



Domain-Specific Appendix: CORTICOSTEROID DOMAIN

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

Corticosteroid Domain-Specific Appendix Version 5.1 dated 16th October, 2023

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating hospitals or intensive care units will be randomized to receive one of up to four steroid-use strategies depending on availability and acceptability:

- No corticosteroid including hydrocortisone (no placebo)
- Fixed duration hydrocortisone for 7 days
- 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 including hydrocortisone (no placebo)
- Fixed duration hydrocortisone for 7 days
- 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

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)		
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol		
Illness Severity State	Moderate State		Severe State	Moderate State		Severe State
Interventions available in this Domain + State	Domain not available		Domain not available	No corticosteroids Fixed duration dexamethasone		No corticosteroids Fixed duration hydrocortisone Shock-dependent hydrocortisone Fixed course dexamethasone
Interventions submitted for approval at this site	N/A		N/A	<input type="checkbox"/> No corticosteroids <input type="checkbox"/> Fixed duration dexamethasone		<input type="checkbox"/> No corticosteroids <input type="checkbox"/> Fixed duration hydrocortisone <input type="checkbox"/> Shock-dependent hydrocortisone <input type="checkbox"/> Fixed duration dexamethasone
Interventions offered at this site in these locations	Ward	ICU	ICU	Ward	ICU	ICU
	N/A	N/A	N/A	<input type="checkbox"/> No corticosteroids <input type="checkbox"/> Fixed duration dexamethasone	<input type="checkbox"/> No corticosteroids <input type="checkbox"/> Fixed duration dexamethasone	<input type="checkbox"/> No corticosteroids <input type="checkbox"/> Fixed duration hydrocortisone <input type="checkbox"/> Shock-dependent hydrocortisone <input type="checkbox"/> Fixed duration dexamethasone

REMAP-CAP: Corticosteroid Domain Summary	
Interventions	<ul style="list-style-type: none"> • No corticosteroid including hydrocortisone (no placebo) • Fixed duration hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock • Fixed duration dexamethasone for 10 days
Unit-of-analysis and Strata	There are eight units-of-analysis for this domain, specified by the combination of shock, influenza, and age strata status. Analysis and Response Adaptive Randomization are applied by shock, influenza status, and age, with borrowing permitted.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain at this time.
Nesting	There is one nest in this domain between fixed duration hydrocortisone and fixed duration dexamethasone.
Timing of Reveal	Randomization with Immediate Reveal and Initiation, or Randomization with Deferred reveal if prospective agreement to participate is required.
Inclusions	<p>Patients will be eligible for this domain if:</p> <ul style="list-style-type: none"> • Patient is aged \geq 28 days old (corrected gestational age) • 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)
Domain-Specific Exclusions	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> • Known hypersensitivity to any corticosteroid • An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven <i>Pneumocystis jiroveci</i> or COVID-19 pneumonia • If in the Severe State, more than 24 hours have elapsed since ICU admission; or if the patient has already been assigned a treatment in another domain in the Moderate State, exclusion will occur if more than 24 hours has elapsed since commencement of sustained organ failure support in an ICU. • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable
Outcome measures	<p>Primary REMAP endpoint: as specified in the REMAP-CAP Core Protocol.</p> <p>Secondary REMAP endpoints refer to REMAP-CAP Core Protocol</p> <p>Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment):</p> <ul style="list-style-type: none"> • Serious Adverse Events (SAE) as defined in REMAP-CAP Core protocol

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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
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
kg	Kilogram
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 (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), 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 and Simulations Appendices. 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 International Statistics Interest Group (ISIG) 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 (www.remapcap.org).

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

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
Professor John Marshall
Dr. Colin McArthur
Dr. Srinivas Murthy
Professor Alistair Nichol
Dr. Padmanabhan Ramnarayan
Professor Andrew Ustianowski
Professor Bala Venkatesh
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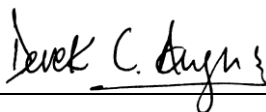
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5. CORTICOSTEROID DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair

Derek Angus



Date

16th October, 2023

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of systemic corticosteroids in patients admitted to hospital with community-acquired pneumonia (CAP).

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 \leq 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 μ g 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 PaO ₂ /FiO ₂ , 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 an 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.

6.2.8. Definitely addressing the role of corticosteroids in CAP.

As outlined above, despite RCTs and meta-analyses, more studies are needed to clarify the effect of corticosteroids on mortality. The most important clinical questions are:

- For patients with CAP who develop septic shock, does administration of hydrocortisone or dexamethasone affect mortality and, if so, does duration of therapy influence this effect?
- For patients with CAP but who do not develop septic shock does administration of hydrocortisone or dexamethasone affect mortality?
- For patients with influenza infection and CAP does hydrocortisone or dexamethasone affect mortality?

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different strategies of corticosteroid utilization in the treatment of CAP.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the REMAP-CAP Core Protocol 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)
- Fixed duration hydrocortisone (IV hydrocortisone 50mg every 6 hours for 7 days) – only available for patients in the Severe State
- 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 is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction).

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on the presence or absence of influenza infection at the time of enrollment (strata-by-intervention interaction).

The analytic structure of this domain enables several questions to be addressed. First, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with shock? Second, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with influenza? Third, is the effect of corticosteroids different when titrated to the period where the patient is clinically in septic shock, rather than by administering a fixed one-week course?

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in core protocol documents.

8.1. Population

The REMAP enrolls patients admitted to hospital with CAP, including patients with suspected or proven influenza (see relevant core protocol documents).

8.1.1. State

This domain is available for patients in the pandemic infection neither suspected nor proven (PINSNP) stratum in either the Moderate or Severe State.

8.1.2. 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 (see REMAP-CAP Core Protocol). Patients eligible for the REMAP 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)
- 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:

- Known hypersensitivity to any corticosteroid
- Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), 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 ICU admission; if the patient has already been assigned a treatment in another domain in the Moderate State, exclusion

will occur if more than 24 hours has elapsed since commencement of sustained organ failure support in an ICU.

- 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

Nil.

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 including hydrocortisone (no placebo)
- Fixed duration hydrocortisone for 7 days
- Shock-dependent hydrocortisone while the patient is in septic shock
- 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 episode of CAP and its direct complications up until study day 28. There is no administration of placebo. If a patient has been receiving any corticosteroid for CAP 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 is documented.

8.3.3. Fixed duration hydrocortisone intervention

This intervention is only available for patients randomized in the Severe State. Patients allocated to the *fixed-duration hydrocortisone* intervention are to be prescribed a course of hydrocortisone 50mg IV every 6 hours for 7 days only. Administration is to commence immediately after the allocation status is revealed at the time of enrollment on study day 1. The 7-day course will be administered

until at least the end of study day 7 and no longer than the end of study day 8. From completion of the 7-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone or dexamethasone, for this episode of CAP and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone or dexamethasone, after completion of the 7-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. All use of systemic corticosteroids is recorded and the reason for any administration from study day 9 onwards is documented.

For patients who are discharged from the ICU before the end of the 7-day course of hydrocortisone, it is the responsibility of ICU staff to prescribe hydrocortisone to complete the 7-day course. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the hydrocortisone after discharge from the ICU and it is not a protocol deviation if the course of hydrocortisone is not completed after ICU discharge.

8.3.4. Shock-dependent hydrocortisone intervention

This intervention is only available for patients randomized in the Severe State. Patients allocated to the *shock-dependent duration hydrocortisone* intervention, will have hydrocortisone, IV 50 mg every 6 hours, commenced if septic shock develops as a result of the patient's initial episode of CAP, 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 CAP and is not being administered for another reason such as untreated hypovolemia or solely to offset the effects of other ICU 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, but during the same ICU admission, 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 ICU discharge.

8.3.5. 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 the allocation status is revealed at the time of enrollment on study day 1. 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 10 days 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 episode of CAP and its direct complications up until study day 28. 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 day 10 is documented.

8.3.6. Duration of study intervention

For all patients in this domain who remain in hospital or ICU 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 to any ICU readmission, up until study day 28, noting that the criteria related to CAP and its direct complications still apply. If septic shock develops during the first or any subsequent ICU admission for a reason other than CAP, such as nosocomial 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 CAP and its direct

complications. All use of systemic corticosteroids is recorded and the reason for any new or additional administration is documented.

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 REMAP primary outcome as specified in the REMAP-CAP Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP 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 REMAP-CAP 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. Domain-specific data collection

9.1.1. 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

9.2. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for the discontinuation of participation in the REMAP-CAP trial.

9.3. Blinding

9.3.1. Blinding

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

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Effectiveness 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
- Noninferiority among active corticosteroid interventions
- Inferiority of any active intervention

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant

differences in one or more secondary endpoints may be capable of being demonstrated. 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

There are eight units-of-analysis for this domain, specified by the combination of shock and influenza strata status and age stratum. Analysis and Response Adaptive Randomization are applied by shock, influenza status, and age. The statistical model will permit borrowing between all strata as specified in the REMAP-CAP Core Protocol.

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.

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. 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 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 septic shock develops.

10.4. 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.

10.5. Nesting

There will be one nest in this domain, between fixed duration hydrocortisone and fixed duration dexamethasone, due to the similarities of the interventions.

10.6. Statistical triggers

The threshold probability for statistical triggers for superiority, effectiveness, inferiority, equivalence, futility, and non-inferiority are those specified in the relevant core protocol documents. At the time of this version of this DSA the REMAP-CAP Core Protocol does not include triggers for futility and non-inferiority. The threshold probability of statistical triggers for futility and non-inferiority will be those specified in future versions of relevant core protocol documents.

10.7. 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 should be aware that the efficacy, superiority, futility, noninferiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints.

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 VFDs or organ failure free days (OFFDs), an increased LOS in ICU or hospital, or death. We will collect these endpoints 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 Core Protocol Section 8.13).

11.3. Domain-specific consent issues

Corticosteroids have been used by clinicians for patients with severe CAP 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 REMAP it is reasonable to presume that some, but far from all, patients at sites that are participating in the REMAP would receive corticosteroid treatment.

Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain. In participants who are pregnant, dexamethasone will be substituted with prednisolone or hydrocortisone.

The choice of which of the four interventions are available at any site (i.e. any two, three or all four interventions) is determined by the participating site. Sites for which standard care in ICU is to routinely administer corticosteroids to patients with septic shock should not participate in the *no corticosteroid* intervention in the Severe State. The remaining three 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* available.

12. GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. 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, in the absence of the REMAP, a proportion of patients with severe CAP 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

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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