Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia – the COVID STEROID trial

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1 Abstract

Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a pandemic of coronavirus disease (COVID-19) with many patients developing severe hypoxic respiratory failure. Many patients have died, and healthcare systems in several countries have been or will be overwhelmed because of a surge of patients needing hospitalisation and intensive care. There is no proven treatment for COVID-19; the care is supportive, including respiratory and circulatory support. For other patient groups with similar critical illness (acute respiratory disease syndrome and septic shock), corticosteroids are used because they reduce the duration of mechanical ventilation, length of stay in the intensive care unit, and potentially also mortality. Corticosteroids have been used in some patients with COVID-19, but the recommendations in clinical guidelines differ; some suggest their use, others against.

Objectives

We aim to assess the effects of low-dose intravenous hydrocortisone on the number of days alive without life-support in adult patients with COVID-19 and severe hypoxia.

Design

International, multicentre, parallel-group, centrally randomised, stratified, blinded, clinical trial.

Inclusion and exclusion criteria

We will screen all adult patients who have documented COVID-19 receiving at least 10 L/min of oxygen independent of delivery system OR mechanical ventilation. We will exclude patients who have an indication for systemic use of corticosteroids, who have invasive fungal infection, who have known hypersensitivity to hydrocortisone, who are pregnant, who the clinical team has decided should not use invasive mechanical ventilation, and those in whom informed consent cannot be obtained.

Experimental intervention

Continuous IV infusion of hydrocortisone 200 mg daily will be given for 7 days in addition to standard care.

Control intervention

Continuous IV infusion of matching placebo (0.9% saline) will be given in addition to standard care (no corticosteroids).

Outcomes

The primary outcome is days alive without life support (invasive mechanical ventilation, circulatory support, or renal replacement therapy) at day 28. Secondary outcomes are serious adverse reactions (anaphylactic reaction to hydrocortisone, new episode of septic shock, invasive fungal infection or clinically important gastrointestinal bleeding); days alive without life support at day 90; days alive and out of hospital at day 90; all-cause mortality at day 28, day 90 and 1 year; and health-related quality of life at 1 year.

Statistics

The primary outcome will be compared using a Wilcoxon test. Differences will be quantified as differences in means and medians along with 95% confidence intervals. The mortality outcomes will be analysed using Fisher's exact test and binomial regression models with log links adjusted for the stratification variables (site, invasive mechanical ventilation, and age) with results quantified as relative risks supplemented with risk differences, both with 95% confidence intervals.

Trial size and testing strategy/design

As the trial is designed to yield results as soon as possible, a blinded statistician will conduct interim analyses after every 250 participants have been followed for 28 days. At maximum, we will randomise 1000 participants implying there will be 3 interim analyses. The alpha values for the 3 interim analyses and the final analysis are 0.000015, 0.003045, 0.018323, 0.044003, respectively as by the O'Brien-Fleming bounds, which preserves type I error at the usual 5%. At each analysis time-point, a Wilcoxon test will be employed to compare the groups on the primary outcome. The trial will be stopped early if the alpha cut-off is crossed at an interim analysis.

Timeline

- April 15th, 2020 Authority approvals and 1st participant randomised
- June 2020 1st interim analysis
- July 2020 2nd interim analysis
- August 2020 3rd interim analysis
- Late 2020 Last participant randomised and primary report on 28-day outcomes submitted.
- Early 2021 Report on 90-day outcomes submitted
- Late 2021 Report on 1-year outcomes submitted

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3 List of abbreviations

AE, Adverse Event

AR, Adverse Reaction

ARDS, Acute Respiratory Distress Syndrome

CI, Confidence Interval

CPAP, Continuous Positive Airway Pressure

CRIC, Collaboration for Research in Intensive Care

CTU, Copenhagen Trial Unit

DMSC, Data Monitoring and Safety Committee

eCRF, Electronic Case Report Form

EudraCT, European Union Drug Regulating Authorities Clinical Trial

GI, Gastrointestinal

GLM, Generalised Linear Model

GRADE, Grading of Recommendations Assessment, Development and Evaluation

HR, Hazard Ratio

HRQoL, Health Related Quality of Life

ICH-GCP, International Conference on Harmonisation on Good-Clinical -Practice

ICMJE, International Committee of Medical Journal Editors

ICU, Intensive Care Unit

IL-6, Interleukin 6

IQR, Interquartile Range

ITT, Intention-to-treat

IV, Intravenous

MD, Mean Difference

OR, Odds Ratio

QoL, Quality of Life

RCT, Randomised clinical trial

RR, Relative Risk

RRI, Relative Risk Increase

RRR, Relative Risk Reduction

SAR, Serious Adverse Reaction

SAE, Serious Adverse Event

SARS, Severe Acute Respiratory Syndrome

SD, Standard Deviation

SR, Systematic review

SSC, Surviving Sepsis Campaign

SUSAR, Suspected Unexpected Serious Adverse Reaction

WHO, World Health Organization

4 Introduction and background

4.1 Severe acute respiratory syndrome coronavirus 2/Coronavirus Disease 19

In December 2019, the Wuhan Municipal Health Committee in China identified an outbreak of viral pneumonia cases of unknown cause (1). A novel coronavirus was soon identified as the cause of the disease (1). This novel virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2) and the disease caused by the virus has been designated coronavirus disease 2019 (COVID-19) (3). Since the initial outbreak in China in December 2019, SARS-CoV-2 has spread globally and COVID-19 has been declared a pandemic by the World Health Organization (WHO) (4). Currently, the number of reported patients with COVID-19 and associated deaths are, as of March 29, 2020, >678.700 and 31.700, respectively (5). There are large outbreaks in China, South Korea, Iran, US and Europe that overwhelm the capacity of hospitals and intensive care units (ICUs).

SARS-CoV-2 causes respiratory tract infection (6). The severity of symptoms varies from mild to severe pneumonia and from mild to severe acute respiratory distress syndrome (ARDS) (6). In a recent study from China, 42% of COVID-19 patients admitted to hospital with pneumonia developed ARDS; of these 52% died (7). Currently, there are no approved therapeutic agents available for COVID-19; the current care is therefore supportive including oxygen, mechanical ventilation and general intensive care (8). However, some patients are treated experimentally with various antiviral drugs or immunomodulatory agents, including corticosteroids (6-9). Only a minority of these interventions have been assessed in the setting of a randomised clinical trial (RCT) (8), and the benefits and harms of these interventions have not yet been documented. As per 29th of March 2020, there were two trial protocols assessing corticosteroids for COVID-19 registered at WHO International Trial Registry Platform (trial registration numbers: NCT04244591, ChiCTR2000029656).

4.2 Sepsis and ARDS

Sepsis is a life-threatening condition with organ failure caused by a dysregulated inflammatory response to infection (10). Sepsis is most often triggered by bacterial infections but can also be caused by severe fungal or viral infections. Patients with sepsis are at risk of developing ARDS, which is a syndrome that follows a disease associated with severe systemic inflammation or severe pneumonia (11). Inflammatory mediators produce severe and diffuse inflammatory exudate of the pulmonary lobules, resulting in hypoxaemic respiratory failure (12). In ARDS, raised plasma inflammatory cytokine levels are associated with a significantly increased risk of death (13).

Trials done in both patients with ARDS and with sepsis have shown that corticosteroids reduce the duration of mechanical ventilation and shock, length of stay in the ICU, and potentially also mortality (Table 1) (14-16). Thus, corticosteroids are both used in patients with moderate/severe ARDS and in those with sepsis. However, the use of corticosteroids in ARDS caused by viral infections is controversial, since these drugs are immunosuppressive, and in observational studies, corticosteroids are associated with prolonged time to viral clearance (17). Although the risk-benefit ratio of corticosteroids in ARDS induced by viral infection has not been determined, the drugs are often used in clinical practice (6, 7, 9).

4.3 Corticosteroids in ARDS due to coronavirus

No RCT of corticosteroids in patients with COVID-19 has been published to date. Results from observational studies on corticosteroids for COVID-19 are difficult to interpret, primarily due to the risk of confounding by indication. Arabi et al. reported results of an observational study among patients with Middle East Respiratory Syndrome (MERS), which is an infection caused by a coronavirus with ~80% sequence homology to SARS-CoV-2 (18). In that study, the use of corticosteroids was associated with delayed clearance of coronavirus but was not associated with a difference in mortality after adjustment for time-varying confounders. However, results of analyses of associations between use of corticosteroid and mortality differed markedly according to the methods used for data analysis (18).
In an observational study of patients admitted to hospital with COVID-19, higher levels of interleukin-6 (IL-6) – an inflammatory mediator – were associated with increased risk of death (6). Among COVID-19 patients with ARDS, 46% of those who received methylprednisolone treatment died, while 62% of those who did not receive methylprednisolone treatment died suggesting beneficial effect of corticosteroids (7). In the newly released Surviving Sepsis Campaign guidelines on the management of critically ill adults with COVID-19, use of low-dose corticosteroids for shock reversal is suggested over no use (weak recommendation, low quality of evidence) and the use of corticosteroids is suggested over no use for those with ARDS (weak recommendation, low quality of evidence) (19). In contrast, the WHO recommends against the use corticosteroids in COVID-19 (20).

4.4 Type and dose of corticosteroids for sepsis and ARDS

The type, dose, and duration of corticosteroids for treatment of sepsis and ARDS are controversial. Various regimens have been used in different trials (Table 1) (21). Generally, studies with short-course high-dose corticosteroids for sepsis did not show a reduction in mortality or showed increased mortality, whereas

studies employing long-course low-dose steroids showed shock reversal and more heterogenous beneficial effects on mortality (22). Clinical guidelines published in 2018 stated that the optimal corticosteroid dose and duration of treatment are still uncertain (23). A later dose-response meta-analysis suggested that long course (7 days) low-dose (200–300 mg per day) hydrocortisone treatment with cumulative dose ≥ 1,000 mg was beneficial for the reduction of 28-day mortality in patients with sepsis (24). Similarly, a meta-analysis of corticosteroids for ARDS showed no beneficial effect of short-course high-dose treatment, whereas early initiation of longer course low-dose corticosteroids reduced duration of mechanical ventilation and mortality (25).

Type and dose of corticosteroid in the COVID STEROID trial

For the COVID STEROID trial, participants in the intervention arm will receive intravenous infusion of hydrocortisone 200 mg per day for 7 days or until hospital discharge without tapering, which is the exact protocol used in patients with septic shock (16).

Table 1. Estimates on the effects of corticosteroid vs. placebo/no treatment in critically ill patients with severe infection and/or severe respiratory failure. Most data are from recently updated systematic reviews (SRs) of RCTs, except those from viral acute respiratory distress syndrome (ARDS) and COVID-19 ARDS.

	Septic shock (26)	ARDS (19)	Community acquired pneumonia (27)	Viral ARDS (19)	COVID-19 ARDS (7)
Evidence base	SR of 22 RCTs, including 7297 participants	SR of 7 RCTs, including 851 participants	SR of 13 RCTs, including 2005 participants	SR of 10 observational studies on other corona viruses	1 observational study in 84 patients from 1 Chinese hospital
Corticosteroid used	Hydrocortisone 18 trials Methylprednisolone 2 trials		Hydrocortisone 6 trials Methylprednisolone or prednisolone 5 trials Dexamethasone 1 trials Prednisone 1	Not reported	Methylprednisolone
Daily dose (hydrocortisone-equivalent)	200-300 mg/day		200-400 mg/day	Not reported	Not reported
Mortality	RR 0.98 [0.89 to 1.08]	RR 0.75 [0.59 to 0.95]	RR 0.67 [0.45 to 1.01]	OR 0.83 [0.32 to 2.17]	HR 0.38 [0.20 to 0.72]
Admission to ICU	-	-	RR 0.69 [0.46 to 1.03]		
Need for ventilation	-	-	RR 0.45 [0.26 to 0.79]		
Days ventilated	MD −0.75 [−1.34 to -0.17] days	MD -4.93 [-7.81 to -2.06] days	-		
Days in shock	MD −1.52 [−1.71 to -1.32] days	-	-		
Days in ICU	MD −0.75 [−1.34 to −0.17] days	-	-		
Days in hospital	MD −0.87 [−2.17 to 0.44] days	-	MD -1.22 [-2.08 to -0.35] days		
Adverse events Secondary infections Hyperglycaemia Gastrointestinal bleeding Encephalopathy	 RR 1.05 [0.95 to 1.16] RR 1.11 [1.07 to 1.16] RR 1.09 [0.80 to 1.46] RR 1.99 [0.37 to 10.84]		 - RR 1.49 [1.01 to 2.19] RR 0.82 [0.33 to 1.62] RR 1.65 [0.88 to 3.08]		

ARDS: acute respiratory distress syndrome; SR: systematic review; RCTs: randomised clinical trials; mg: milligrams; RR: relative risk; OR: odds ratio; HR: hazard ratio; MD: mean difference; ICU: intensive care unit

4.5 Ethical justification and trial rationale

Patients with COVID-19 and severe hypoxia (the hallmark of ARDS) are at high risk of death (6, 7). There is no proven treatment for COVID-19; the care is supportive, including respiratory and circulatory support. For other patient groups with similar critical illnesses, lower dose corticosteroids are used because they mitigate critical illness and potentially also mortality without serious adverse reactions. Therefore, there is reason to believe that similar positive effects can be obtained in patients with COVID-19 and severe hypoxia without serious adverse reactions. If so, the vera participants in the COVID STEROID trial will benefit from participation. Because the trial will be conducted to the highest of methodological standards with ongoing assessment of the known serious adverse reactions to corticosteroid, including three planned interim analyses, any serious adverse reactions for single participants and the group of participants receiving corticosteroid will be assessed and handled. The control group will receive placebo and best clinical care without corticosteroids as it is presently recommended for these patients in Denmark. We, the COVID STEROID trial group, find this justifiable both medically and ethically.

The patients to be enrolled in the COVID STEROID trial cannot consent due to the combination of severe infection and severe hypoxia. No other patient groups may be investigated to improve the treatment of COVID-19 as no other patient groups have the combination of SARS-CoV-2 infection and severe hypoxia. In addition, COVID-19 with severe hypoxia is a medical emergency that requires immediate interventions including life-supportive interventions. Therefore, we cannot delay enrolment and need to use the consent procedures for emergency research.

Informed consent will be obtained according to Danish law, i.e. the consent procedures for temporarily incompetent patients for all patients (https://www.retsinformation.dk/Forms/R0710.aspx?id=192671). The COVID STEROID trial patients will be enrolled after informed consent from a doctor (first trial guardian), who is independent of the trial, who has knowledge of the clinical condition and who is familiar with the trial protocol to such extent that he/she can judge for each patient, if it will be reasonable to enrol the patient in the trial. As soon as possible after enrolment, consent will be obtained from the patient's next of kin and another doctor (second trial guardian). The second trial guardian is also independent of the trial, has knowledge of the clinical condition, and is familiar with the trial protocol to such extent that he/she can judge for each patient, if it will be reasonable to enrol the patient in the trial. Participants, who regain competence, will be asked for informed consent as soon as possible (Appendix 7, 18.7). The process leading to informed consent will follow all applicable regulations. The consenting subjects will be provided with written and oral information about the trial allowing them to make an informed decision about participation in the trial. Written information and the consent form will be subject to review and approval

by the ethical committee system. The consenting party can at any time, without further explanation, withdraw consent.

4.6 Trial conduct

The COVID STEROID trial will comply with the published trial protocol, the Helsinki Declaration in its latest version (28), the International Conference on Harmonization on Good-Clinical-Practice (GCP) guidelines (29), General Data Protection Regulation and national laws including Databeskyttelsesloven. The Management Committee of the trial will oversee the conduct. We have written the protocol in accordance with the SPIRIT 2013 Statement (30) and will register the trial in the www.clinicaltrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT) registries before the enrolment of the first participant. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities within 7 days. Enrolment will start after the approval by the Ethics Committee, the Danish Medicines Agency and the Capital Region Knowledge Center for Data Compliance (legal department). We will publish the approved protocol at www.cric.nu and submit a manuscript with main points of the protocol including description of design, rationale and the detailed statistical analysis plan to a peer-reviewed medical journal.

5 Trial objectives

The objective of the *Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia – COVID STEROID trial* is to assess the effects of low-dose IV hydrocortisone versus placebo on the number of days alive without life-support in adult patients with COVID-19 and severe hypoxia.

6 Trial design

The COVID STEROID trial is an international, investigator-initiated, multicentre, parallel-group, blinded, centrally randomised, stratified, clinical trial.

6.1 Randomisation

Patients with COVID-19 fulfilling all inclusion criteria and no exclusion criteria will be randomised. The 1:1 randomisation will be centralised and web-based according to the computer-generated allocation sequence list, stratification variable (trial site, invasive mechanical ventilation (y/n), age below 70 years (y/n)), and varying block size at Copenhagen Trial Unit (CTU) to allow immediate and concealed allocation to one of the two intervention groups. The allocation sequence list will exclusively be known to the data manager at CTU and will be unknown the unblinded trial site staff preparing the trial medication (section 6.2), to the clinicians, to the investigators and statistician conducting the analysis. Each trial participant will be allocated a unique screening number.

6.2 Blinding

We will mask the allocation for the participants, the clinical staff, the trial Management Committee, the trial site staff registering the outcome parameters and the trial statistician, who will conduct the analyses with the two intervention groups coded as e.g. X and Y. A dedicated team of trial site staff (medical-, pharmacy- or nurse students or pharmacists, research nurses or doctors) who are certified in medicine handling procedures will unblinded prepare the trial medication and perform daily data entry about the administration of the trial medications including any protocol violations. This unblinded team of trial site staff will not be involved in the care of trial participants, outcome assessment, or in the statistical analyses. They will be instructed not to reveal the allocation under any circumstances.

Trial medication preparation

We will use shelf-medications from the hospital department's pharmacy for both intervention and control medication. To ensure blinding, the trial medications will be prepared with infusion set by the unblinded trial site staff, and the participants and clinical staff will thus remain blinded to the treatment allocation. The hydrocortisone solution is stable for at least 24 hours at ambient temperature (< 25 °C) after the reconstituted solution has been diluted in the infusion solvent (saline 0.9%) (a letter from Pfizer confirming the stability is provided in Appendix 4, 18.4). The temperature logging will be as per the trial site pharmacies standard procedures.

Consequently, for each participant, the trial medication will be prepared once daily and administered as continuous infusions. If patient characteristics (e.g. limited IV access, self-removal of lines, or mobilisation) or site characteristics (limited number of infusion pumps or staff) do not allow continuous infusion, we will

allow bolus injections (in the form of the reconstituted hydrocortisone solution diluted in saline 0.9%) every 6 hours.

Preparation of hydrocortisone

The hydrocortisone sodium succinate (Solu-Cortef™, Pfizer, Denmark) sterile powder is white, odourless, and soluble in water (31). First, the hydrocortisone (100 mg per vial) will be mixed with the solvency (water for injection, 2 ml per vial) using the Act-O-Vial system (31). The vial will be mixed for 20 seconds and then rested for 3 minutes. The mixture will be withdrawn in a 2 ml syringe where it can be inspected visually for the presence of particles and discoloration prior to administration (31).

Continuous infusion

The mixture of two vials of hydrocortisone of 100 mg and solvency (total 200 mg, 4 ml) will be injected under sterile conditions into a bag of 100 ml of isotonic saline (0.9%) to a total volume of 104 ml and a concentration of 2 mg/ml. For each participant allocated to hydrocortisone, this bag of 104 ml (200 mg, 2 mg/ml) of hydrocortisone in isotonic saline solution will be delivered to the clinical staff and administered to the participant as a continuous IV infusion using a volumetric infusion pump over 24 hours.

Bolus injection

The mixture of two vials of hydrocortisone and solvency (total 200 mg, 4 ml) will be mixed in 4 10-ml syringes (1 ml hydrocortisone (50 mg) per 10-ml syringe) under sterile conditions with 9 ml of isotonic saline (0.9%) to a total volume of 10 ml per syringe. For each participant allocated to hydrocortisone, 4 10-ml syringes (50 mg of hydrocortisone in isotonic saline, total volume 10 ml) will be delivered to the clinical staff and administered as IV bolus injection every 6 hours to a total daily dose of 200 mg (40 ml).

Preparation of placebo

The placebo is matching isotonic saline (0.9%).

Continuous infusion

For each participant allocated to placebo, 4 ml of saline (0.9%) will be injected under sterile conditions into a bag of 100 ml of isotonic saline (0.9%). This bag of 104 ml isotonic saline will be delivered to the clinical staff and administered to the participant as a continuous IV infusion using a volumetric infusion pump over 24 hours.

Bolus injection

For each participant allocated to placebo, 4 10-ml syringes (10 ml of isotonic saline prepared under sterile conditions) will be delivered to the clinical staff and administered as IV bolus injection every 6 hours to a total daily dose of 40 ml.

6.3 Unblinding

Unblinding of the intervention for a participant

The intervention may be unblinded if deemed necessary by the treating clinician or the investigator for treatment or safety reasons. The sponsor or his delegate will break the blinding for a participant if there is clinical suspicion of an unexpected serious adverse reaction (SUSAR) and judge the 'expectedness' of this according to the product information. Any SUSAR will be reported to the authorities accordingly.
Unblinding of the intervention for a participant can be performed around the clock by contacting the sponsor or his delegate. The sponsor or his delegate will contact the unblinded trial site staff from who the trial allocation is available.

Unblinding of the entire trial

The Management Committee may stop and unblind the trial if there are clear indications that one intervention is superior to the other based on the recommendations from the Data Monitoring and Safety Committee (DMSC) or other relevant data.
The members of the DMSC will remain blinded unless 1) they request otherwise or 2) an interim analysis has provided strong indications of one intervention being beneficial or harmful.

6.4 Participant timeline

We will strive to enrol participants as soon as they fulfil the inclusion criteria, and no later than within 48 hours of initiation of invasive mechanical ventilation. The allocated intervention will be continued for 7 days after randomisation or until discharge from participating site (whichever occurs first). We will follow the patients for 14 days after randomisation (day forms) and identify survivors at days 28, 90, and 1-year in electronic patient records or in registries. At 1-year, we will contact surviving participants or their next of kin for health-related quality of life (HRQoL) follow-up.

End of trial

The trial will end when the last patient enrolled has completed 1-year follow up (last-patient last-visit). We will report the end-of-trial no later than 90 days after the last patient has been enrolled to the Danish Medicines Agency and Ethics Committee.

7 Selection of participants

All patients admitted to an active trial site will be considered for participation. Patients will be eligible if they comply with the inclusion and exclusion criteria (full definitions are presented in Appendix 3, 18.3). We aim to include the patients as early as possible.

7.1 Inclusion criteria

All the following criteria must be fulfilled:

- Aged 18 years or above **AND**
- Confirmed SARS-CoV-2 (COVID-19) requiring hospitalisation **AND**
- Use of one of the following:
    - Invasive mechanical ventilation **OR**
    - Non-invasive ventilation or continuous use of continuous positive airway pressure (CPAP) for hypoxia **OR**
    - Oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system

7.2 Exclusion criteria

We will exclude patients who fulfil any of the following criteria:

- Indication for use of systemic corticosteroids
- Invasive mechanical ventilation for more than 48 hours
- Invasive fungal infection
- Fertile woman (< 60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG
- Known hypersensitivity to hydrocortisone
- A patient for whom the clinical team has decided not to use invasive mechanical ventilation
- Previously randomised into the COVID STEROID trial

- Informed consent not obtainable

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment (Appendix 8, 18.8).

7.3 Participant discontinuation and withdrawal

The procedure for handling withdrawal of consent from a participant will follow Danish regulations.

Discontinuation and withdrawal at the choice of the participant or the proxy

A participant, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment.
For incapacitated participants, consent can be withdrawn at any time by the person(s), who has given proxy-consent. To limit the amount of missing data, we will collect as much data as possible from each participant. Therefore, the investigator will ask the participant or the proxy if they allow continued data registration and follow-up at 1-year.

Discontinuation and withdrawal at the choice of the investigator

A participant may have the intervention stopped by the clinician or investigator at any time, if:

- The participant experiences intolerable adverse reactions or events (including Serious Adverse Reactions (SARs) or Suspected Unexpected Serious Adverse Reactions (SUSARs)) suspected to be related to the trial intervention.
- The clinicians in conjunction with the coordinating investigator decide it to be in the interest of the participant
- Withdrawal from active therapy
- The participant is subject to compulsory hospitalisation.

In these cases, the collection of data and the follow-up will continue, and the participant will remain in the intention-to-treat population.

Discharge

Participants who are discharged or transferred to a non-participating hospital department will be regarded as discharged, and the trial allocation and daily data registration will be stopped upon discharge. The patient will still be followed through the electronic health records, including registration of data for days alive and out of hospital. Participants who are discharged or transferred to a department participating in the COVID STEROID trial will continue the allocated intervention at the new trial site for a total treatment duration of 7 days from randomisation. If the participant is readmitted to a COVID STEROID trial site from a non-participating hospital within 7 days of randomisation, the allocation will also resume for a total treatment duration of 7 days from randomisation.

8 Selection of trial sites and personnel

8.1 Trial sites and setting

Trial sites will be hospitals in Denmark. Trial sites are listed in the section *Administrative information* (p. 4). This section will be updated during the trial, and authorities will be notified.

8.2 Trial personnel

All clinical staff caring for patients will be eligible to care for and give the interventions to the trial participants. The primary trial personnel are constituted of a dedicated team of medical, pharmacy or nurse students or research nurses or doctors who will be trained and certified in all trial-related procedures. Medical students will be eligible to screen and enrol patients, obtain informed consent, prepare trial medication and perform data entry. Nurse and pharmacy students and pharmacists will be eligible to obtain informed consent, prepare trial medication and perform data entry; nurse- and pharmacy students and pharmacists can only screen and enrol of patients if a named doctor or medical student checks and signs the inclusion notes. All participating trial sites will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for trial-related questions.

8.3 Trial interventions

The intervention period is 7 days from randomisation or until hospital discharge, whichever comes first.

8.4 Experimental intervention

Continuous intravenous infusion of hydrocortisone 200 mg over 24 hours (total 104 ml). The trial intervention will be given in addition to standard care. If continuous intravenous infusion is not possible for specific patients (e.g. limited IV access, self-removal of lines, or mobilisation or because the site has a limited number of infusion pumps or staff), we will allow the use of bolus injection of the trial medication (50 mg (10 ml) every 6 hours). As soon as continuous infusion can be established, this is the preferred way of administration.

8.5 Control intervention

Continuous intravenous infusion of matching isotonic saline (0.9%) placebo at a dose volume of 104 ml over 24 hours in addition to standard care (no corticosteroid treatment). If continuous intravenous infusion is not possible at a site, we will allow the use of bolus injection matching saline placebo (10 ml every 6 hours). As soon as continuous infusion can be established, it will be the preferred infusion.

8.6 Co-interventions

All participants in the trial will be given co-interventions at discretion of the treating clinicians. We will recommend against the use of corticosteroids (systemically or as inhalation) and other anti-inflammatory agents (e.g. IL-6 inhibitors) in all trial participants.
Based upon an updated critical appraisal of the literature, the COVID STEROID Management Committee endorses and encourages co-enrolment in the COVID STEROID trial (Appendix 8, 18.8). Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment (Appendix 8, 18.8).

8.7 Concomitant interventions

All other interventions will be allowed as per the clinical team including those affecting CYP3A4, because it is not clinical practice at the trial sites to change the use or dosing of short-term (7-day) hydrocortisone with concomitant use of CYP3A4 inhibitors or inducers. The same procedure has previously been used in a clinical trial assessing the exact same regimens (200 mg hydrocortisone vs. placebo) for septic shock without harming the patients (16) (EudraCT number: 2012-003158-10).

8.8 Monitoring of participants

The participant will be monitored closely due to the severity of their illness. The level of monitoring will be as per the clinical standard of the trial sites including continuous monitoring of oxygen saturation and pulse when severe hypoxia is present; 1-2 hourly measurements of blood pressure and respiratory rate when severe hypoxia is present; and 8-hourly measurement of body temperature; daily measurement of blood values including CRP, leukocyte count, hemoglobin, creatinine, urea and electrolytes; and daily measurements of pH, atrial blood gases, and lactate, blood sugar and electrolyte concentrations. Additional measurements will be done on clinical indications including microbiological cultures, markers of candida infections and ECG.
For participants admitted to the ICU, additional monitoring will include continuous registration of blood pressure, 3-lead ECG, oxygen saturation and 3-6-hourly measurements of pH, atrial blood gases, and lactate, blood sugar and electrolyte concentrations.

These data will not be registered in the COVID STEROID trial eCRF but will be available in the participant's health care records for the Sponsor and/or the authorities if needed.

8.9 Criteria for modification of interventions for a given trial participant

The clinical team may at any time violate the protocol if they find it to be in the best interest of the participant. We will have a COVID STEROID trial hotline to enable discussion around the clock between the clinicians caring for trial participants and the COVID STEROID trial team regarding protocol related issues. Protocol violations will be registered and reported.

8.10 Assessment of participant compliance

We will monitor protocol compliance at the trial site through the electronic case report form (eCRF) and alert trial sites in the case of clear violations (central monitoring). In addition, the trial will be externally monitored according to the GCP Directive and the monitoring plan (section 13).

8.11 Intervention accountability

Both the trial intervention and control medications are routinely used for in-hospital treatment of patients and we will use shelf-medication from the department's pharmacy. The trial medication will only be

handled by the trained trial staff and the clinical staff who are trained and certified for the caring for patients. The methods used for trial medication preparations are described in 6.2.

Trial medications

Active medication: hydrocortisone, powder and solvent solution for intravenous injection, 100 mg (Solu-Cortef™, Pfizer, Denmark, ATC code: H02AB09).
Placebo drug: Isotonic saline, solution for intravenous injection, 9mg/ml (ATC code: B05BB01).
Each saline bag contains 100 ml corresponding to 900mg saline in sterile water. Content of electrolytes/l: 154mmol chloride, 154mmol natrium. Isotonic. Osmolarity 308mmol/l.

Labelling

When the trial drug is prepared, it will be labelled with a COVID STEROID-trial sticker, making clinical personnel aware that the bag contains trial medication (vera or placebo). The sticker will hold information about the participants data, the trial medicines, the date and time of preparation, the expire date and time, the signature of the trial staff preparing the medications and a telephone number for the COVID STEROID-trial 24-h hotline (the labels are presented in Appendix 5, 18.5). To ensure blinding of the clinicians, the sticker will not hold information about the BATCH / LOT numbers of the trial medications. The BATCH / LOT numbers will instead be noted in a trial medication log. This log will not be available for the clinicians.

9 Outcome measures

9.1 Primary outcome

Days alive without life support (i.e. invasive mechanical ventilation, circulatory support or renal replacement therapy) from randomisation to day 28.

9.2 Secondary outcomes

- All-cause mortality at day 28
- Days alive without life support at day 90
- All-cause mortality at day 90

- Number of participants with one or more serious adverse reactions (SARs) at day 14 defined as new episodes of septic shock, invasive fungal infection, clinically important GI bleeding or anaphylactic reaction to IV hydrocortisone
- Days alive and out of hospital at day 90
- All-cause mortality at 1 year after randomisation
- HRQoL at 1 year after randomisation using EQ-5D-5L and EQ-VAS

At selected sites, participants will be invited to a standard lung function test at 1-year.

10 Safety

10.1 Definitions

In the COVID STEROID trial, we will use the definitions below (32):

Adverse event (AE)
Any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR)
Any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.

Serious adverse event (SAE)
Any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious adverse reaction (SAR)
Any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. The SARs are identified in the Summary of Products Characteristics (SmPC) for Solu-Cortef.

Suspected unexpected serious adverse reaction (SUSAR)

Any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with Summary of Products Characteristics (SmPC) for Solu-Cortef).

10.2 Risk and safety issues in the COVID STEROID trial

The trial participants will be hospitalised patients for whom adverse events and reactions are documented routinely in the patient health record (i.e. notes, charges and laboratory reports). We will record the occurrence of SARs in the 14 days following randomisation for all included patients and report them as an outcome measure.

For all patients, we will register daily the presence or absence of potential SARs according to intravenous hydrocortisone in the Danish Summary of Product Characteristics, which are serious and relevant to short course use in critically ill patients, i.e. new episodes of septic shock, invasive fungal infections, clinically important GI bleeding and anaphylaxis.

10.3 Assessment of adverse events

Timing

In all participants, we will assess the occurrence of SARs in the 14 days following randomisation (the maximum intervention period is 7 days; 14 days allow for at least another 7 days of assessment after the intervention, which is clinically relevant in short course use in critically ill patients.

Classification of an event

We will make no inferences about a causal relationship between the intervention and the SARs but register the occurrence in the two groups and report them in the final report according to the definition given above.

As for any SAE, the investigators will report them to the sponsor or his delegate within 24 hours. If such a SAE is deemed related to the intervention by the investigator, it will be considered a SUSAR and reported as such. If the sponsor does not adjudicate the SAE as related to the intervention, this will also be noted in the SUSAR report.

Reporting

Any SAE adjudicated to be related to the trial intervention by the investigator, will be reported within 24 hours to the Sponsor or his delegate. If deemed a SUSAR by the sponsor, he will report it to the Danish Medicine Agency, the Ethics Committee and all trial sites within 7 days. No later than 8 days after the reporting, the Sponsor will inform the Danish Medicines Agency of relevant information on the Sponsor's and the investigator's follow-up action to the life-threatening or fatal SUSAR. Any other SUSARs will be reported to the Danish Medicines Agency no later than 15 days from the time when the Sponsor is informed.

Once a year, the sponsor will submit a list of all SARs that have occurred at all sites during the trial period and a report on safety of the trial subjects to the Danish Medicines Agency and National Ethics Committee. The sponsor will notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) and if earlier than planned, the reasons for stopping the trial.

In addition, we will report all SARs defined in 9.2 as outcome measures and all SUSARs in the final trial report and the results of the trial will be reported on EudraCT within 12 months of 'last-patient-last-visit'.

11 Procedures, assessments and data collection

11.1 Screening

All patients admitted to a participating trial site with confirmed COVID-19 and severe hypoxia (as defined in section 7.1) will be eligible for screening. The screening will be done by the clinical team. When a candidate patient is identified, the clinical team will alert the trial staff, who will seek consent.

11.2 Procedures of informed consent

Participants will be enrolled after consent by proxy is obtained according to Danish regulations. We will follow the normal procedures for collection of informed consent and any modifications to these as approved by the Ethics Committee due to restrictions in physical visits to the hospitals during the current SARS-CoV-2 epidemic. The procedure for informed consent is described in Appendix 6 (17.7).

11.3 Data collection

The screening of participants will be done by the clinical team as described in 10.1. The clinicians will pass on information about eligible participants to the COVID STEROID trial site staff who will hereafter obtain informed consent from the first trial guardian.

After informed consent is obtained, the data below (10.4) will be obtained by the trial site staff from the participant's hospital files, national/regional/hospital registers (source data as defined per site and region) and interview with patient or proxy and entered into the web-based eCRF (the server hosting the database is located at CTU, Rigshospitalet, Region Hovedstaden). For participants transferred from a trial site to a non-trial site, data related to the outcomes will be collected from either hospital files (if accessible) or investigator contact to the non-trial site or health care registers.

11.4 Variables

All variables are defined in Appendix 3 (18.3).

Screening variables

Inclusion and exclusion criteria (7.2 and 7.3)

Baseline variables

- Sex
- Age at admission (date of birth)
- Date of admission to hospital
- Number of days with symptoms before hospital admission
- Department at which the participant was included:
    - Emergency department
    - Hospital ward
    - Intermediate care unit
    - Intensive care unit
- Use of respiratory support at randomisation:
    - Closed system (y/n): Invasive mechanical ventilation or non-invasive ventilation or continuous use of CPAP
        - If yes, latest FiO2 and duration in hours prior to randomisation
    - Open system with an oxygen flow ≥ 10 L/min (y/n)

    - If yes, maximum supplemental oxygen flow on an open system at randomisation (+/- 1 h)

- Treatment for COVID-19 during current hospital admission prior to randomisation:
  - Agents with potential anti-viral action:
    - Hydroxychloroquine
    - Remdesivir
    - Lopinavir/ritonavir
    - Convalescent plasma
    - Other
  - Anti-bacterial agent (y/n)
  - Agents with potential anti-inflammatory action:
    - Corticosteroids (y/n)
    - IL-6 inhibitors (y/n)
    - Other

- Chronic co-morbidities:
  - History of ischaemic heart disease or heart failure (y/n)
  - Chronic hypertension (y/n)
  - Diabetes Mellitus (y/n)
  - Chronic pulmonary disease (y/n)

- Blood values, interventions and vital parameters:
  - Participant weight
  - PaO2 and SaO2 in the most recent arterial blood gas sample prior to inclusion **OR** SpO2 from pulse oximeter if arterial blood gas sample is not available
  - Circulatory support (infusion of vasopressor/inotropes) within the last 24 hours prior to randomisation (y/n)
  - Renal replacement therapy within the last 72 hours prior to randomisation (y/n)
  - Highest plasma lactate within the last 24 hours prior to randomisation

Daily during admission for the first 14 days after randomisation (day form)

- Invasive mechanical ventilation (y/n)

- Circulatory support (infusion of vasopressor/inotropes for a minimum of 1 hour) on this day (y/n)

- Any form of renal replacement therapy on this day including days between intermittent renal replacement therapy (y/n)

- SAR on this day (y/n for each)

- New episodes of septic shock
- Invasive fungal infection
- Clinically important GI bleeding
- Anaphylactic reaction to IV hydrocortisone

Daily registration of major protocol violations the first 8 days (day form 1-8)

- Use of open-label systemic corticosteroids on this day (y/n)

- Trial intervention (y/n): did the patient receive trial medication on this day? (yes/no)

  - If yes: as continuous infusion, bolus injections or both
  - If yes: did the patient receive at least 50% of the planned volume on this day (yes/no)
  - If no, apply reasons: by error/lack of resources, other reason

Discharge form

- Died in hospital

- Discharged from hospital

- Discharged to another hospital participating in the COVID STEROID trial

- Discharged to another hospital not participating in the COVID STEROID trial

Follow-up 28 days after randomisation

- Death (y/n, if yes: date of death)

- Number of days on invasive mechanical ventilation from day 15-28

- Number of days with circulatory support (infusion of vasopressor/inotropes for a minimum of 1 hour) from day 15-28

- Number of days on renal replacement therapy from day 15-28

- Use of extracorporeal membrane oxygenation (ECMO) from randomisation to day 28 (y/n)

Follow-up 90 days after randomisation

- Death (y/n, if yes date of death)

- Number of days on invasive mechanical ventilation from day 29-90

- Number of days with circulatory support (infusion of vasopressor/inotropes for a minimum of 1 hour) from day 29-90

- Number of days on renal replacement therapy from day 29-90

- Date of discharge from hospital

- Additional hospital admissions (y/n, if yes: date of re-admission(s) and discharge(s))

Follow-up 1 year after randomisation

- Death (y/n, if yes date of death)

- HRQoL

  - EQ-5D-5L
  - EQ-VAS

12 Statistical plan and data analysis

The analyses will be done according to the principles stipulated in ICH-GCP guidelines (32). The protocol and detailed statistical analysis plan will be published online at www.cric.nu and in a peer-reviewed journal before randomisation of the last participant.

12.1 Sample size and power

Sample size estimation and testing strategy

As the trial is designed to yield results as soon as possible, a blinded statistician will conduct interim analyses after every 250 participants have been followed for 28-days. At maximum, we will randomise 1000 participants implying there will be 3 interim analyses. The alpha values for the 3 interim analyses and the final analysis are 0.000015, 0.003045, 0.018323, 0.044003, respectively as by the O'Brien-Fleming bounds, which preserves type I error at the usual 5% (33). At each analysis time-point, a Wilcoxon test will be employed to compare the groups on the primary outcome. The trial will be stopped early if the alpha cut-off is crossed at an interim analysis. The trial has 85% power to detect a 15% relative reduction in 28-day mortality combined with a 10% reduction in time on life support among the survivors. If the true effect is as described in the power analysis, we have 19% probability of stopping at the second interim analysis (i.e. after 500 participants), 42% probability of stopping at the third interim analysis (i.e. after 750 participants), and 38% probability of running the trial to the full 1000 participants.

The mortality outcomes will be tested in a hierarchical procedure along with the primary outcome (first primary outcome, then 28 days mortality, and finally 90 days mortality) reusing the alpha if the previous

test was significant. If the primary outcome is insignificant at trial conclusion, ordinary 5% level test will be employed for all outcomes, but the results interpreted as exploratory.

Power estimations for secondary outcomes

We expect to have 80% statistical power to detect the following effects for the secondary outcomes based on the trial design described above. Power is reported at the 5% level even though the two mortality outcomes are also part of the primary outcome's hierarchical testing procedure.

- A 21% relative risk reduction for the mortality at day 28 (control event rate 30%)
- A 18% relative risk reduction for the mortality at day 90 (control event rate 40%)
- A 32% relative risk reduction for the number of participants with one or more SARs (control event rate 15%)
- A 15% relative risk reduction for the mortality at 1-year (control event rate 50%)

The estimates of control event rates for mortality at day 28 originate in data of previous coronavirus studies (6, 34); the estimates of the control event rates for mortality at day 90 and the number of patients with SAR is based on best clinical estimate. We expect the following secondary outcomes to be highly skewed (non-normally distributed): Days alive out of hospital at day 90 and HRQoL at 1-year. The power estimations for these are, therefore, somewhat uncertain why we refrain from making these estimates.

12.2 Statistical methods

The analyses will be done in the intention-to-treat (ITT) population defined as all randomised participants for whom there is consent for the use of data.

The primary outcome will be compared using a Wilcoxon test. Differences will be quantified as differences in means and medians along with 95% confidence intervals. The binary outcomes (including mortality outcomes) will be compared using Fisher's exact test and generalised linear models with log links and binomial error distributions adjusted for the stratification variables (site, invasive mechanical ventilation, and age) (35). Differences in binary outcomes will be quantified using relative risks and secondarily risk differences along with 95% confidence intervals.

We will challenge the primary result in analyses adjusted for important baseline risk factors (age, co-morbidities, and use of life-support), in subgroups (Table 2) and in the per-protocol population being the ITT population except those having one or more major protocol violations as defined below (Table 3). If

there is more than 5% missing data for outcomes and/or covariates, we will impute the missing data using multiple imputations.

All analyses will be 2-tailed. Several outcome measures (SARs, days alive without the use of life support at day 28 and 90) are composite; we will also report each component of these outcomes as recommended (32) in a supplement to the main report.

Table 2. Heterogeneity of the intervention effects on the primary outcome will be analysed in the following subgroups based on baseline characteristics

Subgroup	**Definition**	**Expected direction of the interaction**	**Statistical test**
Elderly patients	Patients ≥70 years versus <70 years of age	Larger effect of hydrocortisone in the younger population	Test of interaction in the adjusted analysis described above; P-value 0.01
Therapeutic agents against COVID-19	Patients who receive agents with potential action against COVID-19 versus no such agents	Larger effect of hydrocortisone in patients receiving agents with potential action against COVID-19	Test of interaction in the adjusted analysis described above; P-value 0.01
Invasive mechanical ventilation	Patients who receive invasive mechanical ventilation versus oxygen by other delivery systems	Larger effect of hydrocortisone in patients who receive invasive mechanical ventilation	Test of interaction in the adjusted analysis described above; P-value 0.01
Shock	Patients with shock versus without shock	Larger effect of hydrocortisone in patients with shock	Test of interaction in the adjusted analysis described above; P-value 0.01
Chronic lung disease	Patients with chronic lung disease versus no lung disease	Larger effect of hydrocortisone in	Test of interaction in the adjusted analysis

		patients with chronic lung disease	described above; P-value 0.01

Table 3. The definitions of major protocol violations, the exclusion of which will form the per-protocol population

Intervention group	**Major protocol violation definition**
Hydrocortisone	Failure to administer trial medication per protocol OR open-label corticosteroid administered
Placebo	Failure to administer trial medication per protocol OR open-label corticosteroid administered

Effect measures

We will present the effects on the primary outcome as raw mean differences as well as median differences. For binary outcomes, we will report results as raw and adjusted relative risks and absolute risk differences, computed using generalized linear models (GLMs) with appropriate link functions (log links) and binomial error-distribution. Results will be presented with 95% confidence intervals (CI) for the analyses of the primary outcome (P-value 0.05) and 99% CIs for those of the secondary outcomes (P-value 0.01) due to the multiplicity of these. Significance of results will be based on the test described under testing strategy.

Interim analysis

We will conduct three interim-analyses; one after every 250 patients have been followed for 28 days.
The DMSC will analyse the primary outcome and the rate of SARs on all three interim analyses as described in the charter (Appendix 6, 18.6). The DMSC will submit their recommendations to the Management Committee, which make the final decision regarding the continuing, pausing or stopping of the trial as described in the DMSC charter.
After completion of the first interim analysis (250 patients have been followed for 28 days), the recommendations from the DMSC and the conclusion reached by the Management Committee will be submitted to the Ethics Committee.

Early stopping criteria

We will employ O'Brien-Fleming bounds which imply the following significant cut-offs (0.000015, 0.003045, and 0.018323) at the three interim analyses, respectively. At each analysis time-point, a Wilcoxon test will be employed to compare the groups for the primary outcome. The trial will be stopped early if the alpha cut-off is crossed at an interim analysis.

13 Quality control and quality assurance

The sponsor and his delegates will be responsible for organising the trial sites including education of the local investigators, the trial site staff and clinical staff before the initiation of the trial. This education will be continuously documented in the site master file.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of participants and entry of data. Clinical staff at the trial sites will be responsible for screening of eligible patients and the treatment of trial participants.

13.1 Monitoring

The trial will be externally monitored according to the GCP Directive and the monitoring and data verification plan including the documentation of informed consent of trial participants. The monitoring and data verification plan will be developed together with the GCP unit of Copenhagen University Hospital and adhered to by the staff monitoring all trial sites.

After the consent is obtained, Sponsor and his delegates will have access to the participants hospital files for quality control and monitoring. Sponsor will allow direct access to source data for GCP monitoring or control visits by the Danish national authorities overseeing drug trials. In addition, we will use central monitoring of site through the eCRF, including adherence to the protocol.

13.2 Drug traceability measures

The registration of the batch numbers and the expiry dates of the hydrocortisone and saline used, and the identity of the clinician administering the hydrocortisone and saline will be registered as per standard practice at the sites. These data will not be registered in the trial documents but can be obtained by the Sponsor or the authorities if needed. We believe that this is a safe procedure because both the

hydrocortisone and saline used in the COVID STEROID trial has been in clinical use for many years and the safety of single doses cannot be questioned. The same procedure was approved by the Danish Medicines Agency in the CLASSIC feasibility trial (EudraCT no. 2014-000902-37) and CLASSIC trial (EudraCT number 2018-000404-42).

14 Legal and organisational aspects

14.1 Finance

Trial funding

The trial is funded by grants from the Novo Nordisk Foundation (5.000.000 DKK), Copenhagen University Hospital Rigshospitalet (1.875.000 DKK) and Pfizer (220.290 DKK). The funding organisation has not been or will not be involved in the design, conduct, analyses, or reporting of the trial nor will it have ownership of the data. The Sponsor and trial staff have no financial affiliations to the Novo Nordisk Foundation or Pfizer.

Compensation

The trial sites will not receive case money. The grant money will be spent on salary for the dedicated team of trial staff (up to 40.000 DKK per month dependent on the workload); longer travel done by members of this team; the trial management; and statistical and data support.

Insurance

The trial participants are covered by the Danish Law 'Lov om Patientskadeerstatning'.

15 Plan for publication, authorship and dissemination

All trial results, whether positive, negative or neutral, will be published preferably in a peer-reviewed medical journal. Furthermore, the results will be published at the Collaboration for Research in Intensive Care (CRIC) home page (www.cric.nu). We will adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement (36), including the accountability of all patients screened (Appendix 2, 18.2). Before unblinding the intervention groups, the Management Committee will write two abstracts based on the statistical report with the group allocation masked, one assuming the experimental intervention group

is X and the control intervention group is Y, and one assuming the opposite. Then, the allocation code will be unmasked.

Authorship will be granted according to the guidelines from the International Committee for Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

The listing of authors will be as follows on the primary publication: MW Petersen will be first author, TS Meyhoff the second, M Helleberg the third, MBN Kjær the fourth, the next authors will be the site investigators according to the number of included participants per site, then the other members of the Management Committee, and the trial site staff. A. Perner will be the last and corresponding author.

The Management Committee may grant additional authorships depending on personal input as per the Vancouver definitions. Investigators on sites may be granted authorship on sub-study publications if they contribute significantly as per the Vancouver definitions.

The DMSC and investigators not qualifying for authorship will be acknowledged with their names under 'the COVID STEROID trial investigators' in an *appendix* to the final manuscript.

The funding sources will be acknowledged, but they will have no influence on the data handling or analyses, the writing of the manuscript or the decision to publish.

15.1 Sub-studies

Sub-studies will be encouraged if they do not hamper the completion of the main protocol and can be conducted after approval of the specific protocol by the Management Committee and the authorities. Thus, specific protocols for any sub-studies will be submitted to and approved by the relevant authorities and ethic committees before the commencement of such studies. In Appendix 9 (18.9), any proposed sub-studies are listed.

15.2 Intellectual property rights

The COVID STEROID trial group owns the trial data.

15.3 Organisational framework

The COVID STEROID trial will be conducted and managed by the Sponsor, Management Committee, (Appendix 1, 18.1), the dedicated trial site team, the investigators, and the Research Unit at Department of Intensive Care, Rigshospitalet.

16 Trial timeline

- April 15th, 2020 Authority approvals and 1st participant randomised
- June 2020 1st interim analysis
- July 2020 2nd interim analysis
- August 2020 3rd interim analysis
- Late 2020 Last participant randomised and primary report on 28-day outcomes submitted.
- Early 2021 Report on 90-day outcomes submitted
- Late 2021 Report on 1-year outcomes submitted

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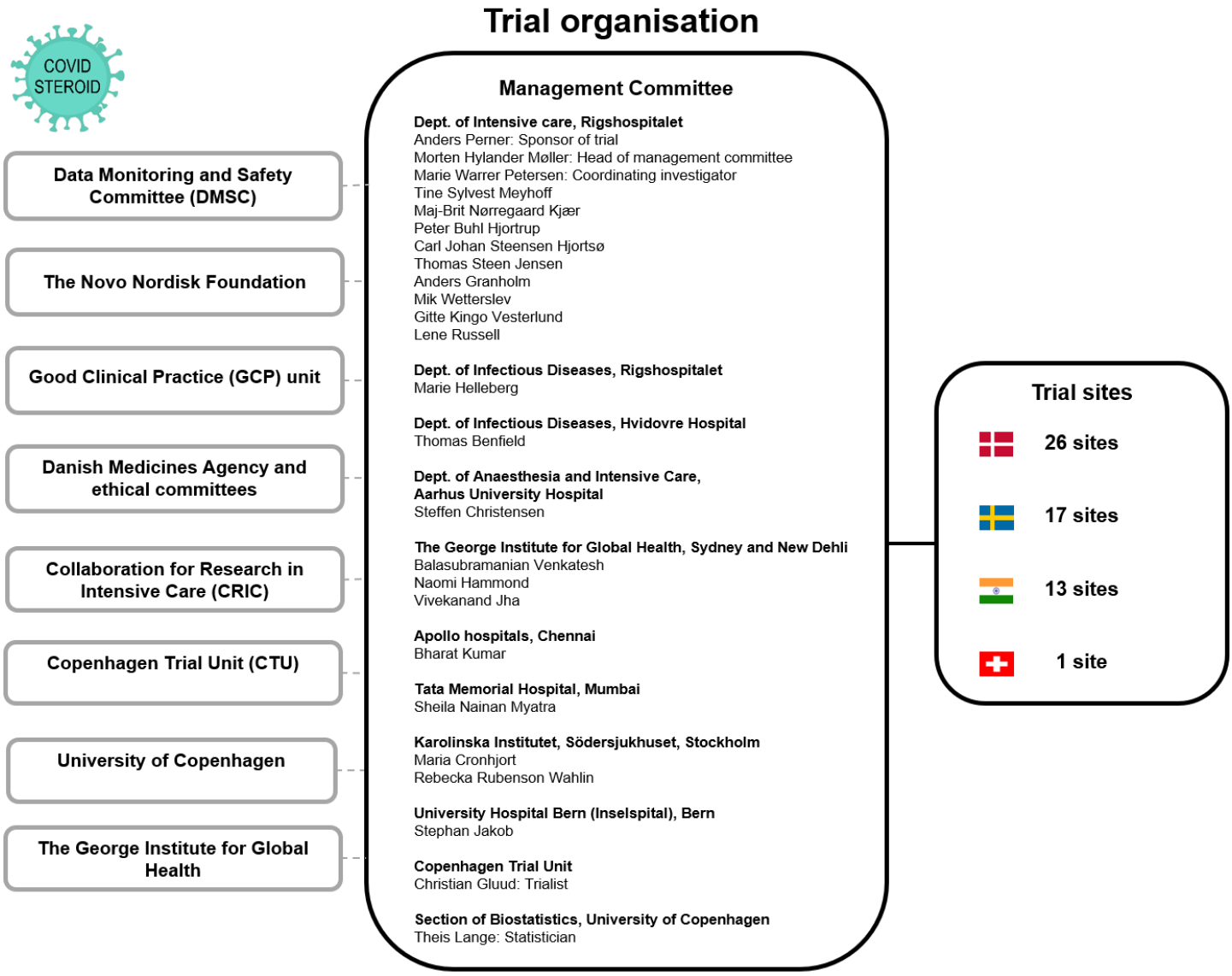
18 Appendices

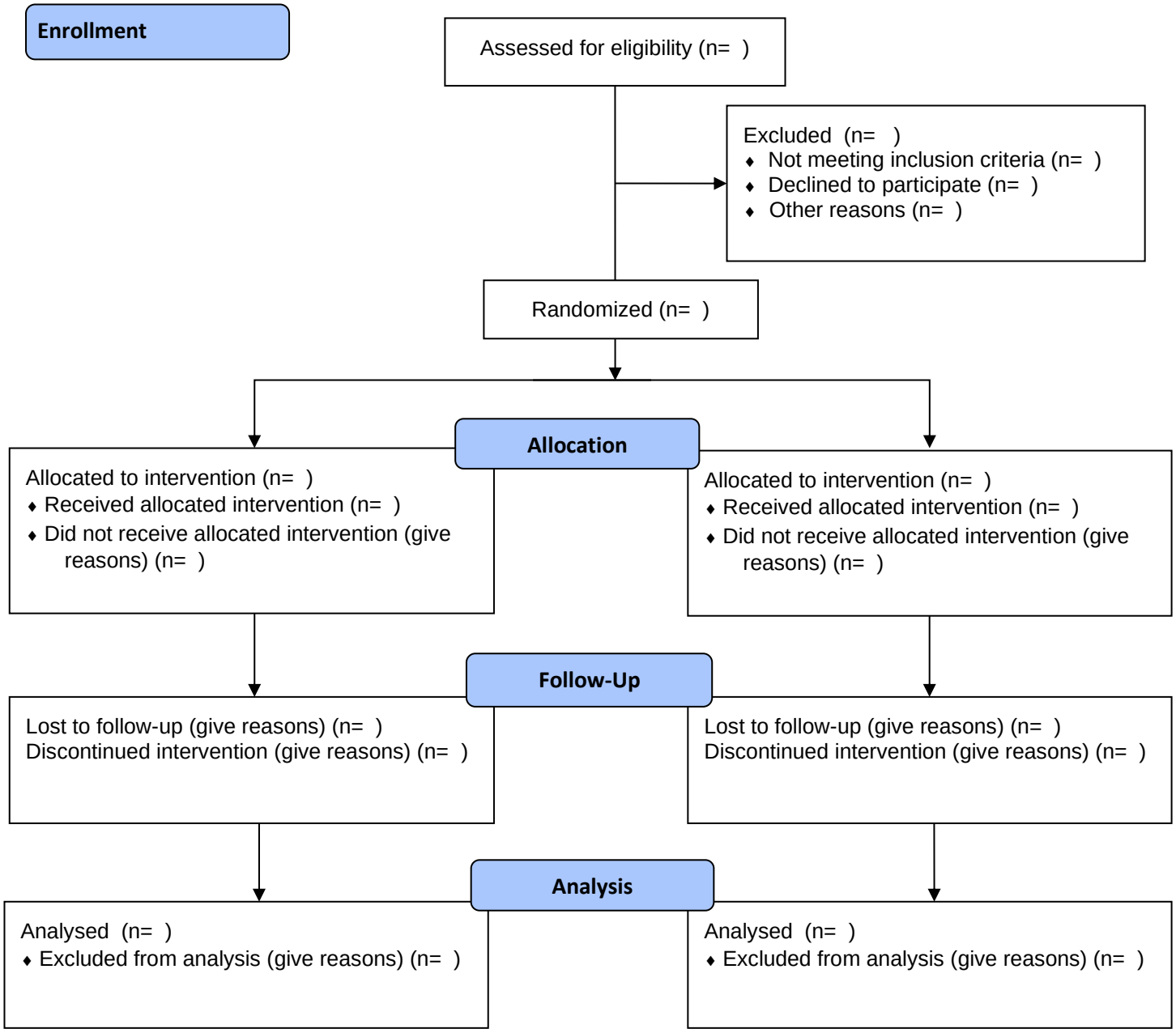
18.1 Appendix 1: Trial organisation diagram



18.2 Appendix 2: Trial flow chart

Please refer to the CONSORT Statement for more information (http://www.consort-statement.org/) (36). The flowchart should be modified to reflect the flow of participants in the trial. The flowchart (n=) will be filled in at the end of the trial.

CONSORT 2010 Flow Diagram



18.3 Appendix 3: Trial definitions

Definition of stratification variables

Site: all participating trial sites (hospitals) will be assigned a number identifying the site.

Invasive mechanical ventilation: use of mechanical ventilation via a cuffed endotracheal tube at the time of randomisation.

Age: the age of the participant in whole years at the time of randomisation. Is the patient above 70 years old? (y/n). The patients will be stratified according to age ≥70 years versus <70 years.

Patient identification

National identification number: CPR number (10 digits without dash) or fictive CPR number if the patient does not have a CPR number.

Definition of the inclusion criteria

Age: defined under *Definition of stratification variables*

Confirmed SARS-CoV-2 requiring hospitalisation**:** We will include patients admitted to a trial site with SARS-CoV-2. We will accept any detections of SARS-CoV-2 approved by the Danish Health Authorities. Currently, detection of SARS-CoV-2 RNA from upper (i.e. pharyngeal swap) or lower airway secretions (i.e. tracheal secretion or bronchoalveolar lavage) is used.

Supplementary oxygen criterion at the time of randomisation:

- Invasive mechanical ventilation: Defined under *Definition of stratification variables* **OR**
- Non-invasive ventilation or continuous use of continuous positive airway pressure (CPAP) for hypoxia: Non-invasive ventilation includes positive pressure ventilation via a tight mask or helmet, continuous use of CPAP (mask, helmet or tracheostomy). This does not include intermittent use of CPAP.
- Oxygen supplementation with an oxygen flow ≥ 10 L/min irrespectively of system used (mask or nasal cannula) or the addition of atmospheric air

Definition of the exclusion criteria

Indication for use of systemic corticosteroids: Systemic corticosteroids (IV, IM, oral or per GI tube; not including nebulised, inhaled or transdermal corticosteroids) for any indications, including:

- Adrenal insufficiency (i.e. primary, secondary or tertiary)
- Anti-emetic treatment (i.e. post-operative or chemotherapy-induced nausea and vomiting)

- Immunosuppressive treatment (i.e. rheumatic diseases, allergic diseases, chronic obstructive pulmonary disease, haematological diseases, chronic kidney diseases, autoimmune hepatitis, inflammatory bowel disease, chronic neurological diseases)

If the clinicians do not find an indication for continuation of treatment with systemic corticosteroids during the current hospital admission, the corticosteroid can be discontinued, and the patient will be eligible for inclusion.

Invasive mechanical ventilation for more than 48 hours: Defined under *Definition of stratification variables*

Invasive fungal infection: Any of the following:

- Suspected invasive fungal infection: presence of plasma markers in blood (e.g. candida mannan antigen and galactomannan antigen)
- Confirmed invasive fungal infection: positive culture from blood, peritoneal fluid or tissue

Pregnancy: Confirmed by positive urine human gonadotropin (hCG) or plasma-hCG.

Known hypersensitivity to hydrocortisone: history of any hypersensitivity reaction to hydrocortisone, including but not limited to urticaria, eczema, angioedema, bronchospasm and anaphylaxis.

A patient for whom the clinical team has decided not to use invasive mechanical ventilation: decision made prior to screening of patient and documented in patient files.

Consent not obtainable: patients where the clinician or investigator is unable to obtain the necessary consent according to the national regulations, including patients with no relatives or patients who are hospitalised against their will.

Definition of baseline variables

Sex: the genotypic sex of the participant
Date of admission to hospital: the date of admission to the first hospital the participant was admitted to during the current hospital admission
Department at which participant was included:

- Emergency department: accident/emergency/casualty/acute department at COVID STEROID trial site
- Hospital ward: medical or surgical ward at COVID STEROID trial site, including dedicated COVID-19 hospital wards
- Intermediate care unit: area of the hospital with higher resources to monitor patients as defined by the site, but invasive mechanical cannot be given.
- Intensive care unit: area of the hospital where invasive mechanical can be given.
- Other: any location in the same or another hospital not covered in the other categories

Use of respiratory support at randomisation:

- Closed system (y/n): Use of invasive mechanical ventilation as defined under *Definition of stratification variables* or use of Non-invasive ventilation or continuous use of continuous positive airway pressure (CPAP) for hypoxia as defined under *Definition of inclusion criteria.* If yes, latest FiO_2 and duration in hours prior to randomisation
- Open system with an oxygen flow ≥ 10 L/min: If yes, the maximum supplemental oxygen flow on an open system at randomisation (+/- 1 h) will be registered.

Treatment during current hospital admission prior to randomisation:

Agents with potential anti-viral action: any treatment that potentially inhibits viral replication, categorised as hydroxychloroquine, remdesivir, protease inhibitor (lopinavir/ritonavir or darunavir/ritonavir), convalescent plasma, or other (e.g. umifenovir (Arbidol, Abidol), Interferon alfa, Interferon beta, Camostat).

Anti-bacterial antibiotics: any antibiotic treatment commenced due to documented or suspected bacterial infection before microbiological results are available

Agents with potential anti-inflammatory action: any treatment with potential anti-inflammatory actions to treat COVID-19 prior to screening, categorised as corticosteroids, IL-6 inhibitors or other.

Co-morbidities: any chronic co-morbidity present in the past medical history prior to admission and defined as follows:

- History of ischemic heart disease or heart failure: previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, NYHA class 3 or 4 or any measured LVEF < 40%.
- Chronic hypertension: Treatment at time of hospital admission with any antihypertensive agent, e.g. diuretics, adrenergic receptor antagonists (alpha/beta/alpha+beta blockers), alpha-2 receptor agonists, calcium channel blockers, ACE-inhibitors, ANG-II receptor antagonists, aldosterone antagonists.

- Diabetes mellitus: Treatment at time of hospital admission with any anti-diabetic medications.
- Chronic pulmonary disease: Treatment at time of hospital admission with any relevant drug indicating chronic pulmonary disease.

Blood values, interventions and vital parameters:

- Participant weight: measured or estimated in kg
- PaO2, SaO2 and lactate prior to inclusion: will be assessed from the most recent arterial blood gas sample; alternatively, if arterial blood gas sample is not available, SpO2 will be assessed from the most recent measure by pulse oximeter.
- Circulatory support: infusion of any vasopressor/inotrope agent for a minimum of 1 hour (i.e. norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) within the last 24 hours prior to randomisation.
- Renal replacement therapy: any form of acute or chronic intermittent or continuous renal replacement therapy (including days between intermittent dialysis) within the last 72 hours prior to randomisation.

Definition of variables assessed in day form (day 1-14)

- Invasive mechanical ventilation (on this day): defined under *Definition of the inclusion criteria.*

- Circulatory support (for at least 1 hour on this day): defined under *Definition of the baseline variables.*

- Any form of renal replacement therapy (on this day): Any form of renal replacement therapy (e.g. dialysis, hemofiltration or hemodiafiltration) at any rate on this day. Including days between intermittent renal replacement therapy.

- SAR on this day (y/n for everyone)

  - New episodes of septic shock: we will define septic shock according to the Sepsis-3 criteria (37):
    - Suspected or confirmed superinfection
    - New infusion (or 50% increase) of vasopressor/inotrope agent (*Definition in the baseline variables*) to maintain a mean arterial blood pressure of 65 mmHg or above
    - Lactate of 2 mmol/L or above in any plasma sample performed on the same day
  - Invasive fungal infection: defined under *Definition of exclusion criteria*
  - Clinically important gastrointestinal (GI) bleeding: any GI bleeding AND use of at least 2 unit of red blood cells on the same day. GI bleed defined as hematemesis, coffee ground emesis, melena, haematochezia or bloody nasogastric aspirate on this day.

- Anaphylactic reaction to IV hydrocortisone: Anaphylactic reactions defined as urticarial skin reaction **AND** at least one of the following observed after randomisation
    - Worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
    - Increased airway resistance (>20% increase in the peak pressure on the ventilation)
    - Clinical stridor or bronchospasm
    - Subsequent treatment with bronchodilators

Definition of variables assessed in day form (day 1-8)

- Use of open-label systemic corticosteroids on this day: Use of any open-label systemic (IV, IM or oral/per GI tube) corticosteroids (i.e. hydrocortisone, methylprednisolone, dexamethasone or prednisolone) in any dose

- Trial intervention: Did the patient receive trial medication on this day: yes, if the trial participant received some of the trial medication on this day; no, if the trial participant received none of the trial medication on this day.
    - If yes, please apply if the trial medication was administered as continuous infusion, bolus injections or both; and if the patient received at least 50% of the planned volume on this day (yes/no)
    - If no, please apply reason for violating the protocol: By error/lack of resources, other reason.

Definitions of outcome measures

<u>Primary outcome</u>

Days alive without life support (i.e. invasive mechanical ventilation, circulatory support or renal replacement therapy) at day 28: will be assessed from the use of life support including invasive mechanical ventilation, vasopressor/inotrope, and renal replacement therapy as defined in *Definition of inclusion criteria*, *Definition of baseline variables* and *Definition of variables assessed in day form.* Total number of days alive without all 3 life supporting interventions within 28 days after randomisation.

<u>Secondary outcomes</u>

- All-cause mortality at day 28 after randomisation: death from any cause within 28 days post-randomisation.

- Days alive without life support (i.e. invasive mechanical ventilation, circulatory support or renal replacement therapy) at day 90: will be assessed from the use of life support invasive mechanical ventilation including vasopressor/inotrope, and renal replacement therapy as defined in *Definition of inclusion criteria*, *Definition of baseline variables* and *Definition of variables assessed in day form.* Total number of days alive without all 3 life supporting interventions within 28 days after randomisation.
- All-cause mortality at day 90 after randomisation: death from any cause within 90 days post-randomisation.
- Number of participants with one or more serious adverse reactions (SARs) at day 14: At least one new episode of either septic shock, invasive fungal infection, clinically important GI bleeding or anaphylactic reaction to IV hydrocortisone as defined under *Definition of variables assessed in day form.*
- Days alive and out of hospital at day 90: will be assessed from the discharge date from the index hospitalisation, the number of days readmitted to hospital (if any) and date of death, if relevant, within the 90-day period
- All-cause mortality at 1 year after randomisation: death from any cause within 1-year post-randomisation.
- Health-Related Quality of Life (HRQoL) at 1 year after randomisation: HRQoL at 1-year (+/- 2 weeks): EQ-5D-5L and EQ-VAS scores (https://euroqol.org/) obtained by survey by mail or phone as chosen by the participant. Non-survivors will be given the worst possible score. If the participant is incapable of answering the questionnaire (e.g. due to cognitive impairment or coma) we will ask proxies to assess HRQoL for the trial participant (proxy point of view) using the questionnaire aimed for proxies. Non-survivors will be given the worst possible score. EQ-5D-5L will be converted to an index value in combination with the EQ-VAS quantitative measure (0-100 points) quantifying self-rated health
- Lung function at 1 year: will be assessed by spirometry at selected sites.

Definitions of other variables assessed during follow up

- Use of ECMO from randomisation to day 28: oxygen supplied through extracorporeal membrane on any day from randomisation to day 28.

Definitions of subgroups

Elderly patients: ≥70 years versus <70 years. Age is defined under *Definition of stratification variables.*

Therapeutic agents against COVID-19: agents with potential action against COVID-19 versus no such agents. Agents with potential anti-viral actions are defined under *Definition of baseline variables.*

Invasive mechanical ventilation: invasive mechanical ventilation versus oxygen by other delivery systems. Invasive mechanical ventilation is defined under *Definition of stratification variables*; oxygen by other delivery system encompass both non-invasive ventilation, continuous use of CPAP and oxygen supplementation with an oxygen flow ≥ 10 L/min irrespectively of system used or the addition of atmospheric air as defined under *Definition of inclusion criteria.*

Shock: patients with shock versus without shock. Shock of any cause in patients requiring infusion of vasopressor/inotrope agent (norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) to maintain a mean arterial blood pressure of 65 mmHg or above AND with a lactate of 2 mmol/L or above in any plasma within 24 hours of randomisation

Chronic lung disease: patients with chronic lung disease versus no lung disease as defined under *Definition of baseline variables.*

18.4 Appendix 4: Letter from Pfizer regarding the stability of Solu-Cortef

Pfizer Medical Information
E-Mail: Medical.Information@Pfizer.com

Kathrine Bruun Svan
Hospitalsapoteket
Rigshospitalet
Blegdamsvej 9,
2100 København Ø

27. marts 2020

Din henvendelse vedrørende SOLU-CORTEF (hydrocortisonnatriumsuccinat)

Kære Kathrine Bruun Svan

Tak for din henvendelse vedrørende vores lægemiddel Solu-Cortef. Vi har registreret, at du ønsker information om stabilitet af Solu-Cortef efter opblanding/fortynding med NaCl.

Vi skal beklage, hvis der i tidligere kommunikation kunne opstå forvirring om stabilitetsinformationen. For Solu-Cortef er der forskel på stabiliteten af produktet efter rekonstitution og stabiliteten af Solu-Cortef efter opblanding/fortynding med godkendte solvenser.

Vi har venligst vedlagt et dokument på engelsk til dig med titlen "*Solu-Cortef: Infusion Administration*", som indeholder den komplette stabilitetsinformation, som vi håber vil være til hjælp og af interesse i relation til din forespørgsel.

Vi håber, at denne information vil være til nytte. Du er velkommen til at kontakte os, hvis du har brug for yderligere materiale.

Med venlig hilsen

Henrik Jørgensen
Senior Medical Information Officer

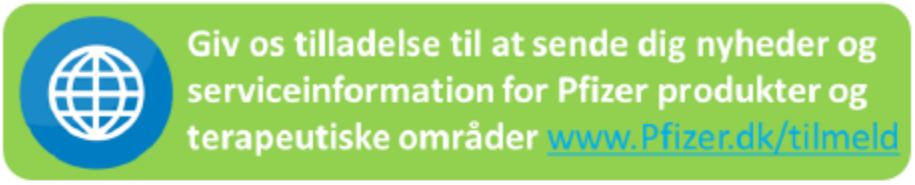
Ref: DK20-000219

Disclaimers
Pfizer respekterer dit privatliv og beskytter dine personoplysninger.

Dine personoplysninger vil blive behandlet i overensstemmelse med vores persondatapolitik for EØS vedrørende medicinske oplysninger, produktklager og lægemiddelsikkerhed, som kan fås på https://privacycenter.pfizer.com/inquiries

Hvis du har spørgsmål vedrørende Pfizers brug af dine personoplysninger, eller hvis du ønsker at få tilsendt en kopi af persondatapolitikken via e-mail eller brevpost, bedes du kontakte os på det lokale Pfizer telefonnummer, eller via e-mail: Medical.Information@Pfizer.com

BEMÆRK VENLIGST, at disse oplysninger kun er beregnet til den person, som specifikt har anmodet om oplysninger om et Pfizer-produkt. Hvis du ikke specifikt har anmodet om disse oplysninger, bedes du kassere dem og ringe til Pfizer for at rapportere dette til os.



SOLU-CORTEF® (hydrocortisone sodium succinate)

Infusion Administration

1. How can Solu-Cortef be prepared for infusion?

First, the Act-O-Vial should be reconstituted as described:[1]

1. Press hard on the plastic cap to force solvent into the lower compartment of the vial.
2. Gently agitate to effect solution.
3. Remove the protective cap, which covers the rubber plug. Sterilize the rubber plug.
4. Insert needle perpendicular through the center of the rubber plug until the tip is just visible.
5. Turn the vial around and withdraw dose.

As per additional Prescribing Information:[2]

To reduce the risk of perforating rubber particles of the stopper, the following points should be considered when solution is withdrawn:

- Take the thinnest possible needle.
- Insert the needle within the small circle, because this is the thinnest area of the rubber.
- Keep the needle vertically to the stopper surface.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration whenever solution and container permit.[1]

2. What is the volume of solvent for infusion that should be added?

The Solu-Cortef 100 mg reconstituted solution may be added to 100 to 1000 mL of 5% glucose in water (or isotonic saline solution or 5% glucose in isotonic saline solution if the patient is not on sodium- or low salt restriction).[1]

The Solu-Cortef 250 mg reconstituted solution may be added to 250 to 1000 mL as above.[1]

In cases where administration of a small volume of fluid is desirable, up to 3 g of Solu-Cortef may be added to 50 mL of the above diluents.[1]

3. What is the stability of the resulting solutions?

➔ <u>After reconstitution with water for injections:</u>

Chemical and physical stability after reconstitution is documented for 6 hours at 25°C.[1]

From a microbiological point of view, the product should be used immediately. Use of other storage times and conditions prior to use are the responsibility of the user and must not be longer than 6 hours at 25°C.[1]

➔ <u>After mixing the reconstituted solution with the infusion solvents:</u>

As per internal information, the resulting diluted solutions for infusion have shown to be stable when stored for 24 hours at ambient conditions, and for 4 hours at 30°C/70%RH.[3,4]

We are aware that there may be published data (e.g., in Trissel, Micromedex or published articles) that have investigated the stability of hydrocortisone sodium succinate when stored in conditions that are inconsistent with the recommendations in the Prescribing Information. Please note, however, that we do not provide this published data because the product and formulation discussed in the published data may not represent the Solu-Cortef formulation, as marketed by Pfizer in Denmark. Furthermore, we are unable to assess the validity of the test methods and their applicability to Solu-Cortef. Therefore, the conclusions in the published data may not apply to Solu-Cortef.

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2. Solu-Cortef/-SAB (hydrocortisone sodium succinate/-sine alcohol benzylicus) Local Prescribing Information (Switzerland). [V: Date of revision of text 03/2019; LC]
3. Hydrocortisone sodium succinate Data on File (E83). Pfizer
4. Hydrocortisone sodium succinate Data on File (E158). Pfizer

18.5 Appendix 5: Trial medication label (Danish)

COVID STEROID trial medicin til klinisk forsøg

Hydrocortison 200 mg (4 ml solvens) i 100 ml isoton NaCl ELLER 104 ml isoton NaCl

Infusionshastighed: 4,3 ml/time

Patient navn.....

Cpr. Nummer.....

Dato og klokkeslæt for blanding af forsøgsmedicinen.....

Signatur.....

Holdbar til 24 timer efter blanding

Må ikke opbevares over 25 °C

Ved spørgsmål kontakt HOTLINE: Tlf: 35 45 72 37

Sponsor: Prof. Anders Perner, Intensiv terapiklinik 4131, Rigshospitalet, Tlf. 35458333

COVID STEROID trial medicin til klinisk forsøg

Hydrocortison 50 mg (1 ml solvens) i 9 ml isoton NaCl ELLER 10 ml isoton NaCl

Til injektion

Patient navn.....

Cpr. Nummer.....

Dato og klokkeslæt for blanding af forsøgsmedicinen.....

Signatur.....

Holdbar til 24 timer efter blanding

Må ikke opbevares over 25 °C

Ved spørgsmål kontakt HOTLINE: Tlf: 35 45 72 37

Sponsor: Prof. Anders Perner, Intensiv terapiklinik 4131, Rigshospitalet, Tlf. 35458333

18.6 Appendix 6: Charter for the independent data monitoring and safety committee

Introduction

The Data Monitoring and Safety Committee (DMSC) will constitute its own plan of monitoring and meetings. However, this charter defines the minimum of obligations and primary responsibilities of the DMSC, its relationship with other trial components, its membership, and the purpose and timing of its meetings, as perceived by the COVID STEROID Management Committee. The charter also outlines the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC are responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the trial. The DMSC will provide recommendations about stopping or continuing the trial to the Management Committee of the COVID STEROID trial. The DMSC may also – if applicable - formulate recommendations related to the selection/recruitment/retention of participants, their management, adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the COVID STEROID Management Committee. The Management Committee will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the COVID STEROID trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC, Susanne Rosthøj from the Department of Biostatistics, University of Copenhagen. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail to discuss the safety for trial participants. The DMSC can, at any time during the trial, request information about the distribution of events, including outcome measures and serious adverse reactions (SARs) according to group allocation. Further, the DMSC can request unmasking of the interventions, if deemed important (see section on ‘closed sessions’). The recommendations of the DMSC

regarding stopping, continuing or changing the design of the trial should be communicated without delay to the COVID STEROID Management Committee. As fast as possible, and no later than 48 hours, the Management Committee has the responsibility to inform all trial sites and investigators, about the recommendation of the DMSC and the Management Committee decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of a clinician, a trialist and a biostatistician that, collectively, has experience in the conduct, monitoring and analysis of randomised clinical trials.

DMSC Clinician

Christian Hassager, Professor in cardiology, Copenhagen University Hospital, Denmark

DMSC Trialist

Manu Shankar-Hari, Clinician Scientist, Reader and Consultant in Intensive Care Medicine, National Institute for Health Research and Kings College, London, United Kingdom

DMSC Biostatistician

Susanne Rosthøj, Department of Biostatistics, University of Copenhagen

Conflicts of interest

The members of the DMSC will fill-in and sign a conflicts of interest form. DMSC membership is restricted to individuals free of conflict of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, or individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. Furthermore. the DMSC members do not own stocks in the companies having products being evaluated by the COVID STEROID trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any DMSC members who develop significant conflicts of interest during the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the trial, the Management Committee will appoint the replacement(s).

Formal interim analysis meetings

Three formal interim analyses meetings will be held to review data related to protocol adherence, treatment efficacy and participant safety. The 3 members of the DMSC will meet when 28-day follow-up data of 250 participants (25% of sample size) have been obtained; when 28-day follow-up data of 500 participants (50% of sample size) have been obtained; and again when 28-day follow-up data of 750 (75% of sample size) participants have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure that the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the Management Committee. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about protocol adherence and the relative efficacy and safety of interventions. To ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participants, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the Management Committee.

Closed reports will include analysis of the primary outcome measure and rates of SARs. These closed reports will be prepared by the independent DMSC biostatistician, with assistance from the trial data manager, in a manner that allow them to remain blinded. The closed reports should provide information that is accurate, with follow-up on the primary outcome that is complete as soon as possible and at latest within one month from the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent DMSC statistician will prepare these open reports in co-operation with the trial data manager. The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Management Committee

The planned interim analyses will be conducted after participants no. 250, no. 500 and no. 750 have been followed for 28 days.

After the interim analysis meetings, the DMSC will make a recommendation to the Management Committee to continue, hold or terminate the trial.

The independent DMSC will recommend pausing or stopping the trial if group-differences in the primary outcome measure, SARs or suspected unexpected serious adverse reactions (SUSARs) are observed at the interim analyses with statistical significance levels adjusted according to the O'Brien-Fleming alfa-spending function (33). If the recommendation is to stop the trial, the DMSC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomised after this interim analysis) or whether a moratorium shall take place (setting the trial at hold) in the further inclusion of participants during these extra analyses. If further

analyses of the participants included after the interim analysis is recommended, the rules for finally recommending stopping of the trial should obey the O'Brien-Fleming stopping boundary (33). Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility will not be an option as an intervention effects less than those estimated in the power calculation for the primary outcome may be clinically relevant as well.

All recommendation will be based on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The Management Committee is jointly responsible with the DMSC for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or change the conduct of the trial made by the DMSC will be considered and accepted or rejected by the Management Committee. The Management Committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

After completion of the first interim analysis (250 patients have been followed for 28 days), the recommendations from the DMSC and the conclusion reached by the Management Committee will be submitted to the Ethics Committee.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the COVID STEROID trial protocol. For the two intervention groups, the DMSC will evaluate data on:

- Days alive without life support at day 28 (including 28-day mortality)
- The number of SARs

The DMSC will be provided with these data from the coordinating centre as:

- Number of participants randomised
- Number of participants randomised per intervention group

- Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating center and when to perform the next analysis of the data. For analyses, the data will be provided in one file as described below.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC

The DMSC will be provided with a SAS file (alternatively R, Excel file, .txt file or STATA as convenient) containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of participants having entered the trial) each contains the data of one participant.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database for the all three interim analyses:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received
3. days_alive_without_lifesup_d28_cum_indic (continuous scale)
4. day_28_indic: 28 day-mortality indicator (2 = censored, 1=dead, 0=alive at day 28)
5. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SAR)

18.7 Appendix 7: Informed consent

Participants will be enrolled after consent by proxy is obtained according to Danish regulations. We will follow the normal procedures for collection of informed consent and any modifications to these as approved by the Ethics Committee due to restrictions in physical visits to the hospitals during the current SARS-CoV-2 epidemic. All consenting parties will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial.

All patients with COVID-19 and severe hypoxia will be temporarily incompetent because of the acute illness, low oxygen saturation and stress-response associated with lack of oxygen. Thus, participants will be enrolled after obtaining informed consent from a doctor (first trial guardian), who is independent of the trial, who has knowledge of the clinical condition and who is familiar with the trial protocol to such extent that he/she can judge for each patient, if it will be reasonable to enrol the patient in the trial.

As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second trial guardian.

The second trial guardian is also a doctor who is independent of the trial, who has knowledge of the clinical condition and who is familiar with the trial protocol to such extent that he/she can judge for each patient, if it will be reasonable to enrol the patient in the trial.

To minimise the risk of transmission of SARS-CoV-2 between trial staff and the next of kin, we will inform and obtain informed consent from the next of kin by telephone. We will contact the next of kin by telephone and arrange a time and date for a telephone conversation with a member of the trial staff (e.g. doctor, research nurse, medical student etc) who is certified in obtaining informed consent. During this conversation, we will arrange how to send the written information to the next of kin (i.e. e-mail, post). We will encourage the next of kin to read the written information before the next conversation. We will also encourage the next of kin to bring a companion; in this case, the telephone conversation will be held with the telephone on speaker. After we have informed the next of kin about the trial, we will ask the next of kin to return the signed consent form either by text message, e-mail or post.

Participants will be asked for informed consent as soon as possible after they regain consciousness. For participants, both oral and written information will be given preferably in person. The participant has the right to bring a companion.

If deemed necessary by the treating doctor, we will inform the patient orally before enrolment. In these instances, we will not include the patient, if he/she declines to participate. If the patient accepts to participate, we will re-inform the patient once he/she has regained full competence, i.e. when the patient receives less than 10 L/min of supplementary oxygen; is not mechanically ventilated; and is awake, alert and oriented as judged by treating clinician. First hereafter, we will collect the informed consent. For these patients, the procedure for obtaining informed consent will follow the same rules as stated above.

All consent forms will be signed by the consenting party and the member of trial staff who have provided trial information for the consenting party. We will emphasise that the consenting party has at least 24 hours to decide whether to give consent or not. Written information and the consent forms will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the participant's next of kin

If information about the participant's next of kin is not available after inclusion, the investigator will seek information from e.g. the participant's general practitioner, the police, nursing homes etc. In these situations, it may take 1-2 weeks to conclude that no next of kin can be identified. If a next of kin is not identified and the participant remains incompetent, the trial intervention will be discontinued. All initiatives to identify the participant's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the participant's next of kin and the participant deceases

If the participant deceases before informed consent has been obtained (due to rapid progression of critical illness or because the participant's next of kin is not yet identified) and the participant has been correctly included in the trial, the collected data will be kept for analysis.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent participants, the participant can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific participant, so we find that this question is redundant, and have omitted the question from the consent form to spare the participant from making unnecessary decisions.

Trial personnel

Screening will be performed by the clinical staff. Collection of informed consent will be performed by the dedicated trial staff. If questions arise during informed consent, responsible trial staff can be reached through a 24-h hotline. All personnel with functions in the COVID STEROID trial will be trained and approved according to GCP-guidelines before engaging in the trial.

18.8 Appendix 8: Co-enrolment

Based upon an updated critical appraisal of the literature, the COVID STEROID Management Committee endorses and encourages co-enrolment in the COVID STEROID trial. The following issues have been considered.

Ethical considerations

Preventing eligible patients from co-enrolment in trials, which they would authentically value participating in, and whose material risks and benefits they understand, violates their autonomy - and thus contravenes a fundamental principle of research ethics (38).

Permitting co-enrolment is in accordance with existing recommendations for the conduct of trustworthy clinical practice guidelines, taking into account benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations, as outlined by the Institute of Medicine, the Guideline International Network, and according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (39-41).
Patient relatives have limited concerns about co-enrolment (42).

General considerations

Critically ill patients receive many different interventions in addition to the trial intervention because of acute and chronic illness. Consequently, the potential for interactions is a prerequisite in clinical trials in critically ill patients, and co-enrolment is thus little different from what occurs in single-enrolment trials (38).

In pragmatic trials, like the COVID STEROID trial, other interventions will be given at random and are therefore difficult to control for. If interaction in fact is an issue, it may be better controlled for if patients are co-enrolled and randomised to more than one intervention.

Clinical research with a potential to inform and improve clinical practice is valuable and should be supported. More high-quality clinical research can be conducted in a timely fashion and more information can be generated to guide clinical practice, if co-enrolment is permitted (43).

Scientific and statistical considerations

Pragmatic clinical trials allowing inclusion of a broad range of trial participants and options for drug treatments and other therapies (co-enrolment) have higher external validity/generalizability than non-pragmatic trials with restrictions regarding trial participants and co-enrolment (44).

Non-pragmatic trials with restrictions regarding study participants and co-enrolment are exposed to drugs and other treatments in a less clinically relevant setting where interactions are largely uncontrolled and poorly evaluated. Co-enrolment in pragmatic trials facilitates evaluation of clinically relevant and patient-important interactions (38).

Co-enrolment into two or more trials does not invalidate the original randomization of the individual trials. Separate analysis of each individual trial, ignoring the issue of co-enrolment into the other trial, will retain the balance of patient characteristics expected by standard random assignment within each trial (38).
The National Institute of Health supports co-enrolment (44); so does the Canadian Critical Care Trials group (http://www.ccctg.ca/Home.aspx) and the Australian New Zealand Intensive Care Society's Clinical Trial Group (http://www.anzics.com.au/Pages/CTG/CTG-home.aspx). We have co-enrolment agreements with the two latter research groups.

Co-enrolment into two or more trials does not seem to affect the natural course of the disease of the other condition being studied (38).

Co-enrolment does not appear to influence patient safety or trial results (45, 46).

Empirically, co-enrolment has a small effect on study power (38).

In conclusion, we highly support and encourage co-enrolment because of overall benefit, including ethical, practical and scientific benefit, and no evidence of harm.

Co-enrolment agreement form

We will encourage engagement in research projects other than the COVID STEROID trial.
Please fill in the information of the trial to be evaluated as counterpart for co-enrolment with the COVID STEROID trial and send it by e-mail to contact@cric.nu.

Once we have received the information below, we will contact the principal/coordinating investigator of the trial and facilitate exchange of protocols and other relevant documents between the Management Committees. You will find a list of titles already considered for co-enrolment by clicking http://www.cric.nu/covid-steroid-trial-co-enrolment-list/

We have prepared the form for only one trial, but please feel free to copy as many forms as you need. The co-enrolment agreement form can be found by clicking http://www.cric.nu/covid-steroid-co-enrolment-form/

Official full/short title of the project:

Contact information of principal/coordinating investigator of the trial:

Name:

E-mail:

18.9 Appendix 9: List of proposed sub-studies

A Bayesian re-analysis of all outcomes reported in primary publication (follow up until day 28).