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Higher vs lower doses of dexamethasone in patients with COVID-19 and severe hypoxia (COVID STEROID 2) trial: Protocol and statistical analysis plan

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Background: The coronavirus disease 2019 (COVID-19) pandemic has resulted in millions of deaths and overburdened healthcare systems worldwide. Systemic low-dose corticosteroids have proven clinical benefit in patients with severe COVID-19. Higher doses of corticosteroids are used in other inflammatory lung diseases and may offer additional clinical benefits in COVID-19. At present, the balance between benefits and harms of higher vs. lower doses of corticosteroids for patients with COVID-19 is unclear.

Methods: The COVID STEROID 2 trial is an investigator-initiated, international, parallel-grouped, blinded, centrally randomised and stratified clinical trial assessing higher (12 mg) vs. lower (6 mg) doses of dexamethasone for adults with COVID-19 and severe hypoxia. We plan to enrol 1,000 patients in Denmark, Sweden, Switzerland and India. The primary outcome is days alive without life support (invasive mechanical ventilation, circulatory support or renal replacement therapy) at day 28. Secondary outcomes include serious adverse reactions at day 28; all-cause mortality at day 28, 90 and 180; days alive without life support at day 90; days alive and out of hospital at day 90; and health-related quality of life at day 180. The primary outcome will be analysed using the Kryger Jensen and Lange test adjusted for stratification variables and reported as adjusted mean differences and median differences. The full statistical analysis plan is outlined in this protocol.

Discussion: The COVID STEROID 2 trial will provide evidence on the optimal dosing of systemic corticosteroids for COVID-19 patients with severe hypoxia with important implications for patients, their relatives and society.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in thousands of deaths and overburdened healthcare systems worldwide.[1] SARS-CoV-2 can cause systemic hyperinflammation and acute respiratory distress syndrome (ARDS),[2] a condition occurring in up to 40% of hospitalised patients with COVID-19.[3-7]

Until recently, the care of COVID-19 patients was primarily supportive, including respiratory support. On 16 June 2020, the preliminary results of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial were publicly announced.[8] In this randomised clinical trial (RCT), 6,425 hospitalised patients with suspected or

confirmed COVID-19 were randomised to open-label dexamethasone 6 mg daily for up to 10 days or usual care.[8] The results demonstrated a 17% relative risk reduction (95% confidence interval (CI) 0.74 to 0.92%) in 28-day mortality with dexamethasone with a possible larger clinical benefit in patients receiving invasive mechanical ventilation.[8]

The results from all critically ill patients included in the RECOVERY trial and 6 other ongoing or recently completed RCTs were summarised in a prospective meta-analysis that demonstrated lower 28-day mortality among patients who received corticosteroids as compared with usual care or placebo (odds ratio (OR) 0.66, 95% CI 0.53 to 0.82).[9] Following these results, updated guidelines from the World Health Organization (WHO), the National Institutes of Health and the Infectious Diseases Society of America now recommend systemic low-dose corticosteroids for 7-10 days in patients with COVID-19 requiring supplemental oxygen.[10-12]

In July 2020, we surveyed doctors at potential COVID STEROID 2 trial sites to assess clinician's preferences for systemic corticosteroid use in patients with severe COVID-19 after the preprint publication of the RECOVERY trial (unpublished data). Among 240 anonymous responders, 56% would use 6 mg of dexamethasone or equivalent, and 36% would use a dose above 6 mg (Figure 1). As for preferences for an upcoming trial, most would enrol patients with severe COVID-19 into a trial of different doses of corticosteroids, primarily into one comparing 12 mg vs. 6 mg of dexamethasone (55%, Figure 2).

With short-term use in healthy volunteers, a dose-dependent activation of the corticosteroid receptor has been observed for increasing doses up to 60 mg of prednisone (equivalent to 12 mg of dexamethasone), suggesting that doses up to 12 mg of dexamethasone may offer additional anti-inflammatory effects, while adverse effects seemed independent of the dosing.[13] Higher doses of dexamethasone have also been used in a RCT in non-COVID-19 patients with ARDS suggesting benefit without an increased risk of serious adverse events.[14] Several ongoing or completed trials have assessed corticosteroids for severe COVID-19 using different types (ie dexamethasone, methylprednisolone, hydrocortisone or prednisone) and doses (median dose in dexamethasone equivalents 15 mg, interquartile range (IQR) 10 to 16 mg) of corticosteroids.[15-29] Most of these trials have not yet been published,[16-18,20,22-26,28,29] and none of them directly compare different dosing regimens, leaving the optimal dosing for severe COVID-19 uncertain.

The aim of the COVID STEROID 2 trial is to compare the effects of 12 mg vs 6 mg of intravenous (IV) dexamethasone for up to 10 days on the number of days alive without life support and other patient-centred outcomes in adult patients with COVID-19 and severe hypoxia. We hypothesise that dexamethasone 12 mg will increase the number of days alive without life support as compared to dexamethasone 6 mg in patients with COVID-19 and severe hypoxia.

2 | METHODS

2.1 | Trial design

The COVID STEROID 2 trial is an investigator-initiated, international, parallel group, blinded, centrally randomised and stratified clinical trial. We plan to enrol 1,000 hospitalised adult patients with COVID-19 and severe hypoxia from sites in Denmark, Sweden, Switzerland and India. All trial results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.[30]

2.2 | Trial conduct

We have prepared the COVID STEROID 2 protocol in accordance with the Standard Protocol Items: Recommendations for Interventional

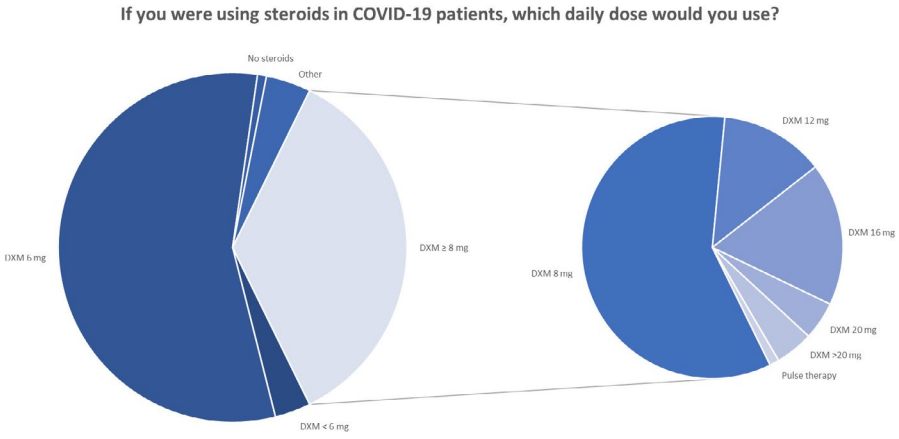

FIGURE 1 Dose preferences in corticosteroid use for COVID-19 patients among 240 survey responders from Denmark, Sweden, Switzerland and India. In the survey, all dose options were stated as equivalents of dexamethasone, betamethasone, hydrocortisone, methylprednisolone and prednisone. COVID-19, coronavirus disease 19; DXM, dexamethasone; mg, milligrams [Colour figure can be viewed at wileyonlinelibrary.com]

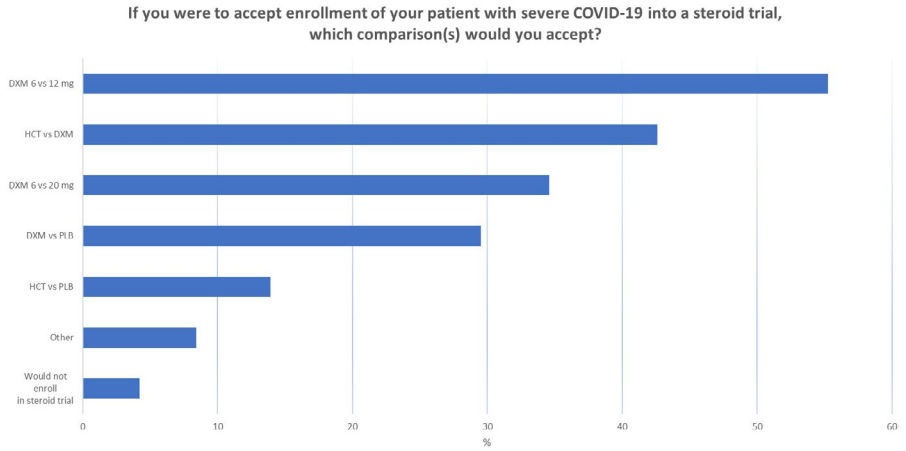

FIGURE 2 Preferences in comparisons for future trial in COVID-19 patients among 237 responders from Denmark, Sweden, Switzerland and India. Survey responders were able to tick one or more comparisons. COVID-19, coronavirus disease 19, DXM, dexamethasone, mg, milligrams, HCT, hydrocortisone; PLB, placebo. [Colour figure can be viewed at wileyonlinelibrary.com]

Trials (SPIRIT) Guidelines (Supporting Information S1).[31] The trial will be conducted in accordance with the trial protocol, the Helsinki Declaration (latest version),[32] the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (latest version)[33] and all applicable laws in the participating countries.

2.3 | Randomisation

Participants will be randomised in a 1:1 ratio to 12 mg vs 6 mg of dexamethasone using a central web-based randomisation system administered by the Copenhagen Trial Unit (CTU). The randomisation will be performed using computer-generated allocation sequence lists stratified by trial site, invasive mechanical ventilation (yes/no) and age below 70 years (yes/no) with varying block sizes.

2.4 | Allocation concealment

The allocation sequence will be unknown to the trial staff preparing the trial medication, the clinicians, the investigators and the statistician conducting the analyses. The group allocations will remain masked (coded as 0 and 1) until two versions of the abstract for the trial report have been written.

2.5 | Blinding

The allocation will be masked for all participants, clinical staff, trial staff reporting outcome data, the COVID STEROID 2 Management Committee and the trial statistician.

Unblinded trial staff will prepare the trial medication and register protocol adherence and any violations (ie trial medication not administered as per protocol and use of open-label corticosteroids, respectively) during the intervention period. The unblinded staff will not be involved in the care of trial participants, the entry of outcome data or the statistical analysis. They will be instructed not to reveal the allocation unless the participant is subject to emergency unblinding.

2.6 | Inclusion criteria

We will screen for enrolment of adults with COVID-19 and severe hypoxia fulfilling the following three inclusion criteria:

- Aged 18 years or above **AND**
- Confirmed SARS-CoV-2 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.

A detailed description of the inclusion criteria is provided in the Supporting Information S2.

2.7 | Exclusion criteria

Any patient fulfilling one or more of the following exclusion criteria at the time of screening will be excluded from the trial:

- Use of systemic corticosteroids for other indications than COVID-19 in doses higher than 6 mg dexamethasone equivalents.
- Use of systemic corticosteroids for COVID-19 for 5 consecutive days or more.
- Invasive fungal infection.
- Active tuberculosis.

- Fertile woman (<60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG.
- Known hypersensitivity to dexamethasone.
- Previously randomised in the COVID STEROID 2 trial.
- Informed consent not obtainable.

We will allow co-enrolment with other clinical trials unless the interventions or protocols of the trials collide. A detailed description of the exclusion criteria is provided in the Supporting Information S3.

2.8 | Trial interventions

We will use shelf-medications from the hospital departments' pharmacies for the trial medication. For each participant, the trial medication will be prepared once daily by the unblinded trial staff and administered as a bolus injection (5 ml) by the clinical staff. All other interventions will be given at the discretion of the treating clinicians.

A list of trade names and a detailed description of the preparation of trial medication used in the COVID STEROID 2 trial is provided in the Supporting Information S4 and S5.

2.8.1 | Higher dose of dexamethasone

For patients randomised to a higher dose of dexamethasone, 12 mg of IV dexamethasone will be given daily as bolus injection (5 ml) for up to 10 days. We will allow the use of betamethasone 12 mg at sites where dexamethasone is not available as these are diastereomers and likely equipotent.[34]

2.8.2 | Lower dose of dexamethasone

For patients randomised to a lower dose of dexamethasone, 6 mg of IV dexamethasone will be given daily as bolus injection (5 ml) for up to 10 days. We will allow the use of betamethasone 6 mg at sites where dexamethasone is not available as these are diastereomers and likely equipotent.[34]

2.8.3 | Intervention period

The intervention period is up to 10 days from randomisation or until hospital discharge or death, whichever is earlier. For each participant, the intervention period will depend on the number of consecutive days with corticosteroid use for COVID-19 before randomisation (ie the number of consecutive days with corticosteroid use will be subtracted from the 10-day intervention period). The intervention period will range from 6 to 10 days as all patients who have received corticosteroids for COVID-19 for 5 consecutive days or more will be excluded from the trial.

2.9 | Outcomes

Detailed definitions of all outcome measures are provided in the Supporting Information S6.

2.9.1 | Primary outcome

Days alive without life support (ie invasive mechanical ventilation, circulatory support or renal replacement therapy (including days in between intermittent renal replacement therapy)) from randomisation to day 28.

2.9.2 | Secondary outcomes

- Number of participants with one or more serious adverse reactions (SARs) to dexamethasone from randomisation to day 28 defined as new episodes of septic shock, invasive fungal infection, clinically important gastrointestinal (GI) bleeding or anaphylactic reaction to IV dexamethasone.
- All-cause mortality at day 28.
- All-cause mortality at day 90.
- Days alive without life support at day 90.
- Days alive and out of hospital at day 90.
- All-cause mortality at day 180.
- HRQoL at day 180 using EQ-5D-5L and EQ-VAS.[35]

2.10 | Registered variables

Detailed definitions of the registered variables are provided in Supporting Information S7. Data will be entered in an online electronic case report form (OpenClinica).

2.10.1 | Baseline variables

1. Sex.
2. Age at enrolment (date of birth).
3. Date of admission to hospital.
4. Number of days with symptoms of COVID-19 before hospital admission.
5. Type of 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: invasive mechanical ventilation or non-invasive ventilation or continuous use of CPAP (including latest fraction of inspired oxygen (FiO_2) and number of days on closed system ventilation prior to randomisation).
   -. Open system ventilation with an oxygen flow ≥ 10 L/min (including maximum supplemental oxygen flow at randomisation ± 1 hour).

7. Limitations of care (ie limitations for invasive mechanical ventilation, circulatory support, renal replacement therapy, or cardiopulmonary resuscitation) at the time of randomisation.
8. Chronic use of systemic corticosteroids for other indications than COVID-19.
9. Treatment for COVID-19 during current hospital admission prior to randomisation:
   -. Agents with potential anti-viral action (ie remdesivir, convalescent plasma, other).
   -. Agents with potential anti-inflammatory action (ie Janus kinase inhibitor, interleukin-6 inhibitors, other).
10. Treatment with systemic antibacterial agents in the 24 hours prior to randomisation.
11. Chronic co-morbidities:
   -. History of ischaemic heart disease or heart failure.
   -. Treatment at the time of hospital admission with any antidiabetic drug indicating diabetes mellitus.
   -. Treatment at the time of hospital admission with any drug indicating chronic pulmonary disease.
   -. Use of immunosuppressive therapy within the last 3-months.
12. Laboratory values, interventions and vital parameters:
   -. Participant weight (kilograms).
   -. Arterial partial pressure of oxygen (PaO_2).
   -. Saturation of oxygen (SaO_2) from arterial blood gas sample (preferred) or pulse oximeter.
   -. Use of circulatory support within the last 24 hours prior to randomisation.
   -. Use of any form of renal replacement therapy within the last 72 hours prior to randomisation.
   -. Highest plasma lactate within the last 24 hours prior to randomisation.

2.10.2 | Variables registered daily during admission for the first 14 days after randomisation (day forms)

1. Use of invasive mechanical ventilation.
2. Use of circulatory support (continuous infusion of vasopressor/inotrope 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)
   -. New episodes of septic shock.
   -. Invasive fungal infection.
   -. Clinically important GI bleeding.
   -. Anaphylactic reaction to IV dexamethasone (only recorded during the intervention period)

2.10.3 | Protocol violations during the intervention period

Protocol violations will be recorded during the intervention period (for up to 10 days).

1. Use of open-label systemic corticosteroids.
2. Trial medication not administered as per protocol (1 bolus injection of either 12 mg or 6 mg dexamethasone according to the allocation on each day during the intervention period).

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/inotrope for a minimum of 1 hour) from day 15-28.
4. Number of days on renal replacement therapy (including days between intermittent renal replacement therapy) from day 15-28.
5. The occurrence of SAR(s) (section 2.10.2) from day 15-28 (if yes, apply date(s)).
6. Use of extracorporeal membrane oxygenation from randomisation to day 28 (y/n)
7. Discharged against medical advice to home/other hospital/other facility, including degree of life support (ie mechanical ventilation, circulatory support, renal replacement therapy) or supplementary oxygen at the time of discharge.

We will not register the occurrence of suspected unexpected serious adverse reactions (SUSARs) in dayforms or at 28-day follow-up as these rarely occur. Instead, SUSARs will be reported directly and without delay by the site investigator to the sponsor.

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 29-90.
3. Number of days with circulatory support (continuous infusion of vasopressor/inotrope for a minimum of 1 hour) from day 29-90.
4. Number of days on renal replacement therapy (including days between intermittent renal replacement therapy) from day 29-90.
5. Date of discharge from hospital.
6. Additional hospital admissions (date(s) of re-admission(s) and discharge(s)).

2.10.6 | Follow-up 180 days after randomisation

1. Vital status (if dead, date of death).
2. HRQoL assessed by EQ-5D-5L.[35]
3. HRQoL assessed by EQ-VAS.[35]

2.11 | General analytic principles

We will conduct the primary analyses of both primary and secondary outcomes in the intention-to-treat (ITT) population (ie all randomised participants for whom consent has been given to use data). For the primary outcome, this analysis will be supplemented with a sensitivity analysis in the per-protocol (PP) population (ie the ITT population except those having one or more major protocol violations as defined in section 2.10.3). All statistical tests will be two-tailed and reported with confidence intervals (CIs).

Significance level is set to 5% including the interim analysis. In practice, this means that a *P*-value below 0.0492 will be considered significant if the trial is not stopped at the interim analysis and accordingly 95.08% confidence intervals will be employed. For all secondary outcomes, we will employ 99% CIs for (*P*-value threshold for significance 0.01) due to the multiplicity of these. If not stopped early, 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, 0.01 significance thresholds will be employed for all additional outcomes, but the results interpreted with caution.

2.12 | Missing data

We will perform complete case analyses if less than 5% of patients have missing data for variables included in the primary or secondary outcome analyses. If 5% or more of patients have missing data for the outcome/covariates in any analysis, we will use multiple imputation with chained equations for that analysis. If multiple imputation is used, we will use the predictive mean matching and logistic regression methods for numerical and categorical variables, respectively, with 25 datasets imputed separately in each treatment group.[36,37] We will include all stratification variables, all variables used in the applicable analyses, important baseline prognostic variables (age, all comorbidities listed above, use of all 3 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 and supplemented with complete case analyses and best-worst/worst-best analyses (as previously described[38]).

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 (site, invasive mechanical ventilation, and age below 70 years) in the ITT population.[39]

Sensitivity analysis of the primary outcome

2. Kryger Jensen and Lange test adjusted for stratification variables (site, invasive mechanical ventilation and age below 70 years) and additional important prognostic baseline risk factors, that is all comorbidities listed above, and use of circulatory support or renal replacement therapy in the ITT population.[39]

3. Kryger Jensen and Lange test adjusted for stratification variables (site, invasive mechanical ventilation and age below 70 years) in the PP population.[39]

4. If 5% or more of patients have missing data and multiple imputation is used: best-worst/worst-best case analyses and complete case analysis.[37]

Subgroup analyses of the primary outcome

5. Test of interaction between the intervention and the pre-planned subgroups (section 2.13.4) by Kryger Jensen and Lange test adjusted for stratification variables (site, invasive mechanical ventilation and age below 70 years) in the ITT population.

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 life support within 28 days).[39] The test builds on combining two regressions; we can therefore adjust as per usual analysis despite the expectation that the outcome will be highly skewed.[39]

Results from all analyses of the primary outcome will be reported as adjusted mean differences and median differences with confidence intervals (see preceding section for details on significance level). Secondarily, we will report the unadjusted (crude) mean differences and median differences.

As the primary outcome is composite, we will report results from the analysis of each component in a supplement to the main report.

2.13.2 | Secondary outcomes

Binary outcomes

We will conduct the following analyses for all binary outcomes (ie number of participants with one or more SARs at day 28; all-cause mortality at day 28, 90 and 180):

Primary analysis

1. Generalised linear models with log links and binomial error distributions adjusted for the stratification variables in the ITT population.[40]

Secondary analysis

2. Fisher's exact test in the ITT population.

3. Kaplan-Meier survival curve for the crude data on all-cause mortality at day 28, 90 and 180.

Results will be reported as adjusted relative risks and secondarily adjusted risk differences with corresponding confidence intervals (see section 2.11 for details on significance level). Secondarily, we will report the unadjusted (crude) relative risks and absolute risk differences.

Continuous outcomes

We will conduct the following analyses for all continuous outcomes (ie days alive without life support at day 90; days alive and out of hospital at day 90; HRQoL at day 180 using EQ-5D-5L and EQ-VAS):

1. Kryger Jensen and Lange test adjusted for the stratification variables in the ITT population.[39]

The results will be reported as adjusted mean differences and median differences with confidence intervals (see preceding section for details on significance level) and unadjusted (crude) mean differences and median differences.

For composite outcomes (ie number of participants with one or more SARs at day 28; days alive without life support at day 90), we will report results from the analysis of each component in a supplement to the main report.

2.13.3 | Power estimations

Sample size and power estimations for the primary outcome

At maximum, we will randomise 1000 participants. A blinded statistician will conduct an interim analysis after the first 500 participants have been followed for 28 days. The alpha values for the interim analysis and the final analysis are 0.0054 and 0.0492, respectively as by the O'Brien-Fleming bounds, which preserves type I error at the usual 5%. 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.

Power estimations for the secondary outcomes

We have 80% statistical power to detect the following effects for the secondary outcomes:

- 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 day 180 (control event rate 50%)

The estimates of control event rates for mortality at day 28 originate in data of previous COVID-19 studies;[4,41] the estimates of the control event rates for mortality at day 90 and the number of participants with SARs are based on our best clinical estimate. We expect the outcomes "days alive out of hospital at day 90" and "HRQoL at 180 days" to be highly skewed (non-normally distributed). The power estimations for these outcomes would be uncertain, and we therefore refrain from making these estimates.

2.13.4 | Pre-planned subgroup analyses

We will assess the heterogeneity of the intervention effects on the primary outcome in the following subgroups based on baseline characteristics:

- Patients ≥ 70 years compared to < 70 years of age: hypothesised larger beneficial effect of higher dose dexamethasone in patients < 70 years of age.
- Patients who receive invasive mechanical ventilation compared to oxygen by other delivery systems: hypothesised larger beneficial effect of higher dose dexamethasone in patients who receive oxygen by other delivery systems.
- Patients who received corticosteroids for COVID-19 for 0 to 2 days compared to 3 to 4 days before enrolment: hypothesised larger beneficial effect of higher dose dexamethasone in patients with short duration (≤2 days) of corticosteroid use before enrolment.
- Patients who receive IL-6 inhibitors at baseline compared to patients who do not receive IL-6 inhibitors at baseline: hypothesised larger beneficial effect of higher dose dexamethasone in patients who receive IL-6 inhibitors at baseline.
- Patients with limitations of care (ie not for invasive mechanical ventilation, circulatory support, renal replacement therapy, cardio-pulmonary resuscitation) compared to patients without limitations of care: hypothesised larger beneficial effect of higher dose dexamethasone in patients without limitations of care.
- Patients with compared to without chronic use of systemic corticosteroids: hypothesised larger beneficial effect of higher dose dexamethasone in patients without chronic use of systemic corticosteroids.
- Patients enrolled in India compared to patients enrolled in Denmark, Sweden and Switzerland: hypothesised different effect of higher dose dexamethasone in patients enrolled in India as compared to patients enrolled in Denmark, Sweden and Switzerland.

Detailed definitions of the subgroups are available in Supporting Information S8.

2.14 | Independent data monitoring and safety committee

We have formed an Independent Data Monitoring and Safety Committee (IDMSC) consisting of a multidisciplinary group of a clinician, a trialist and a biostatistician that, collectively, have experience in

the conduct, monitoring and analysis of randomised clinical trials. The charter for the IDMSC is provided in Supporting Information S9.

2.15 | Interim analysis

The independent statistician of the IDMSC will conduct one blinded interim analysis after 500 participants (50%) have been followed for 28 days. The alpha value for the interim analysis is 0.0054 as by the O'Brien-Fleming bounds, which preserves type I error at the usual 5%.[42] The trial will be stopped early if the alpha cut-off is crossed at the interim analysis.

The IDMSC will be provided with the following outcome data with the two groups masked (eg interventions coded as 0 and 1):

- Days alive without life support (ie invasive mechanical ventilation, circulatory support or renal replacement therapy (including days in between intermittent renal replacement therapy)) from randomisation to day 28.
- Number of participants with one or more SARs or SUSARs from randomisation to day 28.

The data set will also include data on the stratification (ie site, invasive mechanical ventilation, and age below 70 years) and baseline variables.

2.15.1 | Statistical analyses conducted by the IDMSC

1. Days alive without life support at day 28: Kryger Jensen and Lange test adjusted for stratification variables (site, invasive mechanical ventilation, and age below 70 years) in the ITT population.[39]
2. Number of participants with one or more SARs or SUSARs from randomisation to day 28: generalised linear model with log links and binomial error distributions adjusted for the stratification variables (site, invasive mechanical ventilation, and age below 70 years) in the ITT population.[40]

The IDMSC can request additional data from the coordinating centre or unblinding of the intervention groups during the whole course of the trial. The IDMSC will submit their recommendations to the trial Management Committee, which makes the final decision to continue, pause or stop the trial.

2.16 | Monitoring during the study

The trial will be externally monitored according to the GCP Directive. A monitoring and data verification plan has been developed together with the GCP unit at Rigshospitalet, University of Copenhagen.

The trial will also be centrally monitored by the Sponsor or his delegates through the electronic case report form (eCRF), including monitoring of protocol adherence.

2.17 | Close out

We will ensure that a plan for long-term storage of data and source documentation has been made at each site upon completion of the trial.

3 | DISCUSSION

Low-dose systemic corticosteroids are strongly recommended by the WHO for COVID-19 patients with hypoxia.[8] Yet, the optimal dose is still not clear. Higher doses of corticosteroids may offer additional anti-inflammatory effects,[43] but maybe also a be associated with a higher risk of serious adverse events. The COVID STEROID 2 trial intends to provide important evidence on the optimal dosing of corticosteroids for COVID-19 patients with severe hypoxia.

3.1 | Strengths

The COVID STEROID 2 trial has all the strengths of a large international, collaborative trial and will exclusively assess patient-centred outcomes, including days alive without life support, SARs, mortality and HRQoL. In addition, i) we publish this protocol and statistical analysis plan reported according to the SPIRIT guidelines,[31] ii) adhere to the CONSORT statement,[30] iii) external monitoring according to the GCP directive[33] and central monitoring to ensure high quality of the collected data. We will allow co-enrolment with other clinical trials unless the interventions or protocols collide to ensure that the participants are offered all potential beneficial interventions.

We will conduct an interim analysis after 50% of the participants have been followed for 28 days in order to early identify benefits and harms of higher vs. lower doses of dexamethasone. We will supplement the primary reports of the trial with a pre-planned secondary Bayesian analysis of all outcomes collected up to 90 days after randomisation to help interpretation of the trial results. Details on this Bayesian re-analysis will be specified in another protocol before database lockdown.

3.2 | Limitations

The number of COVID-19 patients may decline during the conduct of the trial, hindering the timely recruitment of trial participants.

We expect protocol violations (ie use of open-label corticosteroids and/or failure to administer trial interventions during the intervention period) to occur during the trial. To account for this, we will challenge the primary results of the trial from the ITT population with a sensitivity analysis of the primary outcome in PP population (ie trial participants without protocol violations). Protocol violations will only be recorded during the intervention period for each trial participant, and some participants may receive open-label corticosteroids

after the intervention period. This may affect the results of the trial but will not be challenged in a sensitivity analysis.

Days alive without life support were chosen as the primary outcome of the trial as this is likely important to both patients, relatives and society. A reduction in days with life support will for most patients also mean a reduction in the time spent in the ICU. During the COVID-19 pandemic, numerous ICUs worldwide are experiencing strained capacity.[44] The results of the COVID STEROID 2 trial may not only benefit patients and relatives, but also society by lowering the pressure on the healthcare systems. Mortality may, however, have been a more important outcome to patients and relatives.

3.3 | Perspectives

There are other ongoing trials assessing higher vs. lower doses of corticosteroids for COVID-19 patients with hypoxia. Together, results from all these trials may accrue enough evidence to show benefit or harm from a higher dose of corticosteroids as compared with the standard lower dose (6 mg of dexamethasone or equivalent) in COVID-19 patients with hypoxia. As of 21 August 2020, only a few trials with a similar scope have been registered on ClinicalTrials.gov,[15,45,46] highlighting the need for the COVID STEROID 2 trial.

4 | CONCLUSION

The COVID STEROID 2 trial is an investigator-initiated, international, parallel-grouped, blinded, centrally randomised and stratified clinical trial assessing the effects of higher vs. lower doses of dexamethasone in COVID-19 patients with severe hypoxia. The trial protocol and statistical analysis plan is outlined in this manuscript. The COVID STEROID 2 trial will provide evidence on the optimal dosing of corticosteroids for COVID-19 patients with severe hypoxia with important implications for both patients, relatives, healthcare systems and society in general.

4.1 | Ethical considerations

The trial was registered at the European Union Drug Regulation Authorities Clinical Trials Database (EudraCT, 2020-003363-25) and at ClinicalTrials.gov (NCT04509973) before commencement. The trial was also registered at the Swiss National Clinical Trials Portal (SNCTP000004116) before commencing enrolment in Switzerland and at the Clinical Trials Registry—India (CTRI/2020/10/028731) before commencing enrolment in India.

In Denmark, the trial is approved by the Danish Medicines Agency (2020-07-16), the Committees on Health Research Ethics in the Capital Region of Denmark (H-20051056), and The Capital Region Knowledge Centre for Data Compliance (P-2020-842). In Sweden, the trial is approved by the Swedish Ethical Review Authority (Dnr 2020-02582 and Dnr 2020-04403) and the Swedish Medical Product Agency with the additional requirement that the patient must have GCS ≥ 14 and give consent before inclusion (EudraCT number 2020-003363-25). In Switzerland, the trial was approved by the local ethics committee (BASEC 2020-02165). In India, the trial was approved by the Health Ministry's Screening Committee of the Indian Council of Medical Research (HMSC, proposal ID 2020-9746). All applicable additional approvals will be obtained before start of enrolment in other participating countries than Denmark. The protocol, including the procedure for obtaining informed consent, will be approved by all required authorities in the participating countries before commencing inclusion in the country concerned. Trial information to participants and consent forms used in the COVID STEROID trial are available from www.cric.nu/covid-steroid-2.

4.2 | Data sharing statement

We will make the final de-identified data set available for sharing in accordance with 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-2.

4.3 | Dissemination

We plan to publish the trial results in an international peer-reviewed medical journal irrespective of the findings. The reports will adhere to the CONSORT statement.[30] Upon trial completion, the trial results will also be available from www.cric.nu/covid-steroid-2.

4.4 | Status

The trial was initiated on 27 August 2020 and is expected to be completed in 2021. As of January 25 2021, 492/1,000 participants (49.2%) have been enrolled at 27 trial sites in 22 hospitals in Denmark, India, Sweden and Switzerland. The recruitment is reported daily on www.cric.nu/covid-steroid-2.

5 | TRIAL SPONSOR

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6 | APPLICABLE PROTOCOL REGISTRATION NUMBERS

ClinicalTrials.gov identifier NCT04509973; Ethics committee number H-20051056; EudraCT number 2020-003363-25; Danish Medicines Agency number 2020-07-16; Swiss National Clinical Trials Portal: SNCTP000004116; CTRI number: 2020/10/028731.

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

MWM drafted the first version of this protocol, which was critically revised by all authors. All authors contributed to the design or conduct of the COVID STEROID 2 trial.

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SUPPORTING INFORMATION

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

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