high number of potential biomarkers of interest. This is also referred to as "separate randomization designs" and "separate by treatment interaction designs". The analysis plan will be based on separate estimation of corticosteroid effect in each biomarker-defined subgroup to detect treatment by subgroup interactions. It will determine whether corticosteroid effect differs according to each biomarker, assessed through an interaction measure. We will assess subset-by-treatment interaction by estimating two quantities: (i) measure of influence (efficacy), relying on the value of the estimation of corticosteroids effect in each subset, and (ii) measure of interaction (based on the ratio of the estimated effect in both subsets).[30] In a Bayesian setting, the two criteria can be expressed as posterior probabilities related to the comparison of outcomes across the arms and/or the subsets. This analysis will be performed only for biomarkers with at least 100 available measures.

Role of funding source

The sponsor has no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication

Ethics and dissemination

RECORDS is funded by public grants "Programme d'Investissements d'Avenir" (PIA), reference ANR-18-RHUS-0004 and Programme Hospitalier de Recherche Clinique (PHRC), reference PHRC-20-0778. The protocol was approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020 and by the French National Agency for Drug Safety (ANSM, France) on April 9, 2020. Trial results will be disseminated at relevant clinical conferences and societies, published in peer-reviewed journals

Patients and Public Involvement

The trial protocol will be discussed with France Sepsis Association (an association of patients who recover from sepsis and families of patients who had sepsis) and trial findings will be shared with this entity.

Discussion

RECORDS is the first multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial aimed at discovering signatures enabling administration of hydrocortisone plus fludrocortisone in patients with sepsis and determining the best chance for improved outcome with minimal risk of harm. RECORDS trial relies on the concept that benefit to risk balance of corticosteroids is greater when given to patients with sepsis and evidence of hyperinflammation and intact corticosteroids related intracellular signaling. The RECORDS trial also hypothesizes that different clinical phenotypes of sepsis, i.e. CAP related sepsis, septic shock, or sepsis related ARDS, bacterial or viral sepsis, may share common signatures relevant to corticosteroids responsiveness. The study design is highly innovative integrating a broad range of candidate biomarkers from multi-omics signatures to intelligent algorithms. Candidate biomarkers are to be

selected from various sources including peer-reviewed literature and from our own consortium, thanks to the translational research program embedded into the RECORDS trial. The adaptive design of the study is a clear strength insomuch as unsatisfying biomarkers may rapidly be phased out and new biomarkers may be phased in. All assessed biomarkers must provide readily available results within 24 hours, meaning that the findings of the current trial will be easily translated into clinical practice. We must acknowledge some limits to the current trial including the fact that some complex biomarkers may not be available at all participating centers.

RECORDS trial is a major step in the implementation of precision medicine in sepsis. Indeed, personalized corticosteroid treatments for sepsis, may decrease the burden related to corticosteroids complications by avoiding exposure of patients unlikely to respond to this treatment.

Authors' contributions:

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

Declaration of interest: all authors declare to have no conflict of interest to disclose

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Legends for figures

Figure 1. Study flow chart describing the process of recruitment and randomization.

Artificial Intelligence (AI), Critical Illness-Related Corticosteroid Insufficiency (CIRCI), Dual Specificity Phosphatase 1 (DUSP-1), Fludrocortisone (FC), Glucocorticoid-Induced Leucine Zipper (GILZ), Hydrocortisone (HC), Monocyte Distribution Width (MDW), Respiratory (Resp.), Sepsis Response Signature (SRS).

Figure 2. Flow diagram describing the potential addition and subsequent validation of biomarkers during the trial

Figure 1 Study flow chart describing the process of recruitment and randomization.

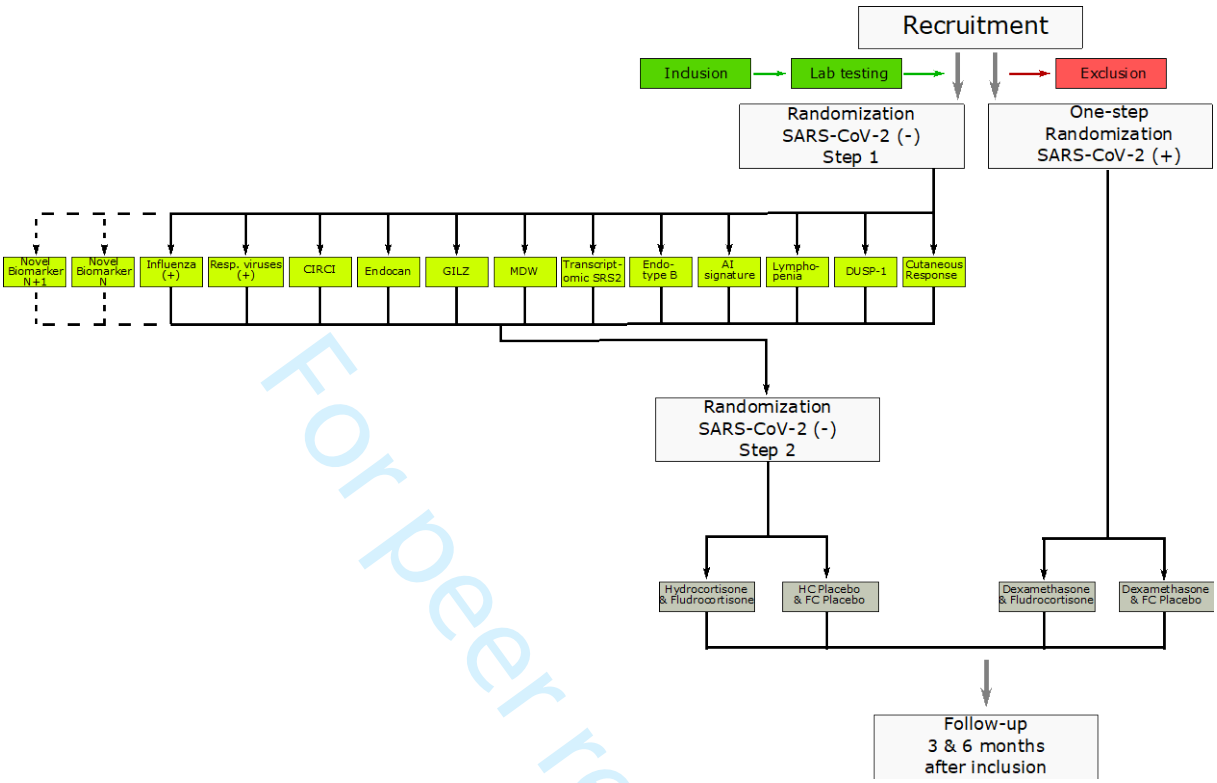
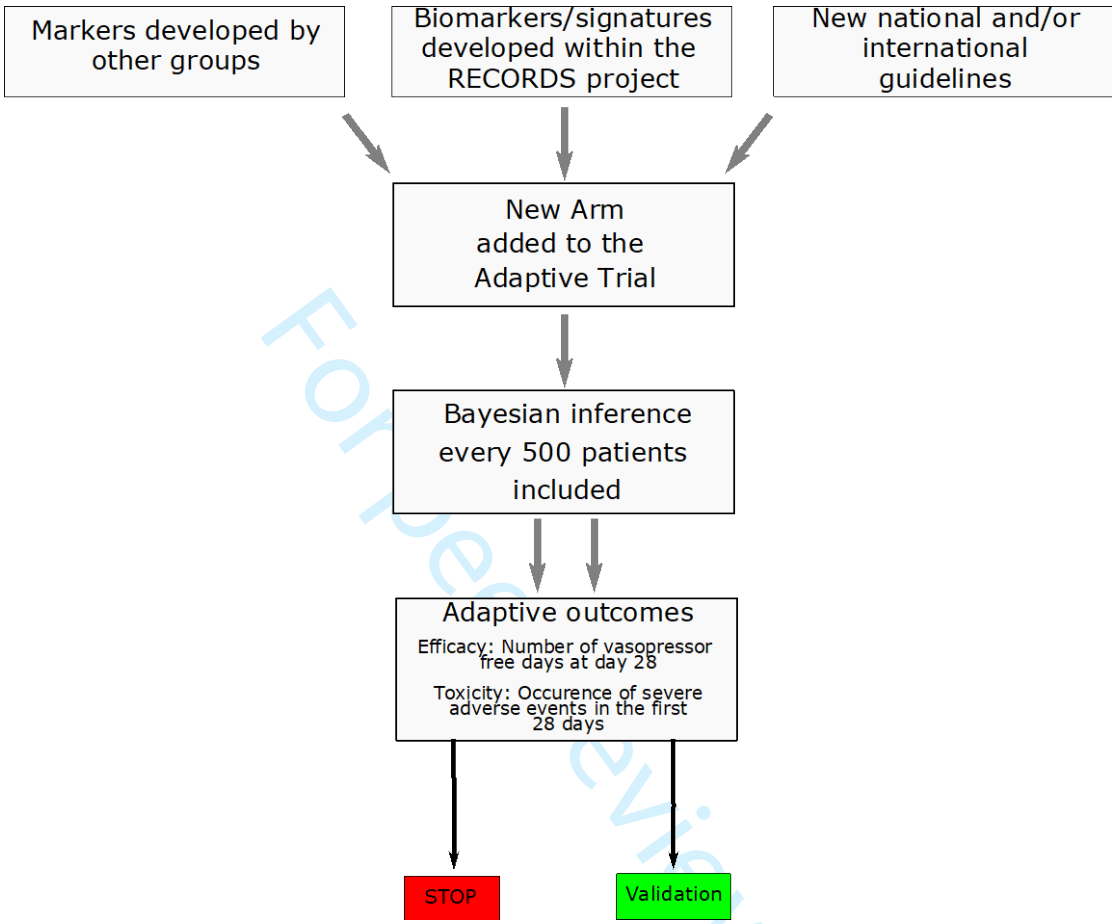


Figure 2 Flow diagram describing the potential addition and subsequent validation of biomarkers during the trial



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Rapid rEcognition of COrticosteRoiD resistant or sensitive Sepsis (RECORDS): study protocol for a Multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial.

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Rapid rEcognition of COrticosteRoiD resistant or sensitive Sepsis (RECORDS): Study protocol for a Multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial.

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Abstract (216)

Introduction. Corticosteroids affect variably survival in sepsis trials, suggesting heterogeneity in patients' response to corticosteroids. The RECORDS trial aimed at defining endotypes associated with adults with sepsis responsiveness to corticosteroids.

Methods and analysis. RECORDS a multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial will randomly assigned to a biomarker stratum 1800 adults with community acquired pneumonia, vasopressor dependent sepsis, septic shock, or Acute Respiratory Distress Syndrome. In each stratum, patients will be randomly assigned to receive a 7-day course of hydrocortisone and fludrocortisone or their placebos. COVID-19 patients be treated with a 10-day standard course of dexamethasone and randomized to fludrocortisone or its placebo. Primary outcome will be 90-day death or persistent organ dysfunction. Large simulation study will be performed across a range of plausible scenarios to foresee power to detect a 5-10% absolute difference with corticosteroids. We will assess subset-by-treatment interaction by estimating in a Bayesian framework two quantities: (i) measure of influence, relying on the value of the estimation of corticosteroids effect in each subset, and (ii) measure of interaction.

Ethics and dissemination. The protocol was approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020. Trial results will be disseminated at scientific conferences and results will be published in peer reviewed journals.

Registration. ClinicalTrials.gov number NCT04280497.

Protocol version N°7.0 dated 11/01/2023

Key words: adults, precision medicine, community acquired pneumonia, ARDS, sepsis, endotypes, multiomics, biomarkers

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Article summary

Strengths and limitations of this study

- Observational period providing preliminary clinical and biological data.
- Ongoing basket adaptative trial integrating biomarkers and signatures, designed to personalize corticosteroid therapy in sepsis.
- Patients free of COVID19 and Influenza are stratified by biomarker/signature and are randomized to receive either combined glucocorticoid (hydrocortisone, or if SARS-CoV-2 positive, open-label dexamethasone) and mineralocorticoid (fludrocortisone) or placebo.
- New biomarkers or signatures are continuously included and assessed in the trial.
- Sequential intermediate analyses using a Bayesian model aimed at identifying relevant predictive biomarkers.

Introduction

The World Health Organization (WHO) identified sepsis as a high priority condition due to its incidence (~49 million cases/year), mortality (~11 million fatalities/year) and morbidity (cognitive decline at 5 years in up to half of survivors).[1] Dysregulated immune and endogenous cortisol responses to infection are hallmarks of sepsis, requiring prompt source control, anti-infective treatment, and cardiorespiratory management. Both overwhelming systemic inflammation and impaired endogenous cortisol response to infection are improved by the administration of corticosteroids.[2] Evidence from 61 trials accounting for 12,192 patients, including both children and adults with sepsis, suggested that corticosteroids saved 1 additional life every 33 treated patients.[3] There was no evidence of any difference in corticosteroids effects on survival between children and adults (Chi2 = 0.29; df = 1; P = 0.62; I2 = 0%), between uncomplicated sepsis, septic shock, ARDS, and CAP (Chi2 = 7.60; df = 3; P = 0.06; I2 = 60.5%). International guidelines (panel including consumers) recommended administrating corticosteroids in sepsis.[4] Likewise, the WHO recommended treatment with corticosteroids for COVID-19 patients requiring respiratory support, in keeping with results from the RECOVERY trial.[5] However, survival benefits of corticosteroids varied across trials highlighting the need to identify optimal target populations for corticosteroids.[6-9] The effects of corticosteroids on survival from sepsis are independent of age, gender, disease severity, type or source of infection, or type of pathogen.[3] No reliable, routinely available diagnostic test predicts the response to corticosteroids in sepsis. Nevertheless, preliminary studies in adults[10] and children with sepsis[11] suggested that transcriptomic signatures may be associated with increased mortality in corticosteroids treated patients. Additionally, machine learning derived for individual prediction outperformed one size-fits-all decisions of hydrocortisone treatment in

septic shock.[12] Theoretically, survival benefits related to the administration of corticosteroids require (i) hyperinflammation in response to an infection and (ii) intact cellular mechanisms enabling corticosteroid bioactivity.[2] Both hyperinflammation and cellular mechanisms enabling corticosteroid bioactivity are potential biomarkers of corticosteroid sensibility or resistance.

The RECORDS trial aims at identifying biomarkers defining sepsis populations who may either benefit or be harmed by corticotherapy. Biomarkers assessed in this trial are selected through analysis of biological and clinical data from a previous cohort,[8] from the observational period of this current trial and from any relevant newly reported cohort.

Methods and analysis

Study design and oversight

The study is divided into two distinctive stages, e.g. a run-in prospective observational cohort followed by a biomarker-guided adaptive randomized controlled trial. As per request from the French National Agency for Drug Safety, randomization is first stratified by SARS-CoV-2 status (see figure 1). Patients tested positive for SARS-CoV-2 patients are then randomized with a 1:1 allocation ratio to receive either dexamethasone and fludrocortisone or dexamethasone and fludrocortisone placebo. Subsequently, patients tested negative for SARS-CoV-2 are tested for influenza. Patients tested positive for Influenza are then randomized for treatment (hydrocortisone (HC) and fludrocortisone (FC) or their respective placebos). Patients negative for SARS-CoV-2 and Influenza are first randomly assigned to a biomarker/signature stratum among all the biomarkers/signatures available at the time of randomization for the patient; then, those patients

are randomized with a 1:1 allocation ratio to either HC and FC or their respective placebos, using the randomization list from this stratified biomarker/signature result. Patients positive to other respiratory viruses are not mandatorily assigned to the arms corresponding to their infections (other respiratory viruses (+)) as they are randomly assigned to any biomarker/signature arms of the two-step randomization (see figure 1 and "Allocation of stratification" section below).

The protocol and qualification of all investigators were approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020 and by the French National Agency for Drug Safety (ANSM, France) on April 9, 2020. Inclusion in the observational part of the trial started on April 10, 2020 in 19 centers in France and ended on June 10, 2021 with last patient follow-up on December 2021. The interventional part of the trial started on June 10, 2021, in 20 centers nationwide. Recruitment is expected to be completed by first trimester of 2025. Follow-up of the last patient is expected to be completed by last trimester of 2025.

Informed written consent of the patient is to be obtained prior to any act related to the study. Whenever the patients are unable to consent themselves, consent of a legally authorized representative is sought (France, art. L 1122-1 CSP). Whenever the patient is unable to consent and in the absence of a legally authorized representative, the ethics committee allowed for consent to be waived. Deferred consent or consent of a legally authorized representative is to be obtained for the continuation of the study procedures and utilization of patient's data and biological samples.

A data safety and monitoring board (DSMB) including experts in intensive care and in infectious diseases, was set up before recruitment of the first patient. DSMB members have full access to the raw data of the trial and meet on a regular basis.

Data monitoring is performed by the sponsor (Assistance Publique-Hôpitaux de Paris *AP-HP, Paris Ile-de-France Ouest Clinical Trial Unit, URC HUPIFO*). The sponsor has full access to patients' charts and checks for accuracy all data recorded onto the electronic case report form (eCRF). Data management is performed by the sponsor.

The Biological Resource Centre of the Raymond Poincaré Hospital (APHP), provides centers with sample kits for biomarker measurements, collects and stores samples obtained from centers.

A central pharmacy (Agence Générale des Equipements et Produits de Santé, AGEPS) labels study drugs and ships them to participating centers. Unused drugs are destroyed by local pharmacist.

The trial is registered at ClinicalTrials.gov under number NCT04280497.

Data access: trial's investigators will have access to all trial's data and will vouch for the integrity of the data. Data will be shared within 6 months of the publication of the results of the primary analysis after trial completion. To access data third party will have to sign with the trial sponsor a data sharing agreement.

Study Participants: inclusion and exclusion criteria, conduct of the trial

Inclusion criteria

ICU patients aged ≥18 years will be eligible for inclusion into the trial if they meet all of the following criteria: 1) proven or suspected infection as the main diagnosis (Sepsis-3 definition)[13], 2) Community Acquired Pneumonia (CAP, as defined by the IDSA/ATS CAP severity criteria, table 1 of Metlay et al., 2019[14]), or vasopressor-dependent sepsis (require vasopressor to maintain mean blood pressure of 65 mmHg and lactate level of < 2 mmol/L), or septic shock[13] or infection-triggered Acute Respiratory Distress Syndrome (ARDS, Berlin definition)[15]), 3) tested for one or

more trial-specific biomarkers (see figure 1), 4) affiliated to the French social security or benefiting from universal health coverage. Patients under guardianship or curatorship may be included.

Exclusion criteria

Patients will not be eligible for the trial if they meet at least one of the following criteria: 1) expected death or withdrawal of life-sustaining treatments within 48 hours, 2) previously enrolled in the study, 3) formal indication for corticosteroids according to most recent international guidelines, 4) vaccination with live virus within the past 6 months, 5) hypersensitivity to hydrocortisone or fludrocortisone or (microsined betamethasone dipropionate) or any of their excipients (SPC), 6) pregnancy, women of childbearing potential not using contraception, 7) nursing women.

Study measurements and procedures

Initial study visit

After obtaining consent, a study visit is performed in order to collect 1) patient demographics, 2) characteristics of infection, 3) severity of illness (SAPS II and SOFA score), 4) pre-existing comorbidities as defined by the Charlson comorbidity index, Clinical Frailty Scale, 5) core temperature and vital signs, 6) central hemodynamic data, 7) standard laboratory data including serum and urinary electrolytes, creatinine, urea, cholesterol, triglycerides and glucose levels, arterial lactate levels, arterial oxygen tension, hemoglobin oxygen saturation, arterial pH, white blood cell count, hemoglobin and hematocrit levels, INR, platelet count, total bilirubin level, microbiology and virology, results of the ACTH test, 8) measurement of biomarkers (serum endocan, monocytes expression of glucocorticoid induced leucine zipper (GILZ) and of dual

specificity protein phosphatase 1 (DUSP-1), monocyte distribution width (MDW), and blood genomic, transcriptomic and metabolomic measurements, exhaled air metabolomic) 9) interventions including mechanical ventilation, renal replacement therapy, vasopressors, administration of open label corticosteroid, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, and antimicrobials, 10) results of the skin vasoconstrictor response to glucocorticoids. The screening visit ends with the randomization of eligible patients within 24 hours of obtaining the results of intelligent algorithms and biomarkers.

Endotyping

In the COVID-19 stratum, patients will be randomized in a single step (figure 1) to receive dexamethasone 6mg per day for 10 days[5] combined with fludrocortisone or its placebo. The added value of a drug exhibiting a mineralocorticoid activity is worth evaluating in view of the role of the angiotensin-converting enzyme 2 receptor and endothelial dysfunction in the pathogenesis of COVID-19.[16] The Influenza virus stratum and non-Influenza respiratory virus stratum aim at filling the evidence gap related to the lack of randomized trial having assessed corticotherapy in viral pneumonia related sepsis.[17] Otherwise, patients' randomization will be stratified according to candidate biomarkers, selected from: 1) signatures described in the literature, 2) biomarkers identified from RECORDS data obtained in the observational period of the study and 3) any national and/or international guidelines (figure 2). At the onset of the trial, 11 biomarkers/signatures had been identified (Critical Illness-Related Corticosteroid Insufficiency (CIRCI)[18], endocan[19], monocyte distribution width (MDW)[20], lymphocyte count[20], transcriptome sepsis response signature (SRS)[10,21], adaptive immunity signature (endotype A/B)[11,22], Glucocorticoid-Induced Leucine Zipper (GILZ)[23], Dual Specificity Phosphatase 1 (DUSP-1),

cutaneous vasoconstrictor to glucocorticoids[24], machine learning algorithm 1[12], machine learning algorithm 2), as described below. The CIRCI stratum is defined by baseline total cortisol of 10µg/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 cosyntropin.[18] Endocan is an endothelial peptidoglycan that contributes to regulate inflammation by counteracting leukodiapesis, a key target for corticosteroids.[19] We identified serum levels of endocan below 12.8ng/ml as a marker of hyperinflammation in the run-in period of RECORDS trial. The Monocyte Distribution Width stratum is defined by MDW >25.[20] The lymphocytes count stratum is defined by lymphocyte count below 870x10^3/ml, according to a recent study suggesting that lymphopenia was associated with corticosteroids resistance.[20] The Transcriptomic Sepsis Response Signature stratum is based on two distinct signatures suggesting immune suppression (SS1) and relative immune competency (SRS2).[21] Using generalized linear model based on a set of seven genes (DYRK2, CCNB1IP1, TDRD9, ZAP70, ARL14EP, MDC1, and ADGRE3), hydrocortisone may be associated with increased mortality in SRS2 patients.[10] The endotype A/B stratum is based on transcriptomic analysis of 100 genes reflecting the adaptive immunity and glucocorticoid receptor signaling. In children with sepsis, two distinct endotypes were identified, endotype A characterized by immune suppression and a higher risk for mortality when compared to endotype B.[22] The Glucocorticoid-Induced Leucine Zipper stratum and Dual Specificity Phosphatase 1 stratum are defined by reduced expression of GILZ and DUSP-1 by unstimulated isolated circulating monocytes. GILZ[23] and DUSP-1 are key endogenous regulators of the immune response. Preliminary data from the observational period of RECORDS suggested an association between the spontaneous expression of GILZ and of DUSP-1 and increased mortality in serious COVID-19 (unpublished). The cutaneous vasoconstrictor response to glucocorticoids stratum is defined according to previous

report in asthma.[24] Briefly, the test is performed by applying 30µg/ml betamethasone to the skin of the forearm. The degree of skin blanching is assessed after 12h of exposure with a score ranging from 0 to 4; 0 no skin blanching, 1 skin blanching is less than 50% of the area of application, 2 skin blanching is more than 50% of the area of application, 3 if blanching recovers the whole area of application, and 4 if blanching expands beyond the area of application. A score of 2 or less indicates resistance to corticosteroids. A photography of the forearm restricted to the tested skin area will be recorded. The intelligent algorithms strata include two algorithms aiming at predicting the response to corticosteroids, one developed through machine learning[12] and another one using other machine learning modeling approaches (unpublished), both being embedded into the eCRF.

Follow-up

All patients are followed-up at 3 and 6 months from randomization. The details of follow-up are given in table 1.

Table 1: Data collection and conduct of the trial

Variables/Visits	Daily data until ICU discharge or 90 days (whichever occurs first)	Specific measures at day 1 & 7	Last study visit (90- and 180-day data)
Vital status	X		X
Location (ICU/date of discharge), hospital ward/date of discharge, rehabilitation centre, long-term facility, home/date of discharge			X

Protocol adherence (receipt of every IMP dose until treatment completion)	X		X
Co-interventions (mechanical ventilation, renal replacement therapy, vasopressors, unblinded corticosteroids, thiamine, vitamin C, other vitamins, nutrition, intravenous fluids, blood products, anticoagulants, sedatives, stress ulcer prophylaxis, & antimicrobials)	X		X
Core temperature (daily lowest & highest value)	X		X
Vital signs (lowest & highest values for heart rate, systolic & diastolic blood pressure)	X		X
Central hemodynamic data	X		
Standard laboratory data (serum and urinary electrolytes, creatinine, urea, cholesterol, triglycerides & glucose levels, arterial lactate levels, arterial oxygen tension& hemoglobin oxygen saturation, arterial pH, white blood cell counts, hemoglobin & hematocrit levels, INR, platelet count, total bilirubin level)	X		
Microbiological or virological samples		X	

Other sampling left at the physicians' discretion	X		
Whole blood samples for measurements of biomarkers		X	
Glasgow coma scale Cognitive function			X
Muscular Disability Rating Scale (MDRS) score			X
Health-Related Quality of Life (HRQoL, EQ-5D-5L)[27]			X
PROMIS® (Fatigue 13a, Ability to participate in social roles and activities 8a, Physical function 8b, Emotional distress-Depression 8b, Emotional distress-Anxiety 8a, Cognitive function 8a)			X

Vital status by day 90 after randomization will be collected from the medical file and/or through phone calls with patients or their legal representative.

Outcomes

The primary outcome for the sequential analyses will be 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.

The primary outcome of the terminal analysis, assessed at 90 days, is a composite of death or persistent organ dysfunction – defined as SOFA score >6 or a continued dependency on either mechanical ventilation, new renal replacement therapy, or vasopressors.[8,25] The primary endpoint is a binary composite variable. Patient will be classified as a success if alive on day 90 and free of vasopressor therapy, mechanical ventilation, renal replacement therapy, and organ dysfunction. Patient will be classified as a failure if (i) death occurred within the 90 days following randomization, (ii) dependent on either vasopressor, mechanical ventilation, RRT, or (iii) exhibited a SOFA score >6.

Secondary outcomes include: 1) Mortality at 7, 14 and 28 days and 6 months; 2) Vasopressor free days: defined as the number of days with permanent hemodynamic stability in the absence of any vasopressor agent including norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin or its analogs. When a patient dies while receiving vasopressors, the number of vasopressor free days is arbitrarily set at 0; 3) Mechanical ventilation free days: defined as the number of days with permanent appropriate oxygenation while the patient is extubated and breathing spontaneously, i.e. no need for non-invasive ventilation, high flow oxygen or continuous positive airway pressure (CPAP). Other uses of non-invasive ventilation (e.g., chronic night-time use for chronic obstructive pulmonary disease) are not compatibilized. When a patient dies while receiving mechanical ventilation or is discharged home while receiving mechanical ventilation, the number of mechanical ventilation free days is arbitrarily set at 0; 4) Organ dysfunction free days: Organ function (including renal function) will be assessed using the SOFA score.[26] Organ dysfunction will be defined by a SOFA score > 6.[8] Organ dysfunction free days is defined by the number of days with a total SOFA score of 6 or less. When a patient dies before the SOFA decreased to 6 or

less, the number of organ dysfunction free days is arbitrarily set at 0; 5) 6-month HRQoL in survivors assessed using the EQ-5D-5L.[27] This standardised questionnaire was developed to provide a simple, generic measure of health for clinical and economic appraisal. It is made up of two components: health status description and health status self-assessment. Health status is assessed using five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Health status self-assessment reports on patients overall health status using a visual analogue scale; 6) Fatigue, ability to partake in social activities, physical function, emotional distress, depression, anxiety and cognitive function are assessed using the PROMIS short form questionnaire 7) Proportion of patients with a decision to withhold and/or withdraw active treatments; 8) ICU and hospital length of stay; 9) Rate of ICU re-admission up to 180 days after randomization.

Safety endpoints include: proportion of patients affected by any serious adverse event associated with corticosteroids, 1) hospital-acquired infection (CDC. Healthcare-Associated Infections (HAIs) progress report. 2020) within 90 days of randomization, 2) hyperglycemia (blood glucose level >150mg/dl) and hypernatremia (serum sodium > 145 mmol/L) during the ICU stay (or up to day 90, whichever occurs first), 3) Gastroduodenal bleeding requiring transfusion or hemostatic treatment during the ICU stay (or up to day 90, whichever occurs first), 4) neurological disorder (coma, stroke or muscle weakness, as defined below) up to 180 days from randomization. Coma is defined by a Glasgow coma score <8 in the absence of sedation. Neuromuscular sequelae are assessed using 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.

Randomization

The period from inclusion to randomization, including the period of laboratory testing for biomarkers, should not exceed 24 hours.

A computer process is used to generate allocation sequences in a 1:1 ratio, independently from healthcare staff, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, or the data analyst.

Randomization will be concealed by being centralized and performed with an internet-centralized service running 24/7 imbedded in the electronic Case Report Form (eCRF). Healthcare staff, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, and the data analyst will be blinded to treatment allocation. Only the central pharmacist, from the General Agency of Equipment and Health Products (AGEPS – APHP) will be unblinded.

Allocation of stratification

Stratification of randomization between the two trial arms first concerns the SARS-CoV2 results, generating a separate 1:1 randomization list for COVID-19 patients between fludrocortisone or its placebo, given all treated with dexamethasone. The second list concerns the Influenza positive patients, between hydrocortisone and fludrocortisone versus their respective placebos. Negative SARS-CoV-2 and Influenza patients are then randomly allocated to a randomization list amongst all assessed biomarkers for each patient based on data and strata cutoffs, and then randomized to hydrocortisone and fludrocortisone or their respective placebos according to the list of the biomarker/signature result. This will ensure the balance of treatment groups among each biomarker/signature strata.

Centers are not required to assess all biomarkers for a given patient. The randomization algorithm will run on all the available biomarkers (a single biomarker is sufficient). The randomization algorithm runs separately while communicating with the eCRF. Data related to biomarker results, virology results and input required for determining intelligent algorithms are sent to the randomization algorithm.

Interventions

Experimental treatments

Investigational medicinal products are presented in numbered boxes, labelled for this study according to the Good Manufacturing Practices under the responsibility of AGEPS. Each numbered box contains enough corticosteroids or placebo to fully treat one patient. A drug box contains 30 vials of hydrocortisone 100mg or placebo and 1 blister of 10 tablets of fludrocortisone 50µg or placebo.

Hydrocortisone hemisuccinate (SERB, Paris) or its placebo is administered as a 50mg intravenous bolus every 6 hours for seven days. Fludrocortisone or its placebo (HAC Pharma, Caen) is administered as a 50µg tablet via a nasogastric tube once a day in the morning, for seven days. COVID-19 patients are to be treated with open label dexamethasone (6mg) once a day over 10 days and 50µg fludrocortisone or its placebo (HAC Pharma, Caen) via a nasogastric tube or orally for patients not requiring a nasogastric tube, once a day in the morning, for seven days.

Allowed co-interventions

Treatments are allowed according to best practice guidelines.[28] These treatments may include, mechanical ventilation, renal replacement therapy, vasopressor therapy, thiamine, nutrition

therapies including multivitamins, intravenous fluids, blood products, sedatives, and antimicrobials. We will carefully record the use of these treatments. All recommended treatments (including IL-6 inhibitors and JAK inhibitors) in severe COVID-19 are authorized to be used in this trial.

Forbidden interventions

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 occurs after randomization (e.g. autoimmune disease), the patient should be treated. In this case, study treatments are to be suspended to avoid the administration of unnecessarily high-dose of hydrocortisone. However, short-duration administration of open-labelled corticosteroids is allowed for prevention of post-extubation laryngeal edema.

Continuous infusion of neuromuscular blocking agents is to be avoided. Whenever neuromuscular blocking drugs are mandatory (e.g. for severe ARDS), it should be interrupted every 12 hours to avoid prolonging the treatment longer than necessary.

Statistical analysis

A full statistical analysis plan will be reported in a separate paper.

Sample size

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. In a recent study,[8] the number of vasopressor-free days at day 28 with

hydrocortisone+fludrocortisone was 17.1±10.8 versus 15.0 ± 11.1 in placebos. 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[29], estimated here at a multiple of fourfold; therefore, to handle potential dropouts, a sample was estimated at 1800 patients. Bayesian inference will be used for sequential analyses.

To detect a 10% absolute risk reduction from 45% to 35% in 90-day all-cause mortality,[8] a sample size of 373 evaluable patients per arm (thus a total of 746 patients) is required to reach 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.

Performance of the Bayesian design

To restrict inclusion to patients most likely to benefit from corticosteroids during trial accrual, an enrichment design will be used, based on treatment-by-subset interaction. Two main objectives will be considered: (1) To estimate corticosteroid marginal effect; and (2) To test for heterogeneity across subsets. We previously reported that this strategy successfully selected patients sensitive to treatment and discarded the less sensitive ones.[30] Performance of design will be challenged using a large simulation study performed across a range of plausible scenarios to foresee power to detect

a 5-10% absolute difference with corticosteroids, considering a fixed sample size of 1800 patients, several sizes of each subset, under several scenarios of treatment effect and interaction.

Data analysis

All patients, whatever their biomarker status will be randomized across the two treatment groups. Statistical analysis will be conducted using "biomarker-by-treatment interaction" with separate tests, given the high number of potential biomarkers of interest. This is also referred to as "separate randomization designs" and "separate by treatment interaction designs".

The analysis plan will be based on separate estimation of corticosteroid effect in each biomarker-defined stratum to detect treatment by subgroup interactions: in other words, it aims at determining whether the corticosteroid effect may differ according to each biomarker/signature results, assessed through an interaction measure.

We will assess subset-by-treatment interaction by estimating two quantities[30]: (i) measure of influence (efficacy), relying on the value of the estimation of corticosteroids effect in each subset, and (ii) measure of interaction, either based on the Gail and Simon statistics or derived from the Millen's criteria based on the ratio of the estimated effect in both subsets.[31] In a Bayesian setting, the two criteria can be expressed as posterior probabilities related to the comparison of outcomes across the arms and/or the subsets. Decision thresholds will be defined based on a grid search to optimize the rate of false positive and false negative findings based on large simulated trials.

This analysis will be performed only for biomarkers with at least 100 available measures. Main interaction measures will consider only patients randomly allocated to the specific strata under study. As sensitivity analyses, we will also consider all the patients with the available biomarker, possibly handling imbalances across treatment arms using propensity score-based approaches.

Analysis of secondary outcomes will be performed at the time of terminal analysis. Mortality will be estimated by the Kaplan-Meier method, compared by the log-rank test across groups. Vasopressor free days, Mechanical ventilation free days, and Organ dysfunction free days, will be compared by the nonparametric Wilcoxon rank sum test. HRQoL will be analyzed by a joint mixed model for longitudinal and survival data, that is, a shared parameter model where the HRQoL and survival models share common random effect(s).

Details of statistical analysis will be reported on a Statistical Analysis Plan.

Role of funding source

The sponsor has no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication

Ethics and dissemination

RECORDS is funded by public grants “Programme d’Investissements d’Avenir” (PIA), part of “France 2030”, reference ANR-18-RHUS-0004 and Programme Hospitalier de Recherche Clinique (PHRC), reference PHRC-20-0778. The protocol was approved by the Ethics Committee (*Comité de Protection des Personnes,* CPP Dijon, France), on April 6, 2020 and by the French National Agency for Drug Safety (ANSM, France) on April 9, 2020. Trial results will be disseminated at relevant clinical conferences and societies, published in peer-reviewed journals

Patients and Public Involvement

The trial protocol will be discussed with France Sepsis Association (an association of patients who recover from sepsis and families of patients who had sepsis) and trial findings will be shared with this entity.

Discussion

RECORDS is the first multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design Basket trial aimed at discovering signatures enabling administration of hydrocortisone plus fludrocortisone in patients with sepsis and determining the best chance for improved outcome with minimal risk of harm. RECORDS trial relies on the concept that benefit to risk balance of corticosteroids is greater when given to patients with sepsis and evidence of hyperinflammation and intact corticosteroids related intracellular signaling. The RECORDS trial also hypothesizes that different clinical or biological phenotypes of sepsis, i.e. CAP related sepsis, septic shock, or sepsis related ARDS, bacterial or viral sepsis, may share common signatures relevant to corticosteroids responsiveness. The study design is highly innovative integrating a broad range of candidate biomarkers from multi-omics signatures to intelligent algorithms. Candidate biomarkers are to be selected from various sources including peer-reviewed literature and from our own consortium, thanks to the translational research program embedded into the RECORDS trial. The adaptive design of the study is a clear strength insomuch as unsatisfying biomarkers may rapidly be phased out and new biomarkers may be phased in. All assessed biomarkers must provide readily available results within 24 hours, meaning that the findings of the current trial will be easily translated into clinical practice. We must acknowledge some limits to the current trial including the fact that some complex biomarkers may not be available at all participating centers.

RECORDS trial is a major step in the implementation of precision medicine in sepsis. Indeed, personalized corticosteroid treatments for sepsis, may decrease the burden related to corticosteroids complications by avoiding exposure of patients unlikely to respond to this treatment.

Authors' contributions:

D. Annane, S. Chevret, J. Fleuriet, and N. Hemming have designed the study. S. Chevret is responsible for statistical analysis plan. D. Annane has obtained funding for the study. D. Annane, S. Chevret, J. Fleuriet, N. Heming have drafted this manuscript. F. Meziani, J. Reignier, P-L Declercq, E. Mercier, G. Muller, G. Colin, X. Monnet, A. Robine, S. Siami, F. Uhel, J-P Quenot, G. Plantefève, J. Badie, F. Schneider, C. Cerf, G. Troché, M. Monchi, J-P Mira, B. François contributed to critical evaluation of the study design, and of the manuscript of which they approved the final version and its submission for publication. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of it.

Declaration of interest: all authors declare to have no conflict of interest to disclose

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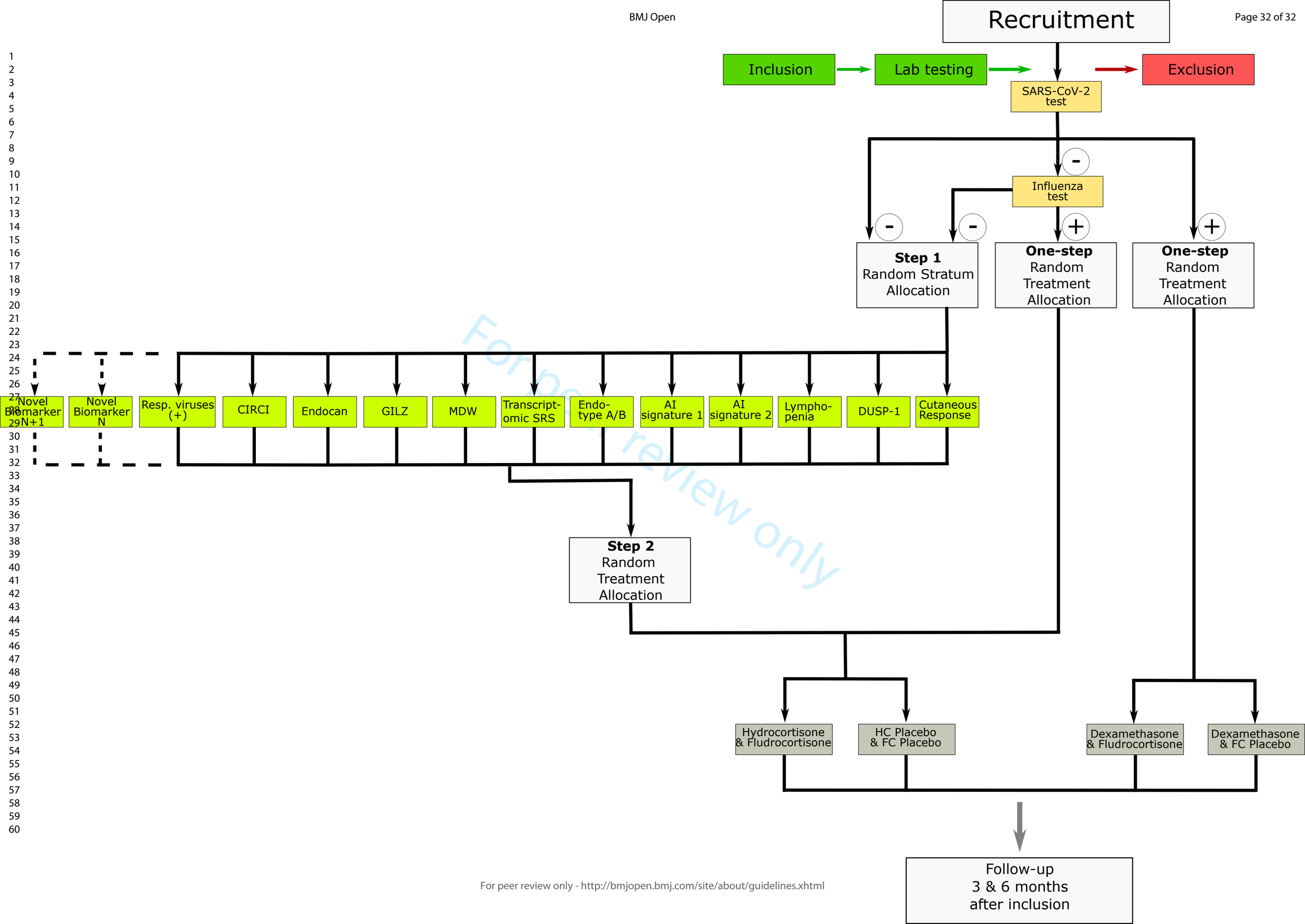
Legends for figures

Figure 1. Study flow chart describing the process of recruitment and randomization.

Artificial Intelligence (AI), Critical Illness-Related Corticosteroid Insufficiency (CIRCI), Dual Specificity Phosphatase 1 (DUSP-1), Fludrocortisone (FC), Glucocorticoid-Induced Leucine Zipper (GILZ), Hydrocortisone (HC), Monocyte Distribution Width (MDW), Respiratory (Resp.), Sepsis Response Signature (SRS).

Figure 2. Flow diagram describing the potential addition and subsequent validation of biomarkers during the trial



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