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ORIGINAL ARITLCE

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Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial—Protocol and statistical analysis plan

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus-2 has caused a pandemic of coronavirus disease (COVID-19) with many patients developing hypoxic respiratory failure. Corticosteroids reduce the time on mechanical ventilation, length of stay in the intensive care unit and potentially also mortality in similar patient populations. However, corticosteroids have undesirable effects, including longer time to viral clearance. Clinical equipoise on the use of corticosteroids for COVID-19 exists.

Methods: The COVID STEROID trial is an international, randomised, stratified, blinded clinical trial. We will allocate 1000 adult patients with COVID-19 receiving ≥10 L/min of oxygen or on mechanical ventilation to intravenous hydrocortisone 200 mg daily vs placebo (0.9% saline) for 7 days. The primary outcome is days alive without life support (ie mechanical ventilation, circulatory support, and renal replacement therapy) at day 28. Secondary outcomes are serious adverse reactions at day 14; 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. We will conduct the statistical analyses according to this protocol, including interim analyses for every 250 patients followed for 28 days. The primary outcome will be compared using the Kryger Jensen and Lange test in the intention to treat population and reported as differences in means and medians with 95% confidence intervals.

Discussion: The COVID STEROID trial will provide important evidence to guide the use of corticosteroids in COVID-19 and severe hypoxia.

1 | INTRODUCTION

Severe acute respiratory syndrome corona-virus-2 (SARS-CoV-2) is a novel coronavirus that has caused an ongoing pandemic of coronavirus disease 2019 (COVID-19).[1] As of 25 June 2020, there have been at least 9 450 000 confirmed cases and 480.000 deaths from COVID-19 globally.[2]

The clinical spectrum of SARS-CoV-2 varies from asymptomatic infection to severe pneumonia and acute respiratory distress syndrome (ARDS).[3,4] Current estimates suggest that between 20% and 40% of hospitalised COVID-19 patients develop ARDS.[3,5-8] Furthermore, 20%-35% of those patients admitted to the intensive care unit (ICU) may develop septic shock.[3,6,7,9,10] Both conditions are associated with high morbidity and mortality.[3,11]

At present, the treatment for critically ill patients with COVID-19 is primarily supportive, including oxygen treatment and mechanical ventilation.

Low-dose corticosteroids may potentially improve oxygenation and reduce lung-tissue damage in COVID-19 by their immunosuppressive actions.[12] Low-dose corticosteroids decrease the time on mechanical ventilation, the duration of shock or time on circulatory support, the length of ICU stay, and may reduce mortality in patients with sepsis and ARDS.[9,13,14] The effects of corticosteroids in viral pneumonia are, however, less certain, and observational data have suggested longer time to viral clearance with corticosteroids potentially due to their immunosuppressive action.[15] At the time of writing the COVID STEROID protocol, no randomised clinical trials of corticosteroids in patients with COVID-19 had been published, and current clinical guidelines are contradictory.[9,16,17]

The aim of the COVID STEROID trial is to assess the effects of low-dose hydrocortisone vs placebo on patient-centred outcome measures in adult patients with COVID-19 and severe hypoxia. In this manuscript, we outline the rationale, methods and the detailed statistical analysis plan for the COVID STEROID trial. We hypothesise that low-dose hydrocortisone will increase the number of days alive without life support as compared to placebo.

2 | MATERIALS AND METHODS

2.1 | Trial design

The COVID STEROID trial is an international, investigator-initiated, multicentre, centrally randomised, stratified, parallel-grouped, blinded, placebo-controlled trial to determine whether hydrocortisone therapy increases the days alive without the need for life support in hospitalised patients with COVID-19 and severe hypoxia. It is anticipated that the study will enroll 1000 adult patients with COVID-19 from participating centers in Denmark, Sweden, Switzerland, and India over a 12-month period.

2.2 | Trial conduct

This protocol has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[18] The trial will adhere to this protocol, the Helsinki Declaration in its latest version,[19] the international guidelines for good clinical practice (GCP),[20] and the national laws in the participating countries.

2.3 | Randomisation

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 sizes.

2.4 | Allocation concealment

Eligible patients fulfilling all inclusion criteria and no exclusion criteria are randomised 1:1 using a centralised web-based system according to a computer-generated allocation sequence list, the stratification variables (trial site, invasive mechanical ventilation [y/n], age <70 years [y/n]) using varying block sizes. The allocation sequence list and block sizes are only known by the data manager at the Copenhagen Trial Unit and remain concealed from the investigators until the trial database has been closed, the data analysed and the abstract for the trial report written in two versions.[21]

2.5 | Blinding

We will mask the allocation for the participants, the clinical staff, the trial investigators, the Management Committee, and the trial statistician who will conduct the analyses and the author group while writing the abstract for the trial report with the two intervention groups coded as 0 and 1. A dedicated team of trial site staff who are certified in medicine handling procedures will prepare and document the trial medication unblinded to the allocation. The team of trial site staff preparing trial medication will not be involved in the care of trial participants, data and outcome registration, or the statistical analyses. They will be instructed not to reveal the allocation under any circumstances, unless the participant must undergo emergency unblinding.

2.6 | Inclusion criteria

We will creen patients for enrolment who fulfil all the inclusion criteria:

- Age ≥18 years.
- Confirmed SARS-CoV-2 (COVID-19) requiring hospitalisation.
- Use of one of the following:

  a. Invasive mechanical ventilation **OR**
  b. Non-invasive ventilation or continuous use of continuous positive airway pressure (CPAP) for hypoxia **OR**
  c. Oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system

A detailed description of the inclusion criteria is available in Supporting Information S1.

2.7 | Exclusion criteria

Patients who fulfil one or more of the exclusion criteria below will be excluded:

- Use of systemic corticosteroids.
- Invasive mechanical ventilation >48 hours prior to screening.
- 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 also register the number of patients who are administratively excluded due to enrolment into another interventional trial for which there is no co-enrolment agreement. A detailed description of the exclusion criteria is available in Supporting Information S2.

2.8 | Trial interventions

We will use shelf-medications from the participating hospital department's pharmacy for intervention and control group according to local availability. Drug details on local trade names used will be recorded; the generic brand will be the same at all trial sites (hydrocortisone vs isotonic saline).

2.8.1 | Intervention

Continuous intravenous (IV) infusion of hydrocortisone 200 mg (4 mL) in 100 mL isotonic saline (0.9%) over 24 hours (total 104 mL). The trial intervention will be given for a maximum of 7 days in addition to standard care. If continuous IV infusion is not possible for specific patients, we will allow the use of bolus injections of the trial medication (50 mg in 10 mL every 6 hours). As soon as continuous infusion can be established, this is the preferred route of administration.

2.8.2 | Control

Continuous IV infusion of matching placebo (0.9% isotonic saline) at a dose volume of 104 mL over 24 hours for a maximum of 7 days in addition to standard care (no systemic corticosteroid treatment). If continuous IV infusion is not possible for specific patients, we will allow the use of bolus injections (10 mL saline every 6 hours). As soon as continuous infusion can be established, this is the preferred route of administration.

A detailed description of the preparation of trial medication is available in Supporting Information S3.

2.8.3 | Intervention period

The intervention period is the time spent at a COVID STEROID trial site from randomisation to a maximum of 7 days. If a patient is discharged and readmitted to a COVID STEROID site within the 7-day period, the allocated intervention will be resumed.

2.9 | Outcome measures

2.9.1 | Primary outcome measure

Days alive without the use of life support (ie invasive mechanical ventilation, circulatory support, and renal replacement therapy) from randomisation to day 28.

2.9.2 | Secondary outcome measures

We have eight secondary outcome measures:

- 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 gastrointestinal bleeding, or anaphylactic reaction.
- All-cause mortality at day 28.
- Days alive without life support at day 90.
- Days alive and out of hospital at day 90.
- All-cause mortality at day 90.
- All-cause mortality at 1 year after randomisation.
- Health-related quality of life (HRQoL) at 1 year assessed by EQ-5D-5L[22].
- HRQoL at 1 year assessed by EQ-Visual Analogue Scale (VAS)[22].

At selected sites, participants will be invited to a standard lung function test at 1-year. Detailed definitions of the outcome measures are available in Supporting Information S4.

2.10 | Registered variables

2.10.1 | Baseline variables

1. Sex.
2. Age at admission (date of birth).
3. Date of admission to hospital.
4. Number of days with symptoms before hospital admission.
5. Department at which the participant was included (ie emergency department, hospital ward, intermediate care unit, intensive care unit).
6. Use of respiratory support at randomisation.
   -. Closed system ventilation: invasive mechanical ventilation, non-invasive ventilation, continuous use of CPAP (including latest fraction of inspired oxygen (FiO_2) and duration (hours) prior to randomisation).
   -. Open system ventilation with an oxygen flow ≥10 L/min (including maximum supplemental oxygen flow at randomisation ±1 hour).
7. Treatment for COVID-19 during current hospital admission prior to randomisation:
   -. Agents with potential anti-viral action (ie hydroxychloroquine, remdesivir, lopinavir/ritonavir, convalescent plasma, other).
   -. Anti-bacterial agents (IV, oral or via gastrointestinal (GI) tube).
   -. Agents with potential anti-inflammatory action (ie corticosteroids, IL-6 inhibitors, other).
8. Chronic co-morbidities (ie history of ischaemic heart disease or heart failure, chronic hypertension, diabetes mellitus, chronic pulmonary disease).
9. Laboratory values, interventions and vital parameters, including participant weight, arterial partial pressure of oxygen (PaO_2), saturation of oxygen from arterial blood gas (SaO_2) or pulse oximeter (SpO_2), circulatory support within the last 24 hours prior to randomisation, renal replacement therapy within the last 72 hours, and highest plasma lactate within the last 24 hours prior to randomisation.

2.10.2 | Daily during admission for the first 14 days after randomisation

1. Use of invasive mechanical ventilation.
2. Use of circulatory support (continuous infusion of vasopressor/inotropes for a minimum of 1 hour).
3. Use of any form of renal replacement therapy, including days between intermittent renal replacement therapy.
4. SAR(s) on this day.

We will not record the occurrence of suspected unexpected serious adverse reactions (SUSAR) in the dayforms as these are extremely rare. Instead, investigators will report SUSAR to sponsor if these occur.

2.10.3 | Protocol violations for the first 7 full days after randomisation

1. Use of open-label systemic corticosteroids.
2. Trial medication administration.
   - -. Route of administration (ie continuous infusion, bolus injections, both).
   - -. Administration as per protocol (at least 50% of planned volume).

2.10.4 | Follow-up 28-days after randomisation

1. Vital status (if dead, date of death).
2. Number of days on invasive mechanical ventilation from day 15-28.
3. Number of days with circulatory support (continuous infusion of vasopressor/inotropes for a minimum of 1 hour) from day 15 to 28.
4. Number of days on renal replacement therapy from day 15 to 28, including days between intermittent renal replacement therapy.
5. Use of extracorporeal membrane oxygenation (ECMO) from randomisation to day 28.

2.10.5 | Follow-up 90 days after randomisation

1. Vital status (if dead, date of death).
2. Number of days on invasive mechanical ventilation from day 29 to 90.
3. Number of days with circulatory support (continuous infusion of vasopressor/inotropes for a minimum of 1 hour) from day 29 to 90.
4. Number of days on renal replacement therapy from day 29 to 90, including days between intermittent renal replacement therapy.
5. Date of discharge from hospital.
6. Additional hospital admissions (date of readmission(s) and discharge(s)).

2.10.6 | Follow-up 1 year after randomisation

1. Vital status (if dead, date of death).
2. HRQoL assessed by EQ-5D-5L.[22]
3. HRQoL assessed by EQ-VAS.[22]

Detailed definitions of the registered variables are available in Supporting Information S5.

2.11 | Missing data

If less than 5% of data are missing for the primary or secondary outcome analyses, a complete case analysis will be performed. If there are more than 5% missing data for outcomes and/or covariates in an analysis, we will multiply impute the missing data for that analysis.[23] We will use multiple imputation with chained equations with the *predictive mean matching* and *logistic regression* methods for numerical and categorical variables respectively with 25 datasets imputed separately in each treatment group.[23,24] We will include all stratification variables, all variables used in the applicable analysis, important baseline prognostic variables (age, all co-morbidities listed above, use of all three life support measures at baseline), and all outcomes available at the time of analysis in the imputation models. If multiple imputation is used, these results will be reported as the primary, with complete case analyses and best-worst/worst-best analyses (as previously described[25]) presented as sensitivity analyses in the supplement.

2.12 | General analytical principles

The primary analyses will be performed in the intention-to-treat (ITT) population defined as all randomised participants for whom there is informed consent to use data. In addition, we will conduct sensitivity analyses for the primary outcome in the per-protocol population defined as all randomised participants who received the intervention as assigned by the protocol (ie without one or more major protocol violations as defined under"Registered variables" and "Supporting Information S5").

The primary outcome in the two groups will be assessed in preplanned interim analyses (see below), and the trial can be stopped early. Significance levels are therefore set dynamically (see sample size section). In addition, a hierarchical testing procedure is planned (see below); the significance level in these test and the corresponding confidence intervals follows from the early-stop-indicated significance level. In addition, all secondary outcomes are analysed exploratively at the 5% level; the results of these are presented with 95% confidence intervals.

2.13 | Statistical analyses

2.13.1 | Primary outcome

Primary analysis of the primary outcome

1. Kryger Jensen and Lange test adjusted for stratification variables in the ITT population.[26]

Sensitivity analyses of the primary outcome

2. Kryger Jensen and Lange test adjusted for stratification variables in the per-protocol population.[26]
3. Missing data: best-worst/worst-best case scenarios and complete case analysis (if multiple imputation is used).

Subgroup analysis of the primary outcome

4. Kryger Jensen and Lange test adjusted for stratification variables in the ITT population in the pre-planned subgroups.[26]

The Kryger Jensen and Lange test is a joint test for no treatment effect on an outcome which can have probability point mass in a single value (ie zero days alive without the use of life support within 28 days).[26] The test builds on combining two regressions; we can therefore adjust as per usual analysis despite the outcome being highly skewed.

Results for the primary outcome, including sensitivity analyses, will be reported as differences in unadjusted means and medians along with bootstrapped confidence intervals (see preceding section for details on significance level), calculated using 100 000 bootstrap samples in each treatment group and the percentile method.[27]

As the primary outcome is composite, we will also report each component of this[28] in a supplement to the main report.

2.13.2 | Secondary outcomes

The following analyses will be employed for all binary secondary outcome measures (ie all-cause mortality at day 28, day 90, and 1 year; occurrence of SARs):

1. Fisher's exact test in the ITT population.
2. Generalised linear models with log links and binomial error distributions unadjusted and adjusted for the stratification variables, age, co-morbidities, and use of life support in the ITT population.[29]

Differences in binary outcomes will be quantified using relative risks (RRs) and secondarily risk differences (RDs) along with confidence intervals (see preceding section about significance levels). A Kaplan-Meier survival curve will be reported for the crude data for the secondary outcomes 28-day, 90-day and 1-year mortality.

The mortality outcomes will be tested in a hierarchical procedure along with the primary outcome (first primary outcome, then 28-day mortality, and finally 90-day mortality) reusing the alpha if the previous test was statistically significant. If the primary outcome is not statistically significant at trial conclusion, ordinary 5% level test will be employed for all outcomes, but the results interpreted as exploratory.

The continuous secondary outcome measures (ie days alive without life support at day 90, days alive and out of hospital at day 90, HRQoL at 1 year) will be analysed as follows:

1. Kryger Jensen and Lange test adjusted for stratification variables in the ITT population.

Results will be reported as differences in unadjusted means and medians along with bootstrapped 95% confidence intervals, calculated as specified above.

For the composite secondary outcome measures (ie SARs, days alive without life support at day 90), we will report each component of these outcomes[28] in a supplement to the main report.

2.14 | Sample size and power estimations for the primary outcome measure

A statistician blinded for the allocation groups will conduct interim analyses after every 250 participants have been followed for 28 days. At maximum, we will randomise 1000 participants implying there may be 3 interim analyses. The alpha values for the 3 interim analyses are 0.000015, 0.003045, 0.018323 respectively as by the O'Brien-Fleming bounds, which preserves type I error at the usual 5%.[30] At each analysis time-point, the Kryger Jensen and Lange 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 (ie after 500 participants), 42% probability of stopping at the third interim analysis (ie after 750 participants), and 38% probability of running the trial to the full 1000 participants.

2.15 | Power estimations for the secondary outcome measures

We expect to have 80% statistical power to detect the following effects for the secondary outcomes based on the trial design described above:

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

The estimates of control event rates for mortality at day 28 originate in data of previous COVID-19 studies[3,31]; the estimates of the control event rates for mortality at day 90 and the number of patients with SARs is based on our 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 outcomes would be somewhat uncertain why we refrain from making these estimates.

2.16 | Pre-planned subgroup analyses

We plan to assess any heterogeneity in intervention effects for the primary outcome in the following 6 subgroup analyses based on patient characteristics at baseline:

1. Geographical region (enrolled in Europe compared to in Asia) (hypothesised difference in effect between geographical regions due to differences in standard care and/or populations).
2. Age (<70 compared to ≥70 years of age; hypothesised larger effect of hydrocortisone in the younger patients <70 years of age due to higher risk of undesirable effects in the elderly).
3. Therapeutic agents against COVID-19 (yes/no) (hypothesised larger effect of hydrocortisone in patients receiving agents with potential action against COVID-19).
4. Invasive mechanical ventilation (yes/no; hypothesised larger effect of hydrocortisone in patients who receive invasive mechanical ventilation)
5. Shock (yes/no; hypothesised larger effect of hydrocortisone in patients with shock)
6. Chronic lung disease (yes/no; hypothesised larger effect of hydrocortisone in patients with chronic lung disease)

Detailed definitions of the subgroups are available in Supporting Information S6.

2.17 | Trial profile

At trial completion, we will report the flow of trial participants according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[32]

2.18 | Data Monitoring and Safety Committee

A Data Monitoring and Safety Committee (DMSC) has been formed, consisting of an independent trialist, a clinician and a biostatistician who collectively have experience in the management of critically ill patients and in the conduct, monitoring and analysis of randomised clinical trials. The charter for the DMSC is presented in Supporting Information S7.

2.19 | Interim analyses

We will conduct three interim-analyses:

1. Interim analysis when 250 participants (25%) have been followed for 28 days.
2. Interim analysis when 500 participants (50%) have been followed for 28 days.
3. Interim analysis when 750 participants (75%) have been followed for 28 days.

For all three interim analyses the DMSC will evaluate data on:

- Days alive without life-support from randomisation to day 28 (primary outcome, including all-cause mortality at day 28).
- Number of patients with one or more SARs and SUSARs from randomisation to day 14 (secondary outcome).

The DMSC will be provided a masked data set (intervention groups as 0 and 1) from the coordinating centre. The data set will include data on stratification variables and outcome measures according to the outcomes above in the two groups.

Based on these data, the DMSC will decide if they request further data from the coordinating centre. The DMSC can request distribution of events, including outcome measures, across the intervention groups at any time during the trial. Furthermore, the DMSC can request unblinding of the intervention groups at any time. The interim analyses will be performed by an independent statistician. The DMSC may recommend to pausing or stopping the trial if a group-difference in the primary outcome, SARs and SUSARs is found in the interim analyses with statistically significant levels based on O'Brien-Fleming bounds as specified above. At each analysis time-point, the Kryger Jensen and Lange test in the ITT population 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.

The DMSC will submit their recommendations to the Management Committee, which make the final decision regarding the continuing, pausing or stopping of the trial.

2.20 | Monitoring during the study

The trial will be externally monitored according to the GCP Directive with a monitoring and data verification plan including documentation

of informed consent for all trial participants. In addition, we will use central monitoring of trial sites through the eCRF, including adherence to the protocol.

2.21 | Close out

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation.

3 | DISCUSSION

The current management of patients with COVID-19 primarily involves supportive care. Together with data from other ongoing randomised clinical trials,[33-41] the COVID STEROID trial data will provide important knowledge on the benefits and harms of the use of corticosteroids in adults with COVID-19 and severe hypoxia. At the time of writing the COVID STEROID protocol, no randomised clinical trials of corticosteroids in patients with COVID-19 had been published, and current clinical guidelines are contradictory.[9,16,17]

3.1 | Strengths

We publish this protocol and detailed statistical analysis plan prior to the analyses of any data in the COVID STEROID trial. The strengths of our trial include the high methodological standards of a large-scale, international, blinded, placebo-controlled, randomised clinical trial, and high external validity with trial sites in both Europe and Asia. We will report patient-centred outcomes, including days alive without life support, SARs, mortality, and HRQoL. The pragmatic design enables all other treatments than the intervention and control to follow standard care. The trial is monitored according to the Good Clinical Practice (GCP) standards.[20] The detailed power calculations, including three planned interim analyses, allow for the earliest possible detection of benefit or harm from the intervention as improvements in the treatment of COVID-19 are urgently warranted. Furthermore, we will perform a pre-planned secondary Bayesian analysis (details to be specified prior to database lockdown) as a supplement to the conventional analyses, which may help interpret the trial results.

3.2 | Limitations

The number of patients with COVID-19 and severe hypoxia may decline over time in the active trial sites. If so, it may be difficult to produce timely results to benefit patients affected in other geographical regions.

All clinical staff are blinded to the allocation. However, hyperglycaemia and manifestation of latent diabetes mellitus are common adverse effects of corticosteroids[42] that may potentially reveal the allocation for the clinical staff. Yet, both hyperglycaemia and diabetes are common complications in critically ill patient in general.[43] However, very few hyperglycaemic episodes were observed in previous randomised trials assessing the intervention used in the COVID STEROID trial in patients with septic shock.[44,45]

The administration of daily trial medication will be subject to protocol violations expected to occur in complex clinical situations. We will perform sensitivity analyses exploring the primary outcome in the per-protocol population deprived of all patients with a protocol violation.

We chose days alive without life support at day 28 as the primary outcome to be able to detect the earliest possible difference in patient-centred outcomes of corticosteroids vs placebo. This may impact both patients and society in general as the number of patients requiring intensive care have exceeded the maximum capacity of the ICUs in several countries. Moreover previous systematic reviews of critically ill patients with severe infection and/or severe respiratory failure have shown a reduction in days ventilated and days in shock with the use of corticosteroids.[9,13] The effect of corticosteroids on mortality is smaller or less certain,[9,13,46] and the outcomes "days alive without life support" and "mortality" are expected to be affected in the same direction by hydrocortisone vs placebo. This is, however, uncertain, and all-cause mortality is likely more important to patients.

3.3 | Perspectives

There are several other trials on corticosteroid in patients with severe COVID-19; together these trials may accrue enough participants to show benefit or harm from corticosteroids before any of the single trials. International collaborative research initiatives have been formed with the aim of harmonising and coordinating data collection to enable prospective meta-analyses of the ongoing randomised trials of corticosteroids for COVID-19.

4 | CONCLUSIONS

In conclusion, the COVID STEROID trial is a large-scale, international, multicentre, blinded, placebo-controlled, randomised clinical trial assessing the effects of low-dose hydrocortisone vs placebo on patient-centred outcomes in adult patients with COVID-19 and severe hypoxia. In this manuscript, we have outlined the protocol and a detailed statistical analysis plan. The trial results will, irrespective of their direction, provide important evidence to inform the clinical decision on the use of corticosteroids in patients with COVID-19 and severe hypoxemia.

4.1 | Ethical considerations and consent to participate

The trial is registered at the European Union Drug Regulation Authorities Clinical Trials Database (EudraCT; 2020-001395-15) and at ClinicalTrials.gov (NCT04348305). It is approved by the Danish Medicines Agency (2020034528), the Danish National Committee on Health Research Ethics (H-20022573), and The Capital Region Knowledge Centre for Data Compliance (P-2020-275) and will be approved by all applicable authorities in the other participating countries before inclusion in these countries.

Consent will be obtained according to national laws on deferred consent for temporary incompetent patients in the participating countries.

4.2 | Data sharing statement

The final de-identified dataset used for analysis will be available for sharing according to the recent International Committee of Medical Journal Editors (ICMJE) recommendations[47] and data sharing agreements adhering to the laws of the participating countries. All trial-related documents are available from www.cric.nu/covid-steroid-trial/.

4.3 | Dissemination

After completion, the trial results will be submitted to a peer-reviewed medical journal irrespective of their direction. In addition, the trial results will be published at www.cric.nu. We will adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement including the accountability of all patients screened.[32]

4.4 | Status

The trial was initiated on 15 April 2020 and is expected to enrol until 2021. At present, 19 sites in Denmark are actively recruiting participants. We have enrolled 30 patients by 16 June 2020.

On 16 June 2020, a press release from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial was published with preliminary results on 28-day mortality for hospitalised patients with suspected or confirmed COVID-19 receiving systemic dexamethasone 6 mg daily for a maximum of 10 days vs no treatment. Overall, dexamethasone reduced the 28-day mortality in all hospitalised patients with suspected or confirmed COVID-19 (rate ratio 0.83, 95% confidence interval [CI] 0.74-0.92; $P = .0007$) with greatest benefit among patients requiring ventilation.[48] On 22 June 2020, the preprint of the RECOVERY trial also became available.[49]

Due to the results of the RECOVERY trial, the Management Committee of the COVID STEROID trial decided to pause enrolment as of 16 June 2020. The trial is officially paused until the full peer-reviewed RECOVERY paper and the results of an ongoing prospective meta-analysis of corticosteroids for COVID-19 are published.

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CONFLICT OF INTEREST

The Department of Intensive Care, Rigshospitalet, has received funds for other research projects from the Novo Nordisk Foundation, Ferring and Fresenius Kabi. Dr Benfield reports grants from Pfizer, grants from Novo Nordisk Foundation, grants from Lundbeck Foundation, grants from Simonsen Foundation, grants and personal fees from GSK, grants and personal fees from Pfizer, personal fees from Boehringer Ingelheim, grants and personal fees from Gilead, personal fees from MSD, grants from Lundbeck Foundation, grants from Kai Hansen Foundation, outside the submitted work. The Department of Intensive Care Medicine, Bern University Hospital (Inselspital), has or has had research & development/consulting contracts with Edwards Lifesciences Services GmbH, Phagenesis Limited and Nestlé. The money was paid into a departmental fund, and none of the authors received any financial gain. The Department of Intensive Care Medicine, Bern University Hospital (Inselspital), has received unrestricted educational grants from the following organisations for organising bi-annual postgraduate courses in the fields of critical care ultrasound, management of extracorporeal membrane oxygenation (ECMO) and mechanical ventilation: Pierre Fabre Pharma AG (formerly known as RobaPharm), Pfizer AG, Bard Medica SA, Abbott AG, Anandic Medical Systems, PanGas AG Healthcare, Orion Pharma, Bracco, Edwards Lifesciences AG, Hamilton Medical AG, Fresenius Kabi (Schweiz) AG, Getinge Group Maquet AG, Dräger Schweiz AG, and Teleflex Medical GmbH. Dr Friberg Hitz has received grants from OrklaCare, UCB, Ellab Fond and Amgen, and received personal payment in relation to lectures and advisory boards, none of which have any relation to the present trial. The remaining authors have no conflicts of interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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