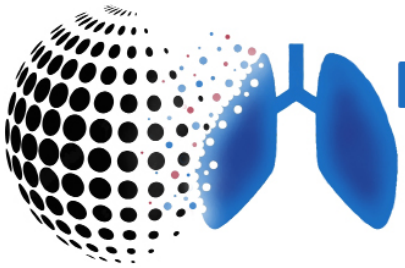

Domain-Specific Appendix:

CORTICOSTEROID DOMAIN

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

Corticosteroid Domain-Specific Appendix Version 4.0 dated 21 July 2020

Summary

In this domain of the REMAP-CAP trial, participants who meet platform entry criteria 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 lower dose hydrocortisone (200 mg daily for 7 days)
- Fixed duration higher dose hydrocortisone (400 mg daily for 7 days)
- Shock-dependent hydrocortisone while the patient is in septic shock

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

☐ No corticosteroid including hydrocortisone (no placebo)

☐Fixed duration lower dose hydrocortisone (200 mg daily for 7 days)

☐Fixed duration higher dose hydrocortisone (400 mg daily for 7 days)

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

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	Severe State
Interventions available in this Domain + State	Domain not available		No corticosteroids Fixed course low dose hydrocortisone Fixed course higher dose hydrocortisone Shock-dependent hydrocortisone	No corticosteroids Fixed course low dose hydrocortisone Shock-dependent hydrocortisone
Interventions submitted for approval at this site	N/A		☐ No corticosteroids ☐ Fixed course low dose hydrocortisone ☐ Fixed course higher dose hydrocortisone ☐ Shock-dependent hydrocortisone	☐ No corticosteroids ☐ Fixed course low dose hydrocortisone ☐Shock-dependent hydrocortisone
Interventions offered at this site in these locations	Ward	ICU	ICU	ICU
	N/A	N/A	☐ No corticosteroids ☐ Fixed course low dose hydrocortisone ☐ Fixed course higher dose hydrocortisone ☐Shock-dependent hydrocortisone	☐ No corticosteroids ☐ Fixed course low dose hydrocortisone ☐Shock-dependent hydrocortisone

REMAP-CAP: Corticosteroid Domain Summary	
Interventions	• No corticosteroid including hydrocortisone (no placebo) • Fixed duration lower dose hydrocortisone for 7 days • Fixed duration higher dose hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock
Unit-of-analysis, state, and Strata	This domain is analyzed in two different statistical models. The interpandemic model includes patients corresponding to the Pandemic Infection Neither Suspected nor Proven (PINSNP) stratum. Within the PINSNP stratum there are four units-of-analysis, specified by the combination of shock and influenza strata status, with borrowing permitted. Analysis and Response Adaptive Randomization are applied by shock and suspected or proven influenza status. Analysis also occurs in the pandemic statistical model, corresponding to the Pandemic Infection Suspected or Proven (PISOP) stratum. The Corticosteroid Domain is available on within the Severe State. In the pandemic statistical model, there are up to two possible units-of-analysis determined by SARS-CoV-2 status, specified as either confirmed or not confirmed, with borrowing permitted. Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived from either the PISOP stratum or the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	Within the interpandemic model, treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Influenza Antiviral Domain. Within the pandemic model, treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the COVID-19 Antiviral Domain and the COVID-19 Immune Modulation Domain.
Nesting	There is one nest, applied only in the pandemic statistical model, comprising the fixed duration lower dose and the fixed duration higher dose interventions.
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are those specified in the relevant core protocol documents. During the COVID-19 pandemic, the platform-level inclusion criteria are different for patients within the PISOP stratum and for patients within the PINSNP stratum. Patients in either stratum are eligible for this domain.
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Known hypersensitivity to hydrocortisone • 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 *Pneumocystis jiroveci* pneumonia • More than 36 hours has elapsed since ICU admission • Patient has been randomized in a trial evaluating corticosteroids, where the protocol of that trial requires ongoing administration of study drug • 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	Primary REMAP endpoint as defined in relevant core protocol documents Secondary REMAP endpoints as defined in relevant 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 relevant core protocol documents

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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
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
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, Section 1.2 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 relevant Core Protocol ((either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID 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 1:0 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 2:0 Approved by the Corticosteroid DSWG on 12 December 2017

Version 3:0 Approved by the Corticosteroid DSWG on 12 July 2019

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

Version 4.0: Approved by the Corticosteroid DSWG on 21 July 2020

4. CORTICOSTEROID DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Prof. Derek Angus

Members:

Ms. Wilma van Bentum-Puijk

Dr. Lennie Derde

Prof. Anthony Gordon

Dr. Sebastiaan Hullegie

A/Prof. Peter Kruger

Dr. Ed Litton

Prof.John Marshall

Dr. Colin McArthur

Dr. Srinivas Murthy

Prof. Alistair Nichol

Prof. Bala Venkatesh

Prof. Steve Webb

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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

Derek C. Angus

Date 21 July 2020

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of systemic corticosteroids in patients with severe community-acquired pneumonia (CAP) or patients with acute illness due to suspected or proven COVID-19 (or both).

6.2. Domain-specific background

There is significant uncertainty regarding the use of corticosteroids in patients with CAP who are treated in 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).

Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist. (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) 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 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. 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) 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. 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)

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.Corticosteroids in COVID-19

Coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in Wuhan, China in December 2019, there is a wide spectrum of symptoms ranging from mild asymptomatic disease to ARDS. The Surviving Sepsis Campaign COVID-19 guidelines recommended against the use of corticosteroids in the absence of ARDS (weak recommendation, low quality evidence), while suggesting corticosteroids may benefit in severe COVID-19 with ARDS (weak recommendation, low quality evidence) (Alhazzani et al., 2020). Further guidance from the World Health Organization does not recommend routine corticosteroid treatment, and that low to moderate corticosteroid doses for COVID-19 should only occur in the context of a clinical trial (World Health Organization, 2020). Given the past efficacy and potential harms of corticosteroids in pneumonia from other causes, there is an urgent need to determine the safety and effectiveness of corticosteroids for the treatment of COVID-19, as called for in the *Lancet* (Russell et al., 2020). At this time, it is not known the appropriate dose for corticosteroids in severe disease due to COVID-19 or the optimal agent to be used, with a wide array of strategies in current practice. Clinical variation across regions is substantial, with choice of agent of hydrocortisone, methylprednisolone or dexamethasone all being used across regions for COVID19 (Fadel et al, 2020; Isodori et al., 2020; recoverytrial.net).

6.2.8.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.

6.2.9. Definitively addressing the role of corticosteroids in severe 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 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 affect mortality?
- For patients with influenza infection and CAP does hydrocortisone affect mortality?
- For patients with COVID-19 does corticosteroid strategy affect outcome?

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different strategies of corticosteroid utilization in the treatment of severe CAP for patients who are eligible for the platform

We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on the allocation to different corticosteroid strategies. The following interventions will be available:

- No corticosteroid (hydrocortisone is not prescribed; no other corticosteroid is permitted; no administration of a placebo)
- Fixed duration lower dose hydrocortisone (IV hydrocortisone 50mg every 6 hours for 7 days)
- Fixed duration higher dose hydrocortisone (IV hydrocortisone 100 mg every 6 hours for 7 days), only in the PISOP stratum.
- Shock-dependent duration hydrocortisone (IV hydrocortisone 50mg every 6 hours while in septic shock)

The following hypotheses apply to patients enrolled in the interpandemic model (i.e. PINSNP patients):

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)

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on allocation status in the Influenza Antiviral Domain. This is a treatment-by-treatment interaction between the interventions in the Corticosteroid Domain and the influenza Antiviral Domain.

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?

The following hypotheses apply to patients enrolled in the pandemic model (i.e. PISOP patients):

We hypothesize that, in patients with suspected or proven pandemic infection, the treatment effect of different corticosteroid strategies is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on allocation status in the COVID-19 Antiviral Domain. This is a treatment-by-treatment interaction between the interventions in the Corticosteroid Domain and the COVID-19 Antiviral Domain.

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on allocation status in the COVID-19 Immune Modulation Domain. This is a treatment-by-treatment interaction between the interventions in the Corticosteroid Domain and the COVID-19 Immune Modulation Domain.

8. TRIAL DESIGN

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

8.1. Population

The REMAP enrolls patients with severe CAP or patients admitted to hospital with acute illness due to suspected or proven pandemic infection who are in the Severe State (see either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol).

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 either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol It is noted that during the COVID-19 pandemic, that platform-level inclusion criteria are different for patients with pandemic infection suspected or proven (PISOP stratum) and for patients in whom pandemic infection is neither suspected nor proven (PINSNP). Patients in either stratum are eligible for this domain. Patients otherwise eligible for the REMAP may have conditions that exclude them from the Corticosteroid Domain.

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in only the Severe State

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

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

- Known hypersensitivity to hydrocortisone
- 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* pneumonia
- More than 36 hours have elapsed since ICU admission (noting that this may be operationalized as more than 24 hours has elapsed since commencement of sustained organ failure support)
- Patient has been randomized in a trial evaluating corticosteroids, where the protocol of that trial requires ongoing administration of study drug
- 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 interventions

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

All interventions will be commenced immediately after allocation status is revealed.

☐ No corticosteroid including hydrocortisone (no placebo)

☐ Fixed duration lower dose hydrocortisone (200 mg daily for 7 days)

☐ Fixed duration, higher dose hydrocortisone (400 mg daily for 7 days)

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

It is required that all sites will participate in the 'No corticosteroid' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

8.3.2. No corticosteroid intervention

Patients allocated to the *no corticosteroid* intervention are not to receive any systemic corticosteroid, including hydrocortisone, for this episode up until study day 28. There is no administration of placebo. If a patient has been receiving any corticosteroid prior to enrollment, this medication must be ceased. Administration of a systemic corticosteroid, including hydrocortisone, is permitted only for the treatment of new illnesses that develop in the course of a patient's ICU stay, such as asthma or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration is documented.

8.3.3. Dosing and duration of administration of corticosteroids

Patients allocated to the *fixed-duration lower dose 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, for this episode of CAP, including CAP due to COVID, and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone, 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 ICU stay, such as asthma 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.

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, including CAP due to COVID, 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.

Patients allocated to the *fixed-duration higher dose hydrocortisone* intervention are to be prescribed a course of hydrocortisone 100mg 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, for this episode of COVID and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone, 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 ICU stay, such as asthma 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 all patients in this domain who remain in ICU after study day 28, data on the administration of corticosteroids is 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 +/- Pandemic Appendix or REMAP-COVID Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the the REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol

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

- SAE as defined in the core protocol documents and qualified in this DSA

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

Refer to Core Protocol Section 8.9 for data collection fields and processes.

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

Hydrocortisone will be administered on an open-label basis.

9.3.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

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 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

This domain is analyzed in two different statistical models, with PINSNP patients evaluated in the interpandemic model and PISOP patients analyzed in the pandemic model.

Within the PINSNP stratum there are four units-of-analysis, specified by the combination of shock and influenza strata status, with borrowing permitted. Analysis and Response Adaptive Randomization are applied by shock and influenza strata status. Analysis and Response Adaptive Randomization are applied by shock and suspected or proven influenza status. The statistical model will permit borrowing between all stratum as specified in Core Protocol.

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.

Within the PISOP stratum analysis also occurs in the pandemic statistical model. Within this stratum there are up to two possible units-of-analysis determined by SARS-CoV-2 status, specified as either confirmed or not confirmed, with borrowing permitted. Response Adaptive Randomization will be

applied to patients in the PISOP stratum using probabilities derived from either the PISOP stratum or the SARS-CoV-2 confirmed stratum. Within the PISOP stratum, patients are only eligible for this domain only in the Severe State.

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 (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 are specified separately for the interpandemic model (PINSNP patients) and the pandemic model (PISOP patients)

10.4.1. Interactions specified in the interpandemic model

An *a priori* interaction with the Antibiotic Domains is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

No interaction with any domain that is exclusively in the pandemic model is possible as analysis occurs in a different statistical model.

No interaction is evaluable between the Ventilation Domain and this domain.

10.4.2. Interactions specified in the pandemic model

No interaction with any domain that is exclusively in the interpandemic model is possible as analysis occurs in a different statistical model.

An *a priori* interaction with the COVID-19 Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. An informative prior that is negative is applied to the interaction between interventions in this domain that include administration of hydrocortisone and the interferon-beta-1a intervention in the Immune Modulation Domain (see Immune Modulation DSA for all details).

An *a priori* interaction with the therapeutic anticoagulation is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the immunoglobulin is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

Within the pandemic statistical model, there is one nest comprising the lower dose fixed duration hydrocortisone intervention and the higher dose fixed duration hydrocortisone intervention. The rationale for this is that the treatment effect of different doses of steroids is likely to be more similar than no steroids.

Within the interpandemic statistical model interventions in this domain will be analyzed without application of nesting. This is because the *shock-dependent duration hydrocortisone* intervention will be more like the *fixed-duration hydrocortisone* intervention in patients who develop septic shock and more like the *no corticosteroid* intervention in patients who do not develop septic shock (i.e. no hydrocortisone is administered). This divergence in potential similarity cannot be accommodated within the statistical model to allow nesting. For reasons of participant safety and relevance to public health, the DSMB are empowered to request a secondary model to be performed which does allow nesting, if the DSMB believes that it is appropriate to do so.

10.6. Threshold probability for superiority, effectiveness, and inferiority

In the interpandemic model, superiority and inferiority are evaluated using the threshold probabilities specified in the Core Protocol.

In the pandemic model, superiority, effectiveness, and inferiority are evaluated using the threshold probabilities specified in the Pandemic Appendix and the REMAP-COVID Core Protocol.

10.7. Threshold odds ratio delta for equivalence and futility

In the interpapndemic model, the threshold odds ratio for equivalence in this domain is that specified in the relevant core protocol documents.

In the pandemic model, the Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio deltas as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one side analysis for futility of active corticosteroid interventions.

10.8. Informative priors

As noted in the interaction section, an informative prior is set for interaction between the interferon-beta-1a intervention in the Immune Modulation Domain (see Immune Modulation DSA for all details).

10.9. Post-trial sub-groups

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

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes are required.

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 relevant core protocol documents.

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 relevant core protocol documents.

11.3. Domain-specific consent issues

As noted in the Background, and endorsed by the World Health Organization, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical. For patients who are not competent to consent, either prospective agreement or entry via waiver of consent or some form of deferred consent can be applied, as required by an appropriate ethical review body. 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 of confirming agreement to participate in this (and other) domains of the platform. Clinicians are directed not to enroll an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient

Hydrocortisone has been used by clinicians for patients with severe CAP for decades. 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.

The choice of which the four interventions are available for PISOP patients and the three interventions for PINSNP patients at any site is determined by the participating site. Sites for which standard care is to routinely administer hydrocortisone to patients with septic shock should not participate in the *no hydrocortisone* intervention. The remaining interventions administer hydrocortisone to patients who have or develop septic shock, but do so for different durations or doses for which may sites will have clinical equipoise.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the relevant core protocol documents. This domain has not received any additional domain-specific funding but such funding may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

Hydrocortisone 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 is no longer a medication protected by patent in any country that is participating in the Platform and the cost of hydrocortisone is 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.

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.

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.

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.

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.

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.

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.

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.