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Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial

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Background: In the early phase of the pandemic, some guidelines recommended the use of corticosteroids for critically ill patients with COVID-19, whereas others recommended against the use despite lack of firm evidence of either benefit or harm. In the COVID STEROID trial, we aimed to assess the effects of low-dose hydrocortisone on patient-centred outcomes in adults with COVID-19 and severe hypoxia.

Methods: In this multicentre, parallel-group, placebo-controlled, blinded, centrally randomised, stratified clinical trial, we randomly assigned adults with confirmed COVID-19 and severe hypoxia (use of mechanical ventilation or supplementary oxygen with a flow of at least 10 L/min) to either hydrocortisone (200 mg/d) vs a matching placebo for 7 days or until hospital discharge. The primary outcome was the number of days alive without life support at day 28 after randomisation.

Results: The trial was terminated early when 30 out of 1000 participants had been enrolled because of external evidence indicating benefit from corticosteroids in severe COVID-19. At day 28, the median number of days alive without life support in the hydrocortisone vs placebo group were 7 vs 10 (adjusted mean difference: −1.1 days, 95% CI −9.5 to 7.3, $P = .79$); mortality was 6/16 vs 2/14; and the number of serious adverse reactions 1/16 vs 0/14.

Conclusions: In this trial of adults with COVID-19 and severe hypoxia, we were unable to provide precise estimates of the benefits and harms of hydrocortisone as compared with placebo as only 3% of the planned sample size were enrolled.

Trial registration: ClinicalTrials.gov: NCT04348305. European Union Drug Regulation Authorities Clinical Trials (EudraCT) Database: 2020-001395-15.

1 | INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] may cause coronavirus disease 2019 (COVID-19)[2]; the clinical presentation of which varies from mild upper respiratory infection to severe acute respiratory distress syndrome (ARDS).[3]

Systemic corticosteroids have been reported to benefit some patients with ARDS and septic shock.[4-6] In the early phases of the COVID-19 pandemic, there were conflicting guidelines on the use of corticosteroids for COVID-19[7-10]; the Surviving Sepsis Campaign advocated its use in critically ill patients with COVID-19[9] whilst the World Health Organization (WHO) initially recommended against it.[7] To address this uncertainty, several clinical trials were initiated.[11-19]

On 15 April 2020, we commenced the 'Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial' aiming to assess the effects of low-dose hydrocortisone vs placebo on patient-centred outcomes. We hypothesised that low-dose hydrocortisone would increase the number of days alive without life support as compared with placebo.

On 16 June 2020, enrolment was paused when 30 participants had been randomised because of a press release from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial reporting benefit from systemic corticosteroids on 28-day mortality in hospitalised patients with COVID-19.[20] The Management Committee of the COVID STEROID trial decided to terminate the trial on 3 September 2020, due to the results from a WHO-initiated prospective meta-analysis (PMA) of ongoing or recently completed trials demonstrating benefit from systemic corticosteroids on 28-day mortality in critically ill patients with COVID-19,[21] which in turn led to an update in the guideline from the WHO strongly recommending the use of systemic corticosteroids for patients with severe or critical COVID-19.[22]

We provided data on 28-day mortality and serious adverse reactions (SARs) for 29 out of 30 trial participants to the PMA published in September 2020,[21] because of the importance of summarising the evidence from all trials assessing corticosteroids in patients with critical COVID-19.

Here, we present the full trial report of the COVID STEROID trial, including 90-day follow-up.

2 | METHODS

2.1 | Trial design

The COVID STEROID trial was an investigator-initiated, multicentre, parallel-group, placebo-controlled, blinded, centrally randomised, stratified clinical trial. We planned to randomise 1000 adult patients with COVID-19 and severe hypoxia in Denmark, Sweden, Switzerland and India. The trial was commenced on 15 April 2020; paused on 16 June 2020; and terminated early on 3 September 2020, after 30 patients had been enrolled at 12 trial sites in Denmark.

Editorial Comment

In this trial, the authors aimed to assess the effects of low-dose hydrocortisone on patient-centered outcomes in adults with COVID-19 and severe hypoxia. The trial was terminated very quickly after starting enrollment, due to unexpected (at trial design) inability to enroll participants. Despite this, the final trial disposition is interesting to note as an example of the challenges for studying important treatments in the setting of very rapidly-changing treatment recommendation changes during the pandemic.

2.2 | Trial conduct

The COVID STEROID trial was conducted in accordance with the published trial protocol,[23] the Helsinki Declaration in its latest version,[24] the International Conference on Harmonization on Good-Clinical-Practice (GCP) guidelines,[25] the General Data Protection Regulation and Danish laws. The trial results are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Supplementary Information S1).[26]

Patients were enrolled after obtaining deferred informed consent for temporary incompetent patients according to Danish law. The trial data and consents were monitored externally by the GCP units of the participating regions in Denmark and centrally by staff from the coordinating centre.

2.2.1 | Randomisation and allocation concealment

Patients fulfilling all inclusion criteria and no exclusion criteria were randomised in a 1:1 ratio to 200 mg of intravenous (IV) hydrocortisone vs placebo using a centralised and web-based randomisation system at the Copenhagen Trial Unit (CTU). The randomisation was performed according to a computer-generated allocation sequence, stratification variables (trial site, use of invasive mechanical ventilation [y/n], age below 70 years [y/n]), and varying block sizes. The allocation sequence was only known by the data manager at the CTU.

2.2.2 | Blinding

The Management Committee, investigators, trial site staff registering outcome data, trial statistician, clinical staff, relatives, and participants were all blinded to the allocation. Trial medication was prepared daily using shelf-medication by a dedicated team of unblinded trial site staff (medical students and/or research nurses and doctors). The unblinded trial site staff were not involved in the care of trial participants, outcome data entry, or statistical analyses.

For the analyses conducted in the present report, the trial statistician received a blinded dataset with the allocation coded as 0 or 1. Of note,

due to the previous publication of data on 28-day mortality and SARs, it was possible to identify the groups 0 and 1 by referral to the PMA.[21]

2.3 | Trial participants

We screened adult patients (18 years or above) with confirmed SARS-CoV-2 infection and severe hypoxia defined as use of either invasive mechanical ventilation, 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. Participants were enrolled at participating hospitals (intensive care units or wards for infectious or pulmonary diseases).

We excluded patients who fulfilled one or more exclusion criteria listed in the Supplementary Information S2. Detailed definitions of the inclusion and exclusion criteria are available from the published trial protocol.[23]

2.4 | Trial interventions

Trial participants received either IV hydrocortisone (200 mg per day) or a matching placebo (isotonic saline) for 7 days or until hospital discharge (whichever came first). The injections had identical appearances.

For patients allocated to hydrocortisone, the trial intervention was given either as a continuous infusion over 24 hours or as bolus injections every 6 hours (50 mg per bolus). For patients allocated to placebo, the trial intervention was given either as a continuous infusion over 24 hours or as bolus injections every 6 hours.

All other interventions were given at the discretion of the treating clinicians. The procedure for trial medication preparation was described in detail in the published trial protocol.[23]

2.5 | Outcomes

Detailed definitions of primary and secondary outcomes are presented in the published trial protocol.[23]

2.5.1 | Primary outcome

The primary outcome was days alive without the use of life support (ie, invasive mechanical ventilation, circulatory support, or renal replacement therapy, including days in between intermittent renal replacement therapy) at day 28.

2.5.2 | Secondary outcomes

The secondary outcomes were:

- Number of participants with one or more serious adverse reactions 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.

2.6 | Statistical analyses

We estimated that 1000 participants would be required to have 85% power to detect a 15% relative reduction in 28-day mortality combined with a 10% reduction in the days on life support among survivors.

Baseline data were presented descriptively in each group and in total with medians with interquartile ranges (IQRs) for continuous variables and numbers with percentages for categorical variables. Because the final sample size was substantially smaller than planned, deviations from the pre-published statistical analysis plan were necessary (details are presented in Supplementary Information S3). For continuous outcomes, results are presented as medians with IQRs in each group and adjusted mean differences with 95% confidence intervals (CIs). For binary outcomes, results are presented as numbers with percentages in each group and adjusted relative risks (RR) with 95% CIs as described previously.[23] All analyses were done in the intention-to-treat (ITT) population defined as all randomised participants for whom there were consent to use data. We had no missing outcome data, and only missing data for baseline lactate in one participant; accordingly, neither multiple imputation nor best-worst/worst-best case analyses were conducted.[23]

2.6.1 | Primary outcome

The primary outcome was evaluated using a linear regression adjusted for invasive mechanical ventilation and age below 70 years. We were unable to adjust for site due to the reduced sample size. The primary analysis was supplemented by a Wilcoxon rank sum test. Descriptive data on the primary outcome are presented in 5 out of 6 pre-planned subgroups (Table 1).

2.6.2 | Secondary outcomes

For all secondary binary outcomes, we employed unadjusted generalised linear models with log links and binomial error distributions (except for SARs due to only 1 event). These were supplemented by Fisher's exact tests.

The secondary continuous outcomes were evaluated as the primary outcome using linear regressions adjusted for invasive mechanical ventilation and age below 70 years and were supplemented by Wilcoxon rank sum tests.

TABLE 1 Baseline characteristics

Baseline characteristics	All patients (n = 30)	Hydrocortisone (n = 16)	Placebo (n = 14)
Median age (IQR)—year	61 (53-73)	59 (52-74)	62 (55-71)
Male sex—n (%)	24 (80)	14 (88)	10 (71)
Median weight (IQR)—kg	86 (75-106)	85 (76-107)	92 (77-106)
Chronic co-morbidities—n (%)			
Ischemic heart disease or heart failure	1 (3)	1 (6)	0 (0)
Hypertension	8 (27)	5 (31)	3 (21)
Chronic pulmonary disease	5 (17)	2 (13)	3 (21)
Diabetes mellitus	4 (13)	2 (13)	2 (14)
Location at enrolment—n (%)			
Emergency department or prehospital setting	0 (0)	0 (0)	0 (0)
Hospital ward	8 (27)	5 (31)	3 (21)
Intermediate care unit	0 (0)	0 (0)	0 (0)
Intensive care unit	22 (73)	11 (69)	11 (79)
Median time from symptom onset to hospital admission (IQR)—days	6 (3-8)	7 (5-8)	6 (0-10)
Median time from hospital admission to randomisation (IQR)—days	4 (1-8)	4 (1-7)	6 (1-8)
Oxygen supplementation			
Invasive mechanical ventilation—n (%)	11 (37)	5 (31)	6 (43)
Median FiO_2 (IQR)	49 (40-61)	55 (45-65)	47 (38-55)
Median duration (IQR)—hour	14 (5-20)	6 (4-20)	15 (13-21)
Non-invasive ventilation or continuous use of CPAP—n (%)	4 (13)	2 (13)	2 (14)
Median FiO_2 (IQR)	55 (53-66)	55-55[b]	45-100[b]
Median duration (IQR)—hour	3 (3-22)	2-3[b]	3-78[b]
Open system ventilation—n ()	15 (50)	9 (56)	6 (43)
Median oxygen flow (IQR)—L/min	15 (14-25)	20 (13-25)	15 (15-19)
Median PaO_2 prior to randomisation (IQR)—kPa	10 (8-12)	11 (9-11)	9 (8-12)
Median arterial oxygen saturation prior to randomisation (%) (IQR)	95 (92-97)	95 (92-96)	95 (92-98)
Use of vasopressors or inotropes—n (%)	10 (33)	5 (31)	5 (36)
Use of any renal replacement therapy[a]—n (%)	1 (3)	0 (0)	1 (7)
Median plasma lactate prior to randomisation (IQR)—mmol/L	1.4 (1.1-1.8)	1.5 (1.1-1.8)	1.4 (1.3-1.8)
Treatment with anti-inflammatory agents—n (%)	0 (0)	0 (0)	0 (0)
Treatment with potential anti-viral agents—n (%)	7 (23)	3 (19)	4 (29)
Remdesivir	5 (17)	1 (6)	4 (29)
Hydroxychloroquine	1 (3)	1 (6)	0 (0)
Lopinavir/ritonavir	0 (0)	0 (0)	0 (0)
Convalescent plasma	2 (7)	0 (0)	2 (14)
Other	1 (3)	1 (6)	0 (0)
Treatment with anti-bacterial agents—n (%)	25 (83)	13 (81)	12 (86)

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; IQR, interquartile range; kg, kilograms; kPa, kilopascal; L, litre; mmol, millimoles; n, number; PaO_2, partial pressure of oxygen.

[a] Including days in between intermittent renal replacement therapy.

[b] Range of values is presented instead of median (IQR) as the group only consists of 2 participants.

2.7 | Post hoc survey of trial site clinicians

We conducted a post hoc fully anonymised survey to assess how clinical practice was influenced by the RECOVERY preprint.[20] We surveyed the clinical preferences for corticosteroid use for COVID-19 among doctors working at planned COVID STEROID trial sites in India, Sweden, Switzerland and Denmark. Moreover, we asked site investigators to submit aggregate data from participating hospitals on the use of corticosteroids in the last 10 COVID-19 patients admitted in July 2020 after the RECOVERY preprint had been published.

3 | RESULTS

The trial was initiated on 15 April 2020, and the first participant was enrolled on 17 April 2020. On 16 June 2020, enrolment was paused after a total of 30 participants had been randomised. Of these, 16 were allocated to hydrocortisone and 14 were allocated to placebo, and all completed follow-up of data at day 90 (Figure 1).

The baseline characteristics of the trial participants are presented in Table 2 and the trial medication administration and protocol violations in Table 3. The trial participants received the trial intervention for a median of 7 days (IQR 6-7 days) in both groups. A total of 3 trial participants (2 allocated to hydrocortisone and 1 allocated to placebo) discontinued the trial intervention for the reasons presented in Figure 1. In the hydrocortisone and placebo groups, 8 and 3 participants had major protocol violations (ie, concomitant use of open-label corticosteroids during the first 14 days after randomisation or less than 50% of planned trial medication volume administered on any day in the intervention period).

3.1 | Outcomes

The outcome data for the 2 groups are presented in Table 4.

There was no statistically significant difference in the days alive without life support at day 28 after randomisation (the primary outcome) in patients allocated to hydrocortisone vs those allocated to placebo (adjusted mean difference: −1.1 days, 95% CI −9.5 to 7.3, $P = .79$).

In total, there was 1 patient with one or more SARs in the trial (hydrocortisone: 1/16; placebo 0/14). There were no statistically significant differences in all-cause mortality at 28 and 90 days (28 days: RR 2.63, 95% CI 0.74 to 16.03, $P = .19$; 90 days: RR 2.04, 95% CI 0.71 to 8.16, $P = .22$), in the days alive without life support at day 90 (adjusted mean difference: −14.7 days, 95% CI −40.4 to 10.9, $P = .25$) or in the days alive and out of hospital at day 90 (adjusted mean difference: −6.5 days, 95% CI −29.6 to 16.7, $P = .57$).

3.2 | Post hoc survey of trial site clinicians

Some results of the survey have already been published elsewhere.[27]

A total of 278 doctors from Denmark (53%), India (40%), Sweden (4%) and Switzerland (3%) responded to the survey on corticosteroid use in patients with COVID-19. The responders primarily worked in ICUs (56%) or departments of anaesthesiology (21%) or infectious diseases (15%).

Most responders would sometimes or always use steroids for patients with COVID-19 (86%; 250 responders), in particular for patients with severe COVID-19 requiring oxygen therapy with a flow of 10-30 L/min (66%; 249 responders), >30 L/min (66%; 249 responders) or non-invasive ventilation or continuous CPAP (68%; 249 responders) or for patients with critical COVID-19 requiring
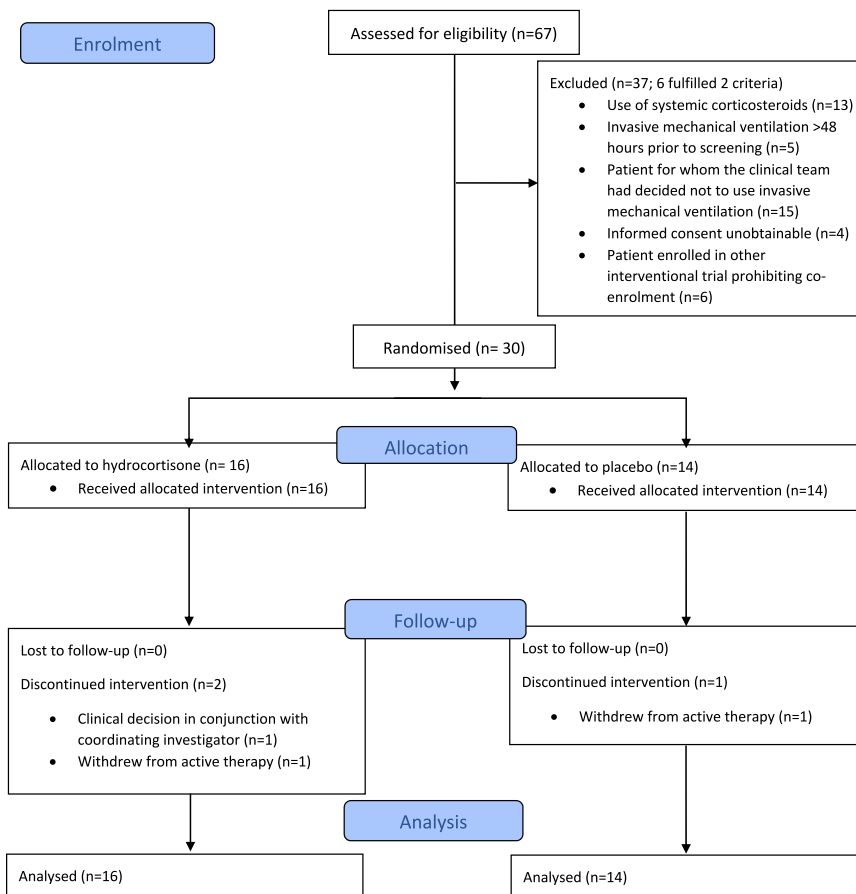

FIGURE 1 Screening, allocation and follow-up [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Trial medication administration and protocol violations

Trial medication administration	Hydrocortisone (n = 16)	Placebo (n = 14)
Treatment duration in days, median (IQR)	7 (6-7)	7 (6-7)
Mode of administration, n (%)		
Continuous infusion	10 (63)	10 (71)
Bolus injections	4 (25)	3 (21)
Both used in the intervention period	2 (13)	1 (7)
Protocol violations		
Participants who did not receive trial medication at all, n (%)	0 (0)	0 (0)
Participant with one or more protocol violations[a]	8 (50)	3 (21)
Less than 50% of planned trial medication volume administered on one or more days, n (%)	5 (31)	3 (21)
Use of open-label steroids, n (%)[b]	3 (19)	1 (7)

Abbreviations: IQR, interquartile range; n, number.

[a] Concomitant use of open-label corticosteroids during the first 14 days after randomisation or less than 50% of planned trial volume administered on each day in the intervention period.

[b] 2 patients were unblinded after the press-release from the RECOVERY trial and received open-label steroid to complete a steroid course of 10 days; 1 patient received open-label steroid due to an allergic reaction to intravenous immunoglobulin; and 1 patient received open-label steroid as antiemetics.

mechanical ventilation (76%; 249 responders) or with septic shock (56%; 249 responders). The preferred corticosteroids were dexamethasone (86%; 240 responders) and methylprednisolone (45%; 240 responders). The dose preference varied with 56% of 240 responders preferring a dose of 6 mg of dexamethasone or equivalent and 36% of 240 responders preferring doses higher than 6 mg of dexamethasone or equivalent.[27] Most would enrol patients in a future trial comparing a higher vs lower dose of dexamethasone, primarily into one comparing 12 mg vs 6 mg of dexamethasone (55% of 237 responders).[27]

A total of 24 ICUs and 3 departments of infectious diseases provided aggregate data on corticosteroid use after the preprint publication of RECOVERY. Of these, 6 ICUs had not had any patients with COVID-19 admitted after the publication of RECOVERY. A median of 10% of patients (IQR 0%-38%) had received corticosteroids before admission to the ICU and median of 100% (IQR 100%-100%) had received corticosteroids during ICU admission. The median dose used for all locations was 10 (IQR 6-15) mg dexamethasone (or equivalent).

4 | DISCUSSION

In this investigator-initiated, multicentre, parallel-group, blinded, centrally randomised, stratified clinical trial, we were unable to provide any precise estimates on the benefits and harms of hydrocortisone vs placebo for any outcomes as only 3% of the planned sample size was enrolled. In our post hoc survey, we found that the dose preferences for corticosteroid use in COVID-19 varied among doctors and that most would enrol their patients into a trial comparing higher vs lower doses of dexamethasone.

4.1 | Strengths

The strengths include all those of a multicentre randomised, placebo-controlled trial. The trial design was pragmatic allowing all other interventions to follow standard care, and only patient-centred outcomes were reported. The trial was monitored externally by local GCP units in Denmark, and we had no missing values for any assessed outcome. The trial was reported in accordance with the CONSORT statement.[26]

4.2 | Limitations

During the planning and commencement of the COVID STEROID trial, the number of COVID-19 patients in Denmark decreased leading to an unexpected low recruitment throughout the inclusion period. The recruitment was also lowered due to enrolment in other interventional trials prohibiting co-enrolment (16% of all excluded patients).

The COVID STEROID trial was terminated early when only 3% of the planned sample size had been enrolled resulting in highly uncertain point estimates.[28] Yet, we consider it important to publish data on all outcomes out of respect for the trial participants and to allow for data to be included in future meta-analyses.

The trial intervention was subject to protocol violations occurring in more than one-third of the participants, likely due to strain on the clinical staff. We planned to explore the effect of these protocol violations by performing a sensitivity analysis of the primary outcome in the per protocol population (ie, participants without one or more protocol violations) but refrained from this due to the small sample size.

Moreover, we were unable to adhere to the published statistical analysis plan due to the reduced sample size and few patients with events for the binary outcomes or the value zero for the continuous outcomes. Consequently, the results presented in this report are based on a post hoc decision on how to analyse the data in a sensible manner adhering to the protocol to the extent possible in accordance with the trial statistician.

TABLE 3 Outcomes in the ITT-population

Primary outcome	Hydrocortisone	Placebo	Adjusted mean differences or relative risks (95% CI)	P value
Days alive without life support at day 28, median (IQR)	7 (2-24)	10 (3-26)	−1.1 (−9.5 to 7.3)	.79[a]
No. of participants with one or more serious adverse reactions, no./total n (%)	1/16 (6%)	0/14 (0%)	—	1.00[b]
All-cause mortality at day 28, no./total n (%)	6/16 (38%)	2/14 (14%)	2.63 (0.74 to 16.03)	.19[c]
All-cause mortality at day 90, no./total n (%)	7/16 (44%)	3/14 (21%)	2.04 (0.71 to 8.16)	.22[d]
Days alive without life support at day 90, median (IQR)	41 (6-86)	72 (52-88)	−14.7 (−40.4 to 10.9)	.25[e]
Days alive and out of hospital at day 90, median (IQR)	31 (8-78)	53 (42-68)	−6.5 (−29.6 to 16.7)	.57[f]

Abbreviations: IQR, interquartile range; n, number.

[a] Computed using a linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 (y/n). Supplemented by Wilcoxon rank sum test ($P =$.88).

[b] Computed using Fisher's exact test.

[c] Computed using an unadjusted generalised linear model with log link and binomial error distribution. Supplemented by Fisher's exact test ($P =$.23).

[d] Computed using an unadjusted generalised linear model with log link and binomial error distribution. Supplemented by Fisher's exact test ($P =$.26).

[e] Computed using a linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 (y/n). Supplemented by Wilcoxon rank sum test ($P =$.40).

[f] Computed using a linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 (y/n). Supplemented by Wilcoxon rank sum test ($P =$.77).

4.3 | Perspectives

Several clinical questions remain unanswered regarding the use of corticosteroids in COVID-19, among others the timing of initiation, optimal dosing regime and duration of treatment. In our survey, we found that the dose preferences for corticosteroid use in COVID-19 varied among doctors and that most would enrol their patients into a trial comparing higher vs lower doses of dexamethasone. The doses used in clinical practice also varied between hospitals. Of note, the dose used was often higher than that used in the RECOVERY trial. Consequently, the higher vs lower doses of dexamethasone in patients with COVID-19 and severe hypoxia (COVID STEROID 2) trial was commenced on 27 August 2020, to provide data on the effect of 12 mg vs 6 mg of dexamethasone in a similar cohort of patients.[27,29] In this trial, we also include patients using corticosteroids at the time of screening and patients who have limitations in the use of life-support to increase the generalisability of the results.

5 | CONCLUSIONS

In this early terminated randomised clinical trial of adult patients with COVID-19 and severe hypoxia, we were unable to provide any precise estimates on the benefits and harms of hydrocortisone vs placebo for any outcomes as only 3% of the planned sample size had been enrolled. We did learn important lessons that have informed the design and conduct of the COVID STEROID 2 trial.[27,29]

TABLE 4 Primary outcome in predefined subgroups

Days alive without life support at day 28, median (IQR)	n	Hydrocortisone, n	Hydrocortisone	Placebo, n	Placebo
Age					
<70 y	21	11	20 (3-28)	10	17 (3-26)
≥70 y	9	5	5 (0-6)	4	5 (2-12)
Therapeutic agents against COVID-19					
Yes	7	3	8 (2-28)[d]	4	4 (3-8)
No	23	13	6 (1-23)	10	18 (4-28)
Invasive mechanical ventilation					
Yes	11	5	14 (5-20)	6	5 (1-12)
No	19	11	6 (2-28)	8	24 (4-28)
Shock					
Yes	4	3	5 (0-14)[d]	1	0[b]
No	26	13	8 (2-28)	13[a]	14 (3-28)
Chronic lung disease					
Yes	5	2	1-1[c]	3	4 (3-14)[d]
No	25	14	11 (4-27)	11	19 (2-28)

Note.: We planned to conduct statistical analyses of subgroup differences on the primary outcome in the ITT population, but refrained from this due to the reduced sample size. Instead, descriptive data for each subgroup is reported. We were unable to report data for the subgroup analysis of geographical region as only Danish patients were included in the trial. Detailed definitions of each subgroup are provided in the published trial protocol.[23]

Abbreviations: IQR, interquartile range; n, number; y, years.

[a] 1 patient had a missing value of lactate but did not require vasopressors or inotropes at baseline and was consequently placed in the subgroup of no shock.

[b] No IQR is reported as the subgroup consists of only 1 trial participant.

[c] Range of values is presented instead of median (IQR) as the subgroup consists of only 2 participants.

[d] Median (range of values) is presented instead of median (IQR) as the subgroup consists of only 3 participants.

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SUPPORTING INFORMATION

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