Domain-Specific Appendix:

CORTICOSTEROID DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Corticosteroid Domain-Specific Appendix Version 6 dated 5th November, 2024

Summary

In this domain, participants meeting Platform entry criteria with severe lower respiratory tract infection will be randomized to receive one of up to four steroid-use strategies depending on availability and acceptability:

- No corticosteroid (no placebo)
- Shock-dependent hydrocortisone while the patient is in septic shock
- Fixed duration dexamethasone for 10 days

At this participating site the following interventions have been selected within this domain:

☐ No corticosteroid (no placebo)

☐Shock-dependent hydrocortisone while the patient is in septic shock

☐Fixed duration dexamethasone for 10 days

This domain includes patients aged ≥ 28 days old (corrected gestational age). In this region, this domain will be offered to eligible participants aged:

☐ ≥ 28 days and < 12 years old

☐ ≥ 12 years and < 18 years old

☐ ≥ 18 years old

In this region:

☐ Patients who are known or suspected of being pregnant will be eligible for the fixed-course dexamethasone intervention

☐ Patients who are known or suspected to be pregnant will be excluded from the fixed-course dexamethasone intervention

This DSA applies to the following States and Stratum:

Age Stratum	≥ 28 days old and <12 years old		≥ 12 years and < 18 years old		≥ 18 years old	
Illness Severity State	Moderate State	Severe State	Moderate State	Severe State	Moderate State	Severe State
Domain-specific strata	N/A	N/A	N/A	N/A	N/A	N/A
Interventions specified in this DSA	• No corticosteroids • Fixed duration dexamethasone	• No corticosteroids • Shock-dependent hydrocortisone • Fixed duration dexamethasone	• No corticosteroids • Fixed duration dexamethasone	• No corticosteroids • Shock-dependent hydrocortisone • Fixed duration dexamethasone	• No corticosteroids • Fixed duration dexamethasone	• No corticosteroids • Shock-dependent hydrocortisone • Fixed duration dexamethasone
Interventions submitted for approval in this jurisdiction	☐ No corticosteroids ☐ Fixed duration dexamethasone	☐ No corticosteroids ☐ Shock-dependent hydrocortisone ☐ Fixed duration dexamethasone	☐ No corticosteroids ☐ Fixed duration dexamethasone	☐ No corticosteroids ☐ Shock-dependent hydrocortisone ☐ Fixed duration dexamethasone	☐ No corticosteroids ☐ Fixed duration dexamethasone	☐ No corticosteroids ☐ Shock-dependent hydrocortisone ☐ Fixed duration dexamethasone

Corticosteroid Domain Summary	
Interventions	The following interventions are offered in this domain • No corticosteroid (no placebo) • Shock-dependent hydrocortisone while the patient is in septic shock • Fixed duration dexamethasone for 10 days
Timing of Reveal	Randomization with Immediate Reveal and Initiation, or Randomization with Deferred Reveal and Initiation if prospective agreement to participate is required.
Population	This domain will be offered to the following patient categories: • Pediatric, Adolescent, and Adult Age Strata • Moderate and Severe Illness Severity States
Domain-Specific Inclusions	Patients will be eligible for this domain if: • Patient is aged ≥ 28 days old (corrected gestational age) • Patient has lower-respiratory tract infection • If in the Severe State, patient has pneumonia • If in the Moderate State, patient is receiving some form of supplemental oxygen
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Confirmed SARS-CoV-2 infection • Hospital-acquired respiratory tract infection, except where the patient has confirmed influenza infection • Known hypersensitivity to any corticosteroid • An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current respiratory tract infection, such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* or COVID-19 pneumonia • If in the Severe State, more than 24 hours has elapsed since commencement of sustained organ failure support. • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Criteria that exclude a patient from one or more interventions are: • It is recognized that there is a wide range of regulatory approaches and attitudes to the evaluation of interventions in pregnant trial participants across participating regions and sites. Known or suspected pregnancy is not an intervention-level exclusion for the fixed-course dexamethasone intervention by default; however, if a site does not have regulatory approval to enroll pregnant patients to the fixed-course dexamethasone intervention, known or suspected pregnancy will be applied as an intervention-specific exclusion and will result in exclusion from the fixed course dexamethasone intervention.
Outcome measures	Primary endpoint: as specified in Core Protocol documents. Secondary endpoints refer to Core Protocol documents. Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment): • Serious Adverse Events (SAE) as defined in core protocol documents
Platform Conclusions	The following Platform Conclusions are possible for this domain: • Efficacy of any active intervention compared with 'no corticosteroid' intervention • Superiority of any active corticosteroid intervention compared with other interventions in this domain • Futility for an active corticosteroid intervention compared with 'no corticosteroid' intervention • Equivalence among active corticosteroid interventions • Inferiority of any active intervention

Unit-of-analysis and Strata	The unit-of-analysis for this domain corresponds to patients who receive an allocation in this domain, further subdivided by the combination of Shock Strata (defined as Shock or No Shock), Influenza Infection Confirmed Strata (defined as Influenza Infection Confirmed or Influenza Infection Not Confirmed), Illness Severity State (defined as Moderate or Severe State), and Age Strata (defined as two strata - Pediatric, and Adolescent and Adult Age Strata). Analysis and Response Adaptive Randomization are applied, with borrowing permitted between States and Strata.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain at this time.
Nesting	None.

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1. ABBREVIATIONS

ADRENAL	ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock Study
APROCCHSS	Activated PROtein C and Corticosteroids for Human Septic Shock
ARDS	Acute Respiratory Distress Syndrome
ARDSNet	Acute Respiratory Distress Syndrome Clinical Trial Network
CAP	Community Acquired Pneumonia
CORTICUS	The Corticosteroid Therapy of Septic Shock Study
COVID-19	Coronavirus Disease 2019
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
HPA	Hypothalamic–Pituitary–Adrenal
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
IV	Intravenous
LOS	Length of Stay
LUNG-SAFE	Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE
MODS	Multiple Organ Dysfunction Score
mg	milligram
OFFD	Organ Failure Free Days
P:F Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VFD	Ventilator Free Days

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see Glossary, Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (principles of statistical analysis and models) a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistical Design Team and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory

aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website.

3. CORTICOSTEROID DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Corticosteroid Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Corticosteroid Domain-Specific Working Group (DSWG) on 19 November 2016

Version 1.1: Approved by the Corticosteroid DSWG on 30 March 2017

Version 2: Approved by the Corticosteroid DSWG on 12 December 2017

Version 3: Approved by the Corticosteroid DSWG on 12 July 2019

Version 3.1: Approved by the Corticosteroid DSWG on 20 April 2020

Version 3.2: Approved by the Corticosteroid DSWG on 20 August 2020

Version 5: Approved by the Corticosteroid DSWG on 09 November 2022

Version 5.1 Approved by the Corticosteroid DSWG on 16 October 2023

Version 6: Approved by the Corticosteroid DSWG on 05 November 2024

Note that Version 4 of the Corticosteroid DSA was finalized on the 21st of July 2020. This version was produced as supplementary material for the publication of results from the REMAP-CAP Corticosteroid Domain (Angus et al., 2020) and was not intended to be submitted for ethical approval.

4. CORTICOSTEROID DOMAIN GOVERNANCE

4.1. Domain members

Chair: Professor Derek Angus

Members:

Professor Djillali Annane

Professor James Chalmers

Professor Graham Cooke

Professor Paul Dark

Dr. Lennie Derde

Professor Anthony Gordon

Dr. Tom Hills

Associate Professor Peter Kruger

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4.2. Contact Details

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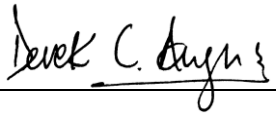
5. CORTICOSTEROID DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Corticosteroid Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Corticosteroid Domain-Specific Appendix. Signed on behalf of the committee,

Chair
Derek Angus



Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain to test the effectiveness of systemic corticosteroid strategy in hospitalized patients with severe lower-respiratory tract infection.

6.2. Domain-specific background

There is significant uncertainty regarding the use of corticosteroids in patients with CAP who are treated in hospital or an ICU. This uncertainty applies to both patients with and without septic shock secondary to CAP. The existing evidence is derived from trials that enrolled overlapping populations. Some trials enrolled patients with septic shock, many of whom had CAP as the source of sepsis, and other enrolled patients with severe CAP, but only a proportion of these patients had septic shock. These trials have largely utilized hydrocortisone as the corticosteroid but have employed a range of doses and delivery strategies (infusion versus intermittent dosing). Since the COVID-19 pandemic, dexamethasone has been used to treat patients in hospital with CAP due to SARS-CoV-2 infection.

Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist in causes of CAP other than COVID-19 (MacDonald, 2018). However, existing evidence is not sufficient to provide guidance to clinicians that is definitive. If there is a benefit, there is limited evidence to suggest that benefit is more likely in patients who are more severely ill (Annane et al., 2018, Venkatesh et al., 2018). It is also recognized that corticosteroids have a range of potentially adverse effects. Clinicians remain uncertain about the role of corticosteroid treatment in patients

with severe CAP. This uncertainty necessitates the conduct of a large pragmatic study to address this question and provide definitive guidance to clinicians.

6.2.1. Corticosteroids in critical illness

In health, endogenous corticosteroids production is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is central to maintaining homeostasis in the face of exogenous stress. Infectious disease is a common source of exogenous stress that is encountered by humans. As part of an integrated response to infection the host produces additional (above normal homeostasis) corticosteroids. It is speculated that this occurs to calibrate the innate and acquired host response to infection so as to protect the host organism from an excessive immune response, which can damage host tissues. Corticosteroids are immunomodulatory hormones that can stimulate, as well as suppress, immune function depending on the type of immune response, the immune compartment, and the cell type involved. (Silverman et al., 2005, Prina et al., 2016) Exogenously administered corticosteroid drugs (e.g. hydrocortisone or dexamethasone) elucidate effects similar to endogenously produced cortisol on the host immune response. Furthermore, critically ill patients may benefit from corticosteroid administration due to the presence of relative adrenal insufficiency or inadequate adrenal function in some cases of severe CAP (Maxime et al., 2009).

6.2.2. Clinical questions regarding corticosteroids in patients with CAP

There are several interrelated and overlapping clinical questions regarding the role of corticosteroids in patients, both adults and children, with severe CAP. The first of these is whether patients who have septic shock as a complication of severe CAP benefit from corticosteroids. The second is whether patients with severe CAP who do not have septic shock benefit from corticosteroids. The third is whether patients with severe CAP due to influenza respond differently to corticosteroids. Fourth is whether there are differences across the age range, from children to adults, in their responsiveness to corticosteroids. Lastly, there is uncertainty about the role of corticosteroids in patients who develop Acute Respiratory Distress Syndrome (ARDS) secondary to severe CAP.

6.2.3. Role of corticosteroids in septic shock secondary to CAP

The studies investigating corticosteroids that enrolled patients with septic shock (or sepsis without shock) included patients with a range of different sites of primary infection. In most trials, around half of enrolled patients had CAP. The results of these studies are varied, and this is reflected in international guidelines.

The 2013 iteration of the Surviving Sepsis Campaign Guidelines suggests that the administration of intravenous (IV) hydrocortisone should be avoided if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability, but that hydrocortisone should be administered if hemodynamic stability cannot be achieved. (Dellinger et al., 2013) This recommendation is graded as a weak recommendation based on low quality evidence. There are two major trials that influenced this recommendation. In a study by Annane et al, hydrocortisone improved the duration of survival (within the first 28 days) but not the number of patients who survived; and resulted in more rapid reversal of septic shock in the (non-stratified) sub-group of patients with relative adrenal insufficiency (Annane et al., 2002). In the CORTICUS study, septic shock was also reversed more rapidly but there was no difference in mortality although this result may have been influenced by inclusion of patients at lower risk of death (Sprung et al., 2008). A more recent Cochrane meta-analysis suggests that corticosteroid treatment reduces mortality among patients with sepsis, but the quality of evidence was rated as low because of imprecision and inconsistency of results across trials, as well as the inclusion of trials with different study populations and the use of different doses and duration of treatment (Annane et al., 2015). The recommendation in the current, 2016 International Surviving Sepsis Campaign Guidelines is not changed from the 2013 recommendation (Rhodes et al., 2017).

Since the publication of the Cochrane meta-analysis and the 2016 Guidelines, two additional trials have been published, but have not provided sufficient clarification. A RCT of hydrocortisone in 3,800 patients with septic shock (ADRENAL) showed no reduction in 90-day mortality. (Venkatesh et al., 2018) In this trial, duration of treatment was 7 days or until ICU discharge, whichever occurred first. For patients who still required vasopressor support on day 7, there was evidence of deterioration after steroids were ceased. The other trial, APROCCHSS, investigating hydrocortisone-plus-fludrocortisone in patients with septic shock, reported lower 90-day mortality in the intervention group (RR 0.88, 95% CI 0.78-0.99) (Annane et al., 2018).

These trials (Table 1) have not resulted in changes to international guidelines. As a consequence of this uncertainty, there is substantial variation in clinical practice. (Annane et al., 2002, Bollaert et al., 1998, Briegel et al., 1999, MacDonald, 2018).

Table 1: Selected studies of corticosteroids in sepsis

Reference	Design, population and intervention	Results
Annane et al. (2015)	Meta-analysis of RCTs of corticosteroids in adult patients with severe sepsis or septic shock	No overall effect on mortality at day 28, ICU discharge or hospital discharge. Reversal of shock occurs more rapidly with corticosteroids. Lower mortality at day 28 for hydrocortisone dose ≤ 300 mg per day for at least 5 days
Venkatesh et al. (2018)	Multicenter RCT (n=3800) in ventilated patients with septic shock of hydrocortisone (200 mg per day via continuous infusion) for 7 days versus placebo	No difference in mortality at day 90, but faster reversal of shock and reduced duration of mechanical ventilation with corticosteroids
Annane et al. (2018)	Multicenter RCT (n=1241) in patients with definite or probable septic shock of hydrocortisone (50 mg every 6 hours and fludrocortisone 50 µg enterally daily) for 7 days versus placebo	Reduced mortality at day 90, with more vasopressor- and organ-failure free days

In both ADRENAL and APROCCHSS hydrocortisone was administered for a maximum of 7 days and ceased even if the patient remained in shock. There is anecdotal evidence that many clinicians, who do choose to administer hydrocortisone to patients with septic shock do not administer for a fixed duration (i.e., 7 days) but will administer hydrocortisone for a shorter or longer duration, corresponding to the duration of shock (as determined by vasopressor administration). This strategy has not been evaluated in randomized clinical trials.

The role of corticosteroids in patients with sepsis but not septic shock is also uncertain, with a recent study reporting that corticosteroids were not effective in preventing the development of shock (Keh et al., 2016). This raises the possibility that the effect of corticosteroids in patients with sepsis may be different depending on the presence of absence of shock at the time of enrollment.

Overall, there is legitimate uncertainty regarding whether corticosteroids are beneficial in patients with septic shock secondary to CAP and, if so whether there are differences in benefit from administration of a fixed-course compared with a duration that is variable corresponding to the duration of septic shock.

6.2.4. Role of corticosteroids in CAP irrespective of septic shock

The clinical manifestations of pneumonia are a product of the interaction between an infective pathogen and the local and systemic inflammatory responses of the host. A more pronounced and aggressive inflammatory response has been shown in several studies to be associated with treatment failure and increased rates of mortality (Antunes et al., 2002). In support of this hypothesis that an over-active immune response is deleterious, higher levels of pro-inflammatory cytokines and chemokines (i.e. IL-6 and IL-8) have been detected in patients with severe CAP and associated with increased rates of mortality (Antunes et al., 2002). This raises the possibility of a beneficial effect of dampening of this 'abnormal' immune response with corticosteroids, irrespective of the presence of septic shock.

A number of trials have evaluated the effect of administration of corticosteroids in patients with severe CAP. These studies have been reviewed by Prina and colleagues (2016), and are summarized in Table 2 (modified from *Prina et al*, 2016). A 2011 Cochrane meta-analysis by Chen et al. (6 RCTs, n=437) suggested that corticosteroid therapy increased the speed of resolution of symptoms and shortened the time-interval to achieve clinical stability but did not demonstrate any effect to reduce mortality (Chen et al., 2011). A more recent meta-analysis by Nie et al. (9 RCTs, n=1001) showed that administration of corticosteroids did not result in a demonstrable decrease in mortality, across all studies, but a beneficial effect on mortality may be present among the sub-group of patients with severe CAP when patients received more than 5 days of corticosteroid treatment (Nie et al., 2012). A 2016 meta-analysis by Wan et al. (9 RCTs, n=1,667 and six cohort studies, n=4,095) of adult CAP were analyzed and the authors reported that treatment with corticosteroids is safe and may reduce the risk of ARDS, and shorten the duration of disease (Wan et al., 2016). These meta-analyses included heterogeneous populations of CAP (mild, moderate and severe CAP) and heterogeneous interventions (low to very high dose of steroids). Another meta-analysis by Cheng et al. (4 RCTs, n=264), which included only patients with severe CAP concluded that, although corticosteroid therapy may reduce mortality for adult patients with severe CAP, the results should be interpreted with caution due to the instability of the pooled estimates (Cheng et al., 2014). The authors concluded that reliable treatment recommendations could only be produced if additional multicenter studies with sufficient statistical power were conducted (Cheng et al., 2014).

Two recent relatively large high quality multicenter RCTs have been published regarding the use of corticosteroids in CAP that were not included in the meta-analyses of patients with CAP. Blum et al. conducted a multicenter, double-blind, randomized, placebo-controlled trial (n=785) of patients with CAP who were randomized to receive either prednisone (50 mg, oral) or placebo for 7 days. The trial

reported that corticosteroids reduced the time to reach clinical stability and that hyperglycemia was more common in the corticosteroid group but that the mortality rate was not different between the two groups (Blum et al., 2015). In the second study, by Torres et al, 2015, a multicenter severe CAP RCT (n=120), participants were randomized to receive either corticosteroids (methylprednisolone at a dose of 0.5mg/kilogram (kg) every 12 hours for 5 days) or not. Treatment with corticosteroids reduced treatment failure in comparison with the placebo group, but not hospital mortality (Torres et al., 2015).

As highlighted in Table 2, the aggregate conclusion from these studies is that there is reasonable evidence to indicate that use of corticosteroids in CAP may result in the following benefits: reduced hospital length of stay (LOS), reduced time to clinical stability, and prevention of ARDS. However, none of these are patient-centered end-points and, as yet, there is no definitive answer regarding the effect of corticosteroids on mortality. This, combined with the huge heterogeneity in current clinical practice indicating clinical equipoise exists, makes now the time to conduct such a large adequately powered study examining patient centered outcomes.

Table 2: Studies on corticosteroids in CAP (adapted from Prina et al, 2016)

Reference	Study design, population and intervention	Main results (effect of corticosteroids)
Confalonieri et al. (2005)	Multicenter RCT (n=46), severe CAP Hydrocortisone (200 mg bolus + infusion (10 mg/hour) for 7 days) versus placebo	Increased PaO2/FiO2, higher chest radiograph score, lower CRP, delayed septic shock, reduced hospital LOS and mortality
Garcia-Vidal et al. (2007)	Retrospective observational study patients with severe CAP, systemic steroids	reduction in mortality
Snijders et al. (2010)	Single center RCT (n=230), CAP Prednisolone (40mg daily for 7 days) versus placebo	Clinical cure at day 7 unchanged Late failure (>72 hours) increased with prednisolone
Meijvis et al. (2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	Reduced hospital LOS
Chen et al. (2011)	Meta-analysis (6 RCTs, n=437), CAP	Faster resolution of symptoms Faster clinical stability Lower rate of relapse
Nie et al. (2012)	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall Reduced mortality in severe CAP
Shafiq et al. (2013)	Meta-analysis (8 RCTs, n=1119), CAP	Reduced hospital LOS, No change in mortality
Cheng et al. (2014)	Meta-analysis (4 RCTs, n=264), severe CAP	Reduced hospital LOS and mortality
Torres et al. (2015)	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	Less treatment failure, No difference for in-hospital mortality

Blum et al. (2015)	Multicenter RCT (n=785), CAP Prednisolone (50mg daily for 7 days) versus placebo	Reduced time to clinical stability
Siemieniuk et al. (2015)	Meta-analysis (12 RCTs, n= 1974), CAP	Reduced all-cause mortality, mechanical ventilation and ARDS, reduced time to clinical stability, shorter duration of hospitalization
Wan et al. (2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, less ARDS

6.2.5. Role of corticosteroids in CAP secondary to influenza

The role of corticosteroids in patients with CAP caused by or occurring in association with influenza infection has been a longstanding controversy. Existing evidence is derived predominantly from observational studies. During the 2009 H1N1 influenza pandemic, among patients admitted to an ICU, approximately one third of patients received corticosteroids (Falagas et al., 2010) as either a primary therapy or as a rescue therapy for patients with severe ARDS (Kumar et al., 2009, Dominguez-Cherit et al., 2009). In children the use of corticosteroids ranged between 9 and 21% (Muthuri et al., 2014). This widespread use occurred despite the absence of any evidence from RCTs regarding the effectiveness of corticosteroids in CAP secondary to influenza. A systematic review and meta-analysis (nine cohort studies, n = 1405, and 14 case-control studies, n = 4700) and a recent secondary analysis of a Spanish cohort study, using propensity matching, showed increased mortality with corticosteroid treatment in influenza H1N1 infection (Zhang et al., 2015, Moreno et al., 2018). However, it is likely that severity of illness will be a confounding factor in these studies and commonly, in studies enrolling patients who are critically ill, adjustment of confounding may be inadequate.

This evidence was used at the beginning of the COVID-19 pandemic to recommend against use of corticosteroids outside of clinical trials. Those trials including RECOVERY & REMAP-CAP demonstrated the benefit of low dose corticosteroids, e.g. dexamethasone 6mg or hydrocortisone 200mg per day, to save lives and reduce the need for ventilation in those patients with pneumonia receiving supplemental oxygen (Angus et al., 2020, Sterne et al., 2020, Horby et al., 2021). Corticosteroids have now become a standard of care for severe COVID-19 pneumonia in both adults and children as a result of high quality RCT evidence (although it should be noted there were no RCTs of corticosteroids in children). Such evidence is now needed for severe influenza pneumonia for both adults and children. This was the conclusion of a recent review article by authors from the Influenza Division of the CDC and others, “RCTs of low-dose or moderate-dose corticosteroids or other immunomodulators are needed to inform their roles in treating severe influenza complications

(Uyeki et al., 2022). As such, the role of corticosteroids in patients with severe CAP secondary to influenza remains uncertain and both beneficial or harmful effects are possible.

6.2.6. Role of corticosteroids in Acute Respiratory Distress Syndrome

ARDS is common in the critically ill and severe CAP is a common primary etiological factor for its development. Several studies have evaluated the effects of corticosteroids in patients with ARDS including patients with severe CAP. Meduri and colleagues conducted a small (n=24) double blind placebo controlled RCT where patients with severe ARDS who failed to improve by day 7 of respiratory failure were randomized to receive methylprednisolone versus placebo. (Meduri et al., 1998) This study demonstrated that corticosteroid treatment reduced ICU mortality, improved oxygenation and reduced the Multiple Organ Dysfunction Score (MODS) (Meduri et al., 1998). The sample size of this study was small and it is also important to note that there were marked differences in baseline characteristics between groups (Meduri et al., 1998). A subsequent Acute Respiratory Distress Syndrome Clinical Trial Network (ARDSNet) study randomized (n=180) patients with late ARDS (day 7 to 28) to receive methylprednisolone or placebo. This study demonstrated no difference in 60-day mortality but an increased death rate in those commenced on steroids after 2 weeks. (Steinberg et al., 2006) There was no increase in nosocomial infections but a trend towards increased neuromyopathy and an increased number of ventilator-free days (VFDs), ICU-free days and shock-free days in the first 28 days after treatment (Steinberg et al., 2006). A recent single center randomized controlled trial (n=197) study of severe sepsis induced ARDS demonstrated that patients randomized to receive hydrocortisone (50mg, IV 6hourly) was associated with significantly improved pulmonary physiology (partial pressure of oxygen in arterial blood and fraction of inspired oxygen concentration ratio (P:F ratio), lung injury score) but had no survival benefit. (Tongyoo et al., 2016). In a more recent multicenter, randomized controlled trial in 17 ICUs across Spain including 277 patients with established moderate-to-severe ARDS, dexamethasone treatment led to an increase in ventilator-free days (between-group difference 4·8 days [95% CI 2·57 to 7·03]; p<0·0001) and reduced 60 day mortality (between-group difference −15·3% [–25·9 to −4·9]; p=0·0047) (Villar et al., 2020).

These findings have variably been interpreted to mean either “current evidence does not support the efficacy of steroids in ARDS” (Agarwal et al., 2007) or “prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables and has a distinct survival benefit” (Meduri et al., 2007). Reflecting this apparent controversy, the recent LUNG-SAFE study reported low levels of usage of corticosteroid in ARDS globally (Bellani et al.,

2016). It is clear that there is uncertainty if patients with severe CAP who develop ARDS should receive corticosteroids.

6.2.7. Corticosteroid-associated complications in critical illness.

The complications associated with the systemic use of corticosteroids treatment have been well described. The duration of administration of corticosteroids in patients with severe CAP is short (up-to a week) and, as a consequence, long-term complications of corticosteroid administration, such as diabetes mellitus, weight gain, and osteoporosis are not considered to be likely. However, risks associated with the short-term use in patients with severe CAP include in increased risk of nosocomial infection (due to the immunosuppressive effect of corticosteroids), hyperglycemia (which can be treated with insulin), and myopathy, which may lead to prolongation of the period of mechanical ventilation and weakness during the recovery phase after critical illness. It remains uncertain, in critically ill CAP patients, what is the overall effect of these potential complications on patient-centered outcomes, including survival.

For children, there are minimal safety data in children less than three months, and for longer courses (greater than five days) of corticosteroids. In the premature infant population, there is a possibility of neurodevelopmental issues from courses of dexamethasone. The risks of prolonged exposure to corticosteroids include the possibility of myopathy, increased rates of infection, and the possibility of neurodevelopmental concerns in the very young population.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different strategies of corticosteroid utilization for hospitalized patients with severe lower-respiratory tract infection.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the Core Protocol documents will differ based on the allocated corticosteroid strategy. The following interventions will be available:

- No corticosteroid (neither dexamethasone nor hydrocortisone is prescribed; no other corticosteroid is permitted; no administration of a placebo)
- Shock-dependent duration hydrocortisone (IV hydrocortisone 50mg every 6 hours while in septic shock) – only available for patients in the Severe State
- Fixed duration dexamethasone* (IV or oral dexamethasone 6mg daily for 10 days while in hospital)

* In children – dexamethasone 0.15 mg/kg (max 6mg/day) for a maximum of 10 days while in hospital. In pregnancy dexamethasone should be replaced by oral prednisolone 40mg one daily or IV hydrocortisone 50mg every 6 hours for 10 days.

We hypothesize that the treatment effect of different corticosteroid strategies depends on:

- the presence or absence of shock at the time of enrollment (strata-by-intervention interaction).
- the presence or absence of confirmed influenza infection at the time of enrollment (strata-by-intervention interaction).
- Patient age.
- Illness Severity State at time of randomization.

8. TRIAL DESIGN

8.1. Population

8.1.1. Age Strata

This domain is available to patients in the Pediatric, Adolescent, or Adult Age Strata, as defined in Core Protocol documents. Eligibility within each stratum may be further constrained by domain-specific eligibility criteria specified below. Participating sites may choose to offer this domain to patients in one or more (or all) of these Age Strata.

8.1.2. Illness Severity State

This domain is available for patients in either the Moderate or Severe State. These States are defined in Core Protocol documents. Participating sites may choose to offer this domain to patients in one or both of these Illness Severity States.

8.1.3. Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in relevant Core Protocol documents. Patients eligible for the Platform may have conditions that exclude them from the Corticosteroid Domain.

8.2.1. Domain inclusion criteria

Participants will be eligible for this domain if:

- Patient is aged ≥ 28 days old (corrected gestational age)
- Patient has lower-respiratory tract infection
- If in the Severe State, patient has pneumonia
- If in the Moderate State, patient is receiving some form of supplemental oxygen (simple facemask, low or high flow nasal oxygen, or non-invasive ventilation)

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- Confirmed SARS-CoV-2 infection
- Hospital-acquired respiratory tract infection, except where the patient has confirmed influenza infection
- Known hypersensitivity to any corticosteroid
- Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current respiratory tract infection, such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* or COVID-19 pneumonia
- If in the Severe State, more than 24 hours have elapsed since commencement of sustained organ failure support
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site.

Patients who are eligible for only a single intervention at a site (i.e., all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- It is recognized that there is a wide range of regulatory approaches and attitudes to the evaluation of interventions in pregnant trial participants across participating regions and sites. Known or suspected pregnancy is not an intervention-level exclusion for the fixed-course dexamethasone intervention by default; however, if a site does not have regulatory approval to enroll pregnant patients to the fixed-course dexamethasone intervention, known or suspected pregnancy will be applied as an intervention-specific exclusion and will result in exclusion from the fixed course dexamethasone intervention.

8.3. Interventions

8.3.1. Corticosteroid strategy interventions

Patients will be randomly assigned to receive one of the following open-label study interventions.

☐ No corticosteroid (no placebo)

☐Shock-dependent hydrocortisone while the patient is in septic shock (Severe State only)

☐Fixed duration dexamethasone for 10 days

8.3.2. No corticosteroid intervention

Patients allocated to the *no corticosteroid* intervention are not to receive any systemic corticosteroid, including hydrocortisone or dexamethasone, for this respiratory tract infection and its direct complications up until study day 28 or hospital discharge, whichever occurs first. There is no administration of placebo. If a patient has been receiving any corticosteroid for their respiratory tract infection or its direct complications prior to enrollment, this medication must be ceased. Administration of a systemic corticosteroid, including hydrocortisone or dexamethasone, is permitted only for the treatment of new illnesses that develop in the course of a patient's hospital stay, such as asthma, airway swelling or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration will be documented.

8.3.3. Shock-dependent hydrocortisone intervention

This intervention is only available for patients in the Severe Illness Severity State at time of randomization. Patients allocated to the *shock-dependent duration hydrocortisone* intervention, will receive hydrocortisone, IV 50 mg every 6 hours, commenced if septic shock develops as a result of the patient's respiratory tract infection, up until study day 28. Hydrocortisone is to be commenced as soon as septic shock is diagnosed, including immediately after enrollment if septic shock has already been diagnosed. For the purposes of this intervention, septic shock is defined as administration of any vasopressor by continuous infusion where the treating clinician believes that the vasopressor requirement is caused by the respiratory tract infection and is not being administered for another reason such as untreated hypovolemia or solely to offset the effects of other interventions such as administration of sedation or mechanical ventilation. The exact dose of vasopressor that defines septic shock is not set by the protocol but is based on the treating clinician's judgement. The rationale for avoiding an exact dose is because no particular dose signifies 'shock' unambiguously. Dosage guidance of vasopressor for initiation of corticosteroids for this intervention is described in a separate operational document.

Hydrocortisone administration is to cease when the clinician believes that septic shock has resolved. Septic shock would always be regarded as having resolved if vasopressor infusion has not been administered in the preceding 24 hours. A clinician may regard septic shock to have resolved if vasopressor infusion is being administered intermittently or at sufficiently low dose. If, after cessation of hydrocortisone, there is redevelopment of septic shock due to CAP (as defined above), then hydrocortisone IV 50 mg every 6 hours is to be recommenced until resolution. Hydrocortisone should be ceased prior to hospital discharge.

8.3.4. Fixed duration dexamethasone

Patients allocated to the *fixed duration dexamethasone* intervention, will have dexamethasone, IV or enteral 6 mg daily for 10 days while in hospital. Administration is to commence immediately after reveal of allocation. The choice of enteral or IV administration is at the discretion of the treating clinician based on the patient's ability to take enteral medication and illness severity including likely gastric absorption rates. In children the dose of dexamethasone will be 0.15 mg/kg (max 6mg/day) for a maximum of 10 days while in hospital. It is expected that most children will spend less than 10days in hospital and therefore duration of therapy will be shorter. In pregnancy dexamethasone should be replaced by oral prednisolone 40mg once daily or IV hydrocortisone 50mg every 6 hours for 10 days while in hospital. From completion of the 10-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone or

dexamethasone, for this respiratory tract infection and its direct complications up until study day 28 or hospital discharge, whichever occurs first. Administration of a systemic corticosteroid, including hydrocortisone or dexamethasone, after completion of the 10-day course is permitted only for the treatment of new illnesses that develop in the course of a patient's hospital stay, such as asthma, airway swelling or treatment of an allergic reaction. In particular longer courses of corticosteroids should be avoided in very young infants. All use of systemic corticosteroids is recorded and the reason for any administration after Study Day 10 will be documented.

8.3.5. Duration of study intervention

For all patients in this domain who remain in hospital after study day 28, data on the administration of corticosteroids are not collected, and administration of corticosteroids after study day 28 is at the discretion of the treating clinician. The interventions in this domain apply up until study day 28 during the index hospitalization, noting that the criteria related to respiratory tract infection and its direct complications still apply. If septic shock develops due to a cause other than the respiratory tract infection, administration of corticosteroids is at the discretion of the treating clinician.

8.4. Concomitant care

New or additional systemic corticosteroids may be administered to any patient who has received an allocation status in this domain for a new clinical indication other than the respiratory tract infection and its direct complications. All use of systemic corticosteroids is recorded and the reason for any new or additional administration will be documented. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

The administration of etomidate after enrollment is not permitted and will be considered a protocol deviation.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome as specified in Core Protocol documents.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- serious adverse events (SAE) as defined in the Core Protocol

There are no additional domain-specific secondary outcome measures. It is accepted as being established that treatment with corticosteroids results in increase in blood sugar levels and decreases the duration of vasoactive therapy. It is not an objective of this trial to re-evaluate these questions but determine the aggregate effect of treatment with corticosteroids on mortality. It is also known that treatment with corticosteroids can result in myopathy and muscle weakness but this effect will be evaluated by the aggregate effect of treatment, in conjunction with other factors, on the duration of mechanical ventilation and long-term outcomes, for participants enrolled at sites that are collecting long-term outcomes.

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional clinical testing is specified in this protocol.

9.2. Domain-specific data collection

9.2.1. Clinical data collection

Additional domain-specific data will be collected.

- Administration of systemic corticosteroids
- Administration of etomidate between index hospital admission and randomization, and between randomization and the end of study day 8

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for the discontinuation of participation in this trial.

9.4. Blinding

All corticosteroids will be administered on an open-label basis.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Efficacy of any active intervention compared with 'no corticosteroid' intervention
- Superiority of any active corticosteroid intervention compared with other interventions in this domain
- Futility of an active corticosteroid intervention compared with 'no corticosteroid' intervention
- Equivalence among active corticosteroid interventions
- Inferiority of any active intervention

One or more active corticosteroid interventions can be declared to be futile in comparison with the 'no corticosteroid' intervention. If this occurs there will be a public declaration of futility with the likely adaptation being removal of futile active corticosteroid interventions from the randomization schedule. This will be an operational decision and will not require an amendment to the DSA, noting that if the point estimate of a futile intervention is in the direction of worse outcome than the 'no corticosteroid' comparator, that removal from the randomization schedule is pre-specified to be mandatory. A harm threshold is not necessary in this domain, as a futility trigger will be achieved before harm thresholds in the setting of regular adaptive analyses.

In the event of one or more active corticosteroid interventions being declared effective, the 'no corticosteroid' intervention will be removed from the randomization schedule. This is pre-specified, via this version of the DSA, and can occur without further amendment of this DSA. In this situation, the domain will continue to randomize to the active corticosteroid interventions to determine the comparative efficacy of active corticosteroid interventions. The trigger for equivalence may be applied following removal of the 'no corticosteroid' intervention. If the trigger for equivalence is to be applied, this will be *a priori* operational decision specified in the Current State document. The decision regarding the reference control can only be made after having achieved a trigger for efficacy as this decision is dependent on patterns of clinical practice at that time. Following removal

of the 'no corticosteroid' intervention the triggers of superiority and inferiority among the remaining active corticosteroid interventions will be available. If a trigger occurs for inferiority when two or more additional active interventions remain within the randomization schedule, the inferior intervention will be removed from the randomization schedule and will be subject of public disclosure. It is noted that public disclosure may also require identification of the active intervention against which the inferiority trigger occurred.

In all other respects the stopping rules for this domain are those outlined in the relevant Core Protocol documents.

10.2. Unit-of-analysis and strata

The unit-of-analysis for this domain corresponds to the patients who receive an allocation in this domain, further subdivided by the combination of: Influenza Infection Confirmed Strata (defined as Influenza Infection Confirmed or Influenza Infection Not Confirmed); Shock Strata (defined as Shock Present or Shock Absent); Age Strata (defined as Pediatric, or combined Adolescent and Adult Age Strata); and Illness Severity State (defined as Moderate or Severe State). The statistical model will permit borrowing between all strata as specified in Core Protocol documents.

It is noted that the definition of shock that is specified in the Core Protocol (presence or absence of inotrope or vasopressor infusion at baseline) determines strata status, and not the definition of septic shock that is used to define administration of hydrocortisone in the *shock-dependent duration hydrocortisone* intervention.

10.3. Application of Response-Adaptive Randomization

Response Adaptive Randomization may be applied. If RAR is applied, the cap on the maximum or minimum proportion of patients assigned to an intervention that is specified in core protocol documents may be modified by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded or to improve power. If required, any such modifications will be an operational decision of the Design Team specified in the Current State document and applied by the SAC.

10.4. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal and

Initiation if prospective agreement to participate is required for this domain (see relevant Core Protocol documents). For patients allocated to the *shock-dependent duration hydrocortisone* intervention, who are not in septic shock at the time of randomization, Immediate Reveal and Initiation is interpreted as intention to commence hydrocortisone if and when septic shock develops.

10.5. Interactions with interventions in other domains

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA or such a future domain.

10.6. Nesting

Nesting is not applicable to this domain.

10.7. Threshold probability for superiority, efficacy, and inferiority

The threshold probability for statistical triggers for superiority, efficacy, and inferiority, are those specified in the relevant Core Protocol documents.

10.8. Threshold odds ratio delta for equivalence and futility

If two interventions within this domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.10. The threshold probability of a statistical trigger for futility will be those specified in the Core Protocol.

10.9. Post-trial Subgroups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- All other potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB are convened under the guidance provided in the core protocol and the DSMB charter. The statistical triggers relevant to this domain are specified above. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. Potential domain-specific adverse events

Potential domain-specific harms related to corticosteroid therapy include hyperglycemia, nosocomial infections and ICU-acquired weakness. However, the relevant clinical endpoint related to these potential harms is a reduction in Ventilation-Free Days or organ failure support free days (OFSDs), an increased ICU or hospital length of stay, or death. These contribute to the Primary Endpoint as described in the Core Protocol.

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant Core Protocol documents).

11.3. Domain risk assessment

Corticosteroids have been used by clinicians for patients with severe respiratory tract infection for decades and are now standard of care for COVID-19 pneumonia. However, there is substantial variation between clinicians within and between countries and hospitals within countries. This variation in practice occurs, predominantly, because the limited high-quality evidence is contradictory. If this domain were not part of this Platform it is reasonable to presume that some, but far from all, patients at sites that are participating in the Platform would receive corticosteroid treatment.

It is noted that there are a range of regulatory approaches and attitudes towards the evaluation of interventions in participants who are pregnant. Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain by default. However, in some regions patients who are known to be pregnant may be excluded from the fixed-course dexamethasone intervention. In regions where enrollment of participants who are pregnant is permitted, dexamethasone will be substituted with prednisolone or hydrocortisone.

Participating sites will have reviewed the interventions in this domain and their clinical appropriateness for evaluation in this population. Enrollment in this domain will only occur if the treating clinician believes that participation is not contrary to the best interests of the patient. The risks and benefits of participation will be outlined in local consent documentation. The choice of which of the interventions are available at any site is determined by the participating site. Sites for which standard care is to routinely administer corticosteroids to patients with septic shock should not participate in the 'no corticosteroid' intervention in the Severe State. The remaining interventions administer corticosteroids to patients who have or develop septic shock, but do so for different durations for which many sites will have clinical equipoise. In the Moderate State all sites will have 'no corticosteroid' intervention and fixed duration dexamethasone intervention available.

11.4. Domain-specific consent issues

Clinicians may choose not to enroll individual patients if they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

For patients who are not competent to consent, and in accordance with local jurisdictional requirements, where permitted entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the Platform are specified in the Core Protocol documents. This domain has not received any additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

Corticosteroids will be provided by participating hospitals on the basis that, if the patient was not participating in the trial, a proportion of patients with severe respiratory tract infection would otherwise have received corticosteroids. Additionally, hydrocortisone and dexamethasone are no longer medications protected by patent in any country that is participating in the Platform and the cost of corticosteroids are minimal.

12.3. Domain-specific declarations of interest

A registry of interests for all members of the International Trial Steering Committee is maintained on the trial website. These are updated periodically and publicly accessible on the study website.

13.REFERENCES

AGARWAL, R., NATH, A., AGGARWAL, A. N. & GUPTA, D. 2007. Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis. *Respirology,* 12**,** 585-90.

ANGUS, D. C., DERDE, L., AL-BEIDH, F., ANNANE, D., ARABI, Y., BEANE, A., VAN BENTUM-PUIJK, W., BERRY, L., BHIMANI, Z., BONTEN, M., BRADBURY, C., BRUNKHORST, F., BUXTON, M., BUZGAU, A., CHENG, A. C., DE JONG, M., DETRY, M., ESTCOURT, L., FITZGERALD, M., GOOSSENS, H., GREEN, C., HANIFFA, R., HIGGINS, A. M., HORVAT, C., HULLEGIE, S. J., KRUGER, P., LAMONTAGNE, F., LAWLER, P. R., LINSTRUM, K., LITTON, E., LORENZI, E., MARSHALL, J., MCAULEY, D., MCGLOTHIN, A., MCGUINNESS, S., MCVERRY, B., MONTGOMERY, S., MOUNCEY, P., MURTHY, S., NICHOL, A., PARKE, R., PARKER, J., ROWAN, K., SANIL, A., SANTOS, M., SAUNDERS, C., SEYMOUR, C., TURNER, A., VAN DE VEERDONK, F., VENKATESH, B., ZARYCHANSKI, R., BERRY, S., LEWIS, R. J., MCARTHUR, C., WEBB, S. A., GORDON, A. C., WRITING COMMITTEE FOR THE, R.-C. A. P. I., AL-BEIDH, F., ANGUS, D., ANNANE, D., ARABI, Y., VAN BENTUM-PUIJK, W., BERRY, S., BEANE, A., BHIMANI, Z., BONTEN, M., BRADBURY, C., BRUNKHORST, F., BUXTON, M., CHENG, A., DE JONG, M., DERDE, L., ESTCOURT, L., GOOSSENS, H., GORDON, A., GREEN, C., HANIFFA, R., LAMONTAGNE, F., LAWLER, P., LITTON, E., MARSHALL, J., MCARTHUR, C., MCAULEY, D., MCGUINNESS, S., MCVERRY, B., MONTGOMERY, S., MOUNCEY, P., MURTHY, S., NICHOL, A., PARKE, R., ROWAN, K., SEYMOUR, C., TURNER, A., VAN DE VEERDONK, F., WEBB, S., ZARYCHANSKI, R., CAMPBELL, L., FORBES, A., GATTAS, D., HERITIER, S., et al. 2020. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA,* 324**,** 1317-1329.

ANNANE, D., BELLISSANT, E., BOLLAERT, P. E., BRIEGEL, J., KEH, D. & KUPFER, Y. 2015. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev***,** CD002243.

ANNANE, D., RENAULT, A., BRUN-BUISSON, C., MEGARBANE, B., QUENOT, J. P., SIAMI, S., CARIOU, A., FORCEVILLE, X., SCHWEBEL, C., MARTIN, C., TIMSIT, J. F., MISSET, B., ALI BENALI, M., COLIN, G., SOUWEINE, B., ASEHNOUNE, K., MERCIER, E., CHIMOT, L., CHARPENTIER, C., FRANCOIS, B., BOULAIN, T., PETITPAS, F., CONSTANTIN, J. M., DHONNEUR, G., BAUDIN, F., COMBES, A., BOHE, J., LORIFERNE, J. F., AMATHIEU, R., COOK, F., SLAMA, M., LEROY, O., CAPELLIER, G., DARGENT, A., HISSEM, T., MAXIME, V., BELLISSANT, E. & NETWORK, C.-T. 2018. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med,* 378**,** 809-818.

ANNANE, D., SEBILLE, V., CHARPENTIER, C., BOLLAERT, P. E., FRANCOIS, B., KORACH, J. M., CAPELLIER, G., COHEN, Y., AZOULAY, E., TROCHE, G., CHAUMET-RIFFAUD, P. & BELLISSANT, E. 2002. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA,* 288**,** 862-71.

ANTUNES, G., EVANS, S. A., LORDAN, J. L. & FREW, A. J. 2002. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J,* 20**,** 990-5.

BELLANI, G., LAFFEY, J. G., PHAM, T., FAN, E., BROCHARD, L., ESTEBAN, A., GATTINONI, L., VAN HAREN, F., LARSSON, A., MCAULEY, D. F., RANIERI, M., RUBENFELD, G., THOMPSON, B. T., WRIGGE, H., SLUTSKY, A. S., PESENTI, A., INVESTIGATORS, L. S. & GROUP, E. T. 2016. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA,* 315**,** 788-800.

BLUM, C. A., NIGRO, N., BRIEL, M., SCHUETZ, P., ULLMER, E., SUTER-WIDMER, I., WINZELER, B., BINGISSER, R., ELSAESSER, H., DROZDOV, D., ARICI, B., URWYLER, S. A., REFARDT, J., TARR, P., WIRZ, S., THOMANN, R., BAUMGARTNER, C., DUPLAIN, H., BURKI, D., ZIMMERLI, W., RODONDI, N., MUELLER, B. & CHRIST-CRAIN, M. 2015. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet,* 385**,** 1511-8.

BOLLAERT, P. E., CHARPENTIER, C., LEVY, B., DEBOUVERIE, M., AUDIBERT, G. & LARCAN, A. 1998. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med,* 26**,** 645-50.

BRIEGEL, J., FORST, H., HALLER, M., SCHELLING, G., KILGER, E., KUPRAT, G., HEMMER, B., HUMMEL, T., LENHART, A., HEYDUCK, M., STOLL, C. & PETER, K. 1999. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med,* 27**,** 723-32.

CHEN, Y., LI, K., PU, H. & WU, T. 2011. Corticosteroids for pneumonia. *Cochrane Database Syst Rev***,** CD007720.

CHENG, M., YANG, J., GAO, Y. D. & PAN, Z. Y. 2014. Corticosteroid therapy for severe community-acquired pneumonia: a meta-analysis-reply. *Respir Care,* 59**,** e118-9.

CONFALONIERI, M., URBINO, R., POTENA, A., PIATTELLA, M., PARIGI, P., PUCCIO, G., DELLA PORTA, R., GIORGIO, C., BLASI, F., UMBERGER, R. & MEDURI, G. U. 2005. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med,* 171**,** 242-8.

DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S., JAESCHKE, R., OSBORN, T. M., NUNNALLY, M. E., TOWNSEND, S. R., REINHART, K., KLEINPELL, R. M., ANGUS, D. C., DEUTSCHMAN, C. S., MACHADO, F. R., RUBENFELD, G. D., WEBB, S. A., BEALE, R. J., VINCENT, J. L., MORENO, R. & SURVIVING SEPSIS CAMPAIGN GUIDELINES COMMITTEE INCLUDING THE PEDIATRIC, S. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med,* 41**,** 580-637.

DOMINGUEZ-CHERIT, G., LAPINSKY, S. E., MACIAS, A. E., PINTO, R., ESPINOSA-PEREZ, L., DE LA TORRE, A., POBLANO-MORALES, M., BALTAZAR-TORRES, J. A., BAUTISTA, E., MARTINEZ, A., MARTINEZ, M. A., RIVERO, E., VALDEZ, R., RUIZ-PALACIOS, G., HERNANDEZ, M., STEWART, T. E. & FOWLER, R. A. 2009. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA,* 302**,** 1880-7.

FALAGAS, M. E., VOULOUMANOU, E. K., BASKOUTA, E., RAFAILIDIS, P. I., POLYZOS, K. & RELLO, J. 2010. Treatment options for 2009 H1N1 influenza: evaluation of the published evidence. *Int J Antimicrob Agents,* 35**,** 421-30.

GARCIA-VIDAL, C., CALBO, E., PASCUAL, V., FERRER, C., QUINTANA, S. & GARAU, J. 2007. Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J,* 30**,** 951-6.

HORBY, P., LIM, W. S., EMBERSON, J. R., MAFHAM, M., BELL, J. L., LINSELL, L., STAPLIN, N., BRIGHTLING, C., USTIANOWSKI, A., ELMAHI, E., PRUDON, B., GREEN, C., FELTON, T., CHADWICK, D., REGE, K., FEGAN, C., CHAPPELL, L. C., FAUST, S. N., JAKI, T., JEFFERY, K., MONTGOMERY, A., ROWAN, K., JUSZCZAK, E., BAILLIE, J. K., HAYNES, R. & LANDRAY, M. J. 2021. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med,* 384**,** 693-704.

KEH, D., TRIPS, E., MARX, G., WIRTZ, S. P., ABDULJAWWAD, E., BERCKER, S., BOGATSCH, H., BRIEGEL, J., ENGEL, C., GERLACH, H., GOLDMANN, A., KUHN, S. O., HUTER, L., MEIER-HELLMANN, A., NIERHAUS, A., KLUGE, S., LEHMKE, J., LOEFFLER, M., OPPERT, M., RESENER, K., SCHADLER,

D., SCHUERHOLZ, T., SIMON, P., WEILER, N., WEYLAND, A., REINHART, K., BRUNKHORST, F. M. & SEPNET-CRITICAL CARE TRIALS, G. 2016. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. *JAMA,* 316**,** 1775-1785.

KUMAR, A., ZARYCHANSKI, R., PINTO, R., COOK, D. J., MARSHALL, J., LACROIX, J., STELFOX, T., BAGSHAW, S., CHOONG, K., LAMONTAGNE, F., TURGEON, A. F., LAPINSKY, S., AHERN, S. P., SMITH, O., SIDDIQUI, F., JOUVET, P., KHWAJA, K., MCINTYRE, L., MENON, K., HUTCHISON, J., HORNSTEIN, D., JOFFE, A., LAUZIER, F., SINGH, J., KARACHI, T., WIEBE, K., OLAFSON, K., RAMSEY, C., SHARMA, S., DODEK, P., MEADE, M., HALL, R., FOWLER, R. A. & CANADIAN CRITICAL CARE TRIALS GROUP, H. N. C. 2009. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA,* 302**,** 1872-9.

MACDONALD, R. D. 2018. Articles That May Change Your Practice: Steroids and Septic Shock. *Air Med J,* 37**,** 343-344.

MAXIME, V., LESUR, O. & ANNANE, D. 2009. Adrenal insufficiency in septic shock. *Clin Chest Med,* 30**,** 17-27, vii.

MEDURI, G. U., GOLDEN, E., FREIRE, A. X., TAYLOR, E., ZAMAN, M., CARSON, S. J., GIBSON, M. & UMBERGER, R. 2007. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest,* 131**,** 954-963.

MEDURI, G. U., HEADLEY, A. S., GOLDEN, E., CARSON, S. J., UMBERGER, R. A., KELSO, T. & TOLLEY, E. A. 1998. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA,* 280**,** 159-65.

MEIJVIS, S. C., HARDEMAN, H., REMMELTS, H. H., HEIJLIGENBERG, R., RIJKERS, G. T., VAN VELZEN-BLAD, H., VOORN, G. P., VAN DE GARDE, E. M., ENDEMAN, H., GRUTTERS, J. C., BOS, W. J. & BIESMA, D. H. 2011. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet,* 377**,** 2023-2030.

MORENO, G., RODRIGUEZ, A., REYES, L. F., GOMEZ, J., SOLE-VIOLAN, J., DIAZ, E., BODI, M., TREFLER, S., GUARDIOLA, J., YEBENES, J. C., SORIANO, A., GARNACHO-MONTERO, J., SOCIAS, L., DEL VALLE ORTIZ, M., CORREIG, E., MARIN-CORRAL, J., VALLVERDU-VIDAL, M., RESTREPO, M. I., TORRES, A., MARTIN-LOECHES, I. & GROUP, G. S. 2018. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med,* 44**,** 1470-1482.

MUTHURI, S. G., VENKATESAN, S., MYLES, P. R., LEONARDI-BEE, J., AL KHUWAITIR, T. S., AL MAMUN, A., ANOVADIYA, A. P., AZZIZ-BAUMGARTNER, E., BAEZ, C., BASSETTI, M., BEOVIC, B., BERTISCH, B., BONMARIN, I., BOOY, R., BORJA-ABURTO, V. H., BURGMANN, H., CAO, B., CARRATALA, J., DENHOLM, J. T., DOMINGUEZ, S. R., DUARTE, P. A., DUBNOV-RAZ, G., ECHAVARRIA, M., FANELLA, S., GAO, Z., GERARDIN, P., GIANNELLA, M., GUBBELS, S., HERBERG, J., IGLESIAS, A. L., HOGER, P. H., HU, X., ISLAM, Q. T., JIMENEZ, M. F., KANDEEL, A., KEIJZERS, G., KHALILI, H., KNIGHT, M., KUDO, K., KUSZNIERZ, G., KUZMAN, I., KWAN, A. M., AMINE, I. L., LANGENEGGER, E., LANKARANI, K. B., LEO, Y. S., LINKO, R., LIU, P., MADANAT, F., MAYO-MONTERO, E., MCGEER, A., MEMISH, Z., METAN, G., MICKIENE, A., MIKIC, D., MOHN, K. G., MORADI, A., NYMADAWA, P., OLIVA, M. E., OZKAN, M., PAREKH, D., PAUL, M., POLACK, F. P., RATH, B. A., RODRIGUEZ, A. H., SARROUF, E. B., SEALE, A. C., SERTOGULLARINDAN, B., SIQUEIRA, M. M., SKRET-MAGIERLO, J., STEPHAN, F., TALAREK, E., TANG, J. W., TO, K. K., TORRES, A., TORUN, S. H., TRAN, D., UYEKI, T. M., VAN ZWOL, A., VAUDRY, W., VIDMAR, T., YOKOTA, R. T., ZAROGOULIDIS, P., INVESTIGATORS, P. C. & NGUYEN-VAN-TAM, J. S. 2014. Effectiveness of neuraminidase inhibitors in reducing

mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med,* 2**,** 395-404.

NIE, W., ZHANG, Y., CHENG, J. & XIU, Q. 2012. Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. *PLoS.One.,* 7**,** e47926.

PRINA, E., CECCATO, A. & TORRES, A. 2016. New aspects in the management of pneumonia. *Crit Care,* 20**,** 267.

RHODES, A., EVANS, L. E., ALHAZZANI, W., LEVY, M. M., ANTONELLI, M., FERRER, R., KUMAR, A., SEVRANSKY, J. E., SPRUNG, C. L., NUNNALLY, M. E., ROCHWERG, B., RUBENFELD, G. D., ANGUS, D. C., ANNANE, D., BEALE, R. J., BELLINGHAN, G. J., BERNARD, G. R., CHICHE, J. D., COOPERSMITH, C., DE BACKER, D. P., FRENCH, C. J., FUJISHIMA, S., GERLACH, H., HIDALGO, J. L., HOLLENBERG, S. M., JONES, A. E., KARNAD, D. R., KLEINPELL, R. M., KOH, Y., LISBOA, T. C., MACHADO, F. R., MARINI, J. J., MARSHALL, J. C., MAZUSKI, J. E., MCINTYRE, L. A., MCLEAN, A. S., MEHTA, S., MORENO, R. P., MYBURGH, J., NAVALESI, P., NISHIDA, O., OSBORN, T. M., PERNER, A., PLUNKETT, C. M., RANIERI, M., SCHORR, C. A., SECKEL, M. A., SEYMOUR, C. W., SHIEH, L., SHUKRI, K. A., SIMPSON, S. Q., SINGER, M., THOMPSON, B. T., TOWNSEND, S. R., VAN DER POLL, T., VINCENT, J. L., WIERSINGA, W. J., ZIMMERMAN, J. L. & DELLINGER, R. P. 2017. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med,* 43**,** 304-377.

SHAFIQ, M., MANSOOR, M. S., KHAN, A. A., SOHAIL, M. R. & MURAD, M. H. 2013. Adjuvant steroid therapy in community-acquired pneumonia: a systematic review and meta-analysis. *J Hosp Med,* 8**,** 68-75.

SIEMIENIUK, R. A., MEADE, M. O., ALONSO-COELLO, P., BRIEL, M., EVANIEW, N., PRASAD, M., ALEXANDER, P. E., FEI, Y., VANDVIK, P. O., LOEB, M. & GUYATT, G. H. 2015. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med,* 163**,** 519-28.

SILVERMAN, M. N., PEARCE, B. D., BIRON, C. A. & MILLER, A. H. 2005. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol,* 18**,** 41-78.

SNIJDERS, D., DANIELS, J. M., DE GRAAFF, C. S., VAN DER WERF, T. S. & BOERSMA, W. G. 2010. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med,* 181**,** 975-982.

SPRUNG, C. L., ANNANE, D., KEH, D., MORENO, R., SINGER, M., FREIVOGEL, K., WEISS, Y. G., BENBENISHTY, J., KALENKA, A., FORST, H., LATERRE, P. F., REINHART, K., CUTHBERTSON, B. H., PAYEN, D., BRIEGEL, J. & GROUP, C. S. 2008. Hydrocortisone therapy for patients with septic shock. *N Engl J Med,* 358**,** 111-24.

STEINBERG, K. P., HUDSON, L. D., GOODMAN, R. B., HOUGH, C. L., LANKEN, P. N., HYZY, R., THOMPSON, B. T., ANCUKIEWICZ, M., NATIONAL HEART, L. & BLOOD INSTITUTE ACUTE RESPIRATORY DISTRESS SYNDROME CLINICAL TRIALS, N. 2006. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med,* 354**,** 1671-84.

STERNE, J. A. C., MURTHY, S., DIAZ, J. V., SLUTSKY, A. S., VILLAR, J., ANGUS, D. C., ANNANE, D., AZEVEDO, L. C. P., BERWANGER, O., CAVALCANTI, A. B., DEQUIN, P. F., DU, B., EMBERSON, J., FISHER, D., GIRAUDEAU, B., GORDON, A. C., GRANHOLM, A., GREEN, C., HAYNES, R., HEMING, N., HIGGINS, J. P. T., HORBY, P., JUNI, P., LANDRAY, M. J., LE GOUGE, A., LECLERC, M., LIM, W. S., MACHADO, F. R., MCARTHUR, C., MEZIANI, F., MOLLER, M. H., PERNER, A., PETERSEN, M. W., SAVOVIC, J., TOMAZINI, B., VEIGA, V. C., WEBB, S. & MARSHALL, J. C. 2020. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA,* 324**,** 1330-1341.

TONGYOO, S., PERMPIKUL, C., MONGKOLPUN, W., VATTANAVANIT, V., UDOMPANTURAK, S., KOCAK, M. & MEDURI, G. U. 2016. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care,* 20**,** 329.

TORRES, A., SIBILA, O., FERRER, M., POLVERINO, E., MENENDEZ, R., MENSA, J., GABARRUS, A., SELLARES, J., RESTREPO, M. I., ANZUETO, A., NIEDERMAN, M. S. & AGUSTI, C. 2015. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA,* 313**,** 677-86.

UYEKI, T. M., HUI, D. S., ZAMBON, M., WENTWORTH, D. E. & MONTO, A. S. 2022. Influenza. *Lancet,* 400**,** 693-706.

VENKATESH, B., FINFER, S., COHEN, J., RAJBHANDARI, D., ARABI, Y., BELLOMO, R., BILLOT, L., CORREA, M., GLASS, P., HARWARD, M., JOYCE, C., LI, Q., MCARTHUR, C., PERNER, A., RHODES, A., THOMPSON, K., WEBB, S. & MYBURGH, J. 2018. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *New England Journal of Medicine,* 378**,** 797-808.

VILLAR, J., FERRANDO, C., MARTINEZ, D., AMBROS, A., MUNOZ, T., SOLER, J. A., AGUILAR, G., ALBA, F., GONZALEZ-HIGUERAS, E., CONESA, L. A., MARTIN-RODRIGUEZ, C., DIAZ-DOMINGUEZ, F. J., SERNA-GRANDE, P., RIVAS, R., FERRERES, J., BELDA, J., CAPILLA, L., TALLET, A., ANON, J. M., FERNANDEZ, R. L., GONZALEZ-MARTIN, J. M. & DEXAMETHASONE IN, A. N. 2020. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med,* 8**,** 267-276.

WAN, Y. D., SUN, T. W., LIU, Z. Q., ZHANG, S. G., WANG, L. X. & KAN, Q. C. 2016. Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. *Chest,* 149**,** 209-19.

ZHANG, Y., SUN, W., SVENDSEN, E. R., TANG, S., MACINTYRE, R. C., YANG, P., ZHANG, D. & WANG, Q. 2015. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. *Crit Care,* 19**,** 46.