Supplementary Materials for 'Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial – protocol and statistical analysis plan'

Supplementary Materials

Supplementary Material 1: Definition of the inclusion criteria

Age: the age of the participant in whole years at the time of randomisation.

Confirmed SARS-CoV-2 requiring hospitalisation**:** We will accept any detections of SARS-CoV-2 approved by the local health authorities in the participating countries. Currently, detection of SARS-CoV-2 RNA from upper (i.e. pharyngeal swap) or lower airway secretions (i.e. tracheal secretion or bronchoalveolar lavage) are used.

Supplementary oxygen criterion at the time of randomisation:

- Invasive mechanical ventilation: use of mechanical ventilation via a cuffed endotracheal tube **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

Supplementary Material 2: Definition of the exclusion criteria

Indication for use of systemic corticosteroids: Systemic corticosteroids (intravenous (IV), intramuscular (IM), oral or per gastrointestinal (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 >48 hours prior to screening: use of mechanical ventilation via a cuffed endotracheal tube for >48 hours

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 subject to compulsory hospitalisation.

Supplementary Material 3: Trial medication preparation

We will use shelf-medications from the hospital department's pharmacy for both intervention and control medication. In regions where Solu-cortef is not available, investigators are advised to follow drug preparation and administration guidelines as stipulated by the manufacturer.

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%) (letter from Pfizer confirming this in Supplementary Material 8). 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 (at trials sites where Solu-cortef is available)

The hydrocortisone sodium succinate (Solu-cortef™, Pfizer) sterile powder is white, odourless, and soluble in water.[50] 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.[50] 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.[50]

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.

Supplementary Material 4: Definition of outcome measures

Primary outcome measure

Days alive without life support at day 28: Total number of days alive without all 3 life supporting interventions within 28 days after randomisation:

- Invasive mechanical ventilation: use of mechanical ventilation via a cuffed endotracheal tube
- 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 levosimendan)
- Renal replacement therapy: any form of acute or chronic intermittent or continuous renal replacement therapy (including days between intermittent dialysis).

Secondary outcome measures

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: total number of days alive without all 3 life supporting interventions (as defined under 'Primary outcome measure') within 90 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 of the following:

- New episode of either septic shock: septic shock will be defined according to the Sepsis-3 criteria:[51]
    - Suspected or confirmed superinfection
    - New infusion (or 50% increase) of vasopressor/inotrope agent (i.e. norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) 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:

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

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. 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.

Supplementary Material 5: Definition of registered variables

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. The patients will be stratified according to age <70 years versus ≥70 years.

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.
- Hospital ward: medical or surgical ward, 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, 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, New York Heart Association (NYHA) functional class 3 or 4 or any measured left ventricular ejection fraction (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, angiotensin converting enzyme (ACE)-inhibitors, angiotensin-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.

Participant weight: measured or estimated in kilograms (kg).

PaO_2, SaO_2 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, SpO_2 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 levosimendan) 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: use of mechanical ventilation via a cuffed endotracheal tube on this day.

- 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 levosimendan).

- Any form of renal replacement therapy: 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.

Number of participants with one or more SARs at day 14: At least one of the following:

- New episode of either:
- Septic shock: septic shock will be defined according to the Sepsis-3 criteria [51]:
    - Suspected or confirmed superinfection
    - New infusion (or 50% increase) of vasopressor/inotrope agent (i.e. norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) to maintain a mean arterial blood pressure of 65 mmHg or above
    - Lactate of 2 mmol/L or above despite adequate fluid resuscitation in any plasma sample performed on the same day
- Invasive fungal infection:
    - Suspected invasive fungal infection: presence of plasma markers in blood (e.g. candida mannan antigen and galactomannan antigen) or
    - Confirmed invasive fungal infection: positive culture from blood, peritoneal fluid or tissue
- Clinically important gastrointestinal (GI) bleeding: any GI bleeding AND use of at least 2 unit of red blood cells on the same day. GI bleeding is 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 dayforms (day 1-8)

Protocol violations will be registered for the first 7 full days after randomisation. To allow data extraction from the electronic medical journals with fixed time points for data registration (e.g. 6 am to 5.59 am), administration of trial medication will be registered in 8 dayforms corresponding to full 7 days after randomisation.

- 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 other variables assessed during follow up

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

Supplementary Material 6: Definition of subgroups

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 Definition of age: the age of the participant in whole years at the time of randomisation	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 Definition of therapeutic agents against COVID-19: any treatment that potentially inhibits viral replication, i.e. hydroxychloroquine, remdesivir, protease inhibitor (lopinavir/ritonavir or darunavir/ritonavir), convalescent plasma, or other (e.g. umifenovir, interferon alfa, interferon beta, camostat)	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 Definition of invasive mechanical ventilation: use of mechanical ventilation via a cuffed endotracheal tube at the time of randomisation.	Larger effect of hydrocortisone in patients who receive invasive mechanical ventilation	Test of interaction in the adjusted analysis described above; P-value 0.01

	Definition of oxygen by other delivery system: 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		
Shock	Patients with shock versus without shock Definition of shock: shock of any cause requiring infusion of vasopressor/inotrope agent (i.e. norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) to maintain a mean arterial blood pressure ≥ 65 mmHg AND with a lactate ≥ 2 mmol/L in any plasma within 24 hours of randomisation	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 Definition of chronic lung disease: treatment at time of hospital admission with any relevant drug indicating chronic lung disease	Larger effect of hydrocortisone in patients with chronic lung disease	Test of interaction in the adjusted analysis described above; P-value 0.01

Supplementary Material 7: 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 of critical care, 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 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 alpha-spending function.[30] 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 alpha-spending function.[30]

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

- Mortality at day 28

- The number of patients with ≥1 SAR(s) and/or SUSAR(s)

The DMSC will be provided a masked data set (as group 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 evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre 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 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 which intervention each group received.

3. strat_site (numeric; integer): the trial site identity code.

4. strat_inv_vent_indic: invasive mechanical ventilation indicator (1=yes, 0=no).

5. strat_age_indic: age indicator (1=below 70 years, 0=equal to or larger than 70 years).

6. days_alive_without_lifesup_d28_cum_indic (numeric; integer): the number of days alive without life support at day 28.

7. day_28_indic: 28-day mortality indicator (1=dead, 0=alive at day 28)

8. SAR_indic: SAR indicator (1 = one or more SAR(s), 0 = no SAR)

9. SUSAR_indic: SUSAR indicator (1 = one or more SUSAR(s), 0 = no SUSAR)

Supplementary Material 8: Letter from Pfizer regarding stability of Solu-cortef

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]

➔ After mixing the reconstituted solution with the infusion solvents:

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.

REFERENCES

1 Solu-Cortef (hydrocortisone sodium succinate) Summary of Product Characteristics (Denmark). [V: Date of revision of text 04/2018; LC]
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