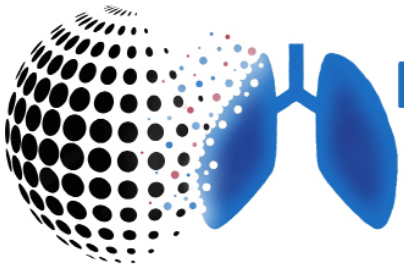

Domain-Specific Appendix:

CORTICOSTEROID DOMAIN

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

Corticosteroid Domain-Specific Appendix Version 2 dated 12 December 2017

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to intensive care units will be randomized to receive either:

- Hydrocortisone intravenous (IV), 50 milligrams every 6 hours for up-to 7 days
- No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo)

REMAP-CAP: Corticosteroid Domain Summary	
Interventions	• Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days. • No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo)
Strata	Analysis and Response Adaptive Randomization are by strata (shock) to allow for strata-by-intervention interaction.
Evaluable Interactions	Intervention-intervention interactions will be evaluated between interventions in this domain and interventions in the Macrolide Duration Domain and interventions in the Antibiotic Domain.
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1
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 other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia • Have received an immunomodulatory dose of systemic corticosteroid therapy in the24 hours prior to the time of enrollment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours. • 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: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment): 1. Serious Adverse Events (SAE) as defined in CORE protocol

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1. ABBREVIATIONS

ADRENAL	ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock Study
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
Severe CAP	Severe Community-Acquired Pneumonia
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 Regions-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

4. CORTICOSTEROID DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Professor Derek Angus

Members:

Ms. Wilma van Bentum-Puijk

Dr. Lennie Derde

Professor Anthony Gordon

Dr. Sebastiaan Hullegie

Associate Professor Peter Kruger

Dr. Ed Litton

Dr. Colin McArthur

Professor Alistair Nichol

Professor 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 12th December 2017

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of immune modulation with corticosteroids in patients with severe community-acquired pneumonia (severe CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. Domain-specific background

There is significant uncertainty regarding the use of corticosteroids in patients with community-acquired pneumonia (CAP) who are treated in an ICU. Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist. However, existing evidence is not sufficient to provide guidance to clinicians that is definitive. 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. Severe CAP is intertwined with the host systemic inflammatory response

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. Interestingly, 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) It has been postulated that a potential dampening of this 'abnormal' immune response to infection, for example by administration of corticosteroids, could improve outcomes.

6.2.2. 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)

6.2.3. Corticosteroids 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 a consideration. 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. Given that the implications for patients of these complications is uncertain, it is vitally important to conduct a study with the ability to assess the aggregate effects of steroids (i.e. the sum of the potentially beneficial and deleterious effects) on an outcome such as mortality. This is the only way in which clinicians can be certain that they are making the correct decision regarding corticosteroid therapy in severe CAP.

6.2.4. Are corticosteroids beneficial in severe CAP?

The evidence regarding the effectiveness of corticosteroids in patients with severe sepsis and severe CAP, in particular, has not been straightforward to interpret clearly. The existing trials can be divided in to those that randomized patients with sepsis and septic shock (including many patients with severe CAP) or those in patients with severe CAP (with or without septic shock) to receive corticosteroid or not (placebo or no placebo).

The studies that enrolled patients with sepsis or septic shock included patients with a range of different sites of primary infection but, typically, around half of included patients will have had CAP. The results of these studies are heterogeneous. The current 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 the study by Annane et al, 2002, hydrocortisone improved the duration of survival (within the first 28

days) and resulted in more rapid reversal of septic shock in the 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 however this may have been influenced by inclusion of a higher proportion of patients at lower risk of death. (Sprung et al., 2008) The more recent Cochrane meta-analysis suggests that corticosteroid treatment reduces mortality among patients with sepsis, but that the overall quality of evidence is low. (Annane et al., 2015) As a consequence, there is substantial variation in clinical practice and existing evidence is best regarded as hypothesis generating. (Annane et al., 2002, Bollaert et al., 1998, Briegel et al., 1999) A large RCT of hydrocortisone in patients with septic shock (ADRENAL) is recruiting currently and is expected to report results during 2017 or 2018. (Venkatesh et al., 2013) The role of corticosteroids in patients with severe sepsis but not septic shock is also uncertain, with a recent study reporting that corticosteroids were not effective in preventing the development of shock. This raises the possibility that the effect of corticosteroids in patients with severe sepsis may be different depending on the presence of absence of shock at the time of enrollment. (Keh et al., 2016)

A number of trials have evaluated the effect of administration of corticosteroids in patients with severe CAP. These studies have been reviewed by Prina et al, 2016, and are summarized in Table 1 (modified from *Prina et al*, 2016). (Chen et al., 2011, Cheng et al., 2014, Confalonieri et al., 2005, Garcia-Vidal et al., 2007, Meijvis et al., 2011, Nie et al., 2012, Shafiq et al., 2013, Siemieniuk et al., 2015, Snijders et al., 2010, Torres et al., 2015, Wan et al., 2016, Prina et al., 2016) A 2011 Cochrane meta-analysis by Chen et al, 2011 (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, 2012 (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 corticosteroid treatment. (Nie et al., 2012) A 2016 meta-analysis by Wan et al, 2016 (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 Acute Respiratory Distress Syndrome (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, 2014 (4 RCTs, n=264), which includes 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 pooled estimates. (Cheng et al., 2014) The authors concluded that reliable treatment recommendations could only be raised if additional multicenter studies with sufficient statistical power are conducted. (Cheng et al., 2014)

6.2.4.1. Recent Randomized controlled trials

Two recent relatively large high quality multicenter RCTs have been published regarding the use of corticosteroids in CAP that are not included in the meta-analyses of patients with CAP. Blum et al, 2015 conducted a multicenter, double-blind, randomized, placebo controlled trial (n=785) of patients with CAP who were randomized to receive either prednisone (50 milligrams (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. (Torres et al., 2015)

As highlighted in Table 1 the aggregate conclusion from these studies is that there is reasonable evidence to indicate that use of corticosteroids in CAP results 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 with the huge heterogeneity in current clinical practice indicating clinical equipoise exists, makes now the time to conduct such a large adequately powered and patient centered outcome orientated study.

Table 1: 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	↑PaO2/FiO2, ↑chest radiograph score, ↓CRP, delayed septic shock, ↓hospital LOS and ↓mortality
(Garcia-Vidal et al., 2007)	Retrospective observational study patients with severe CAP, systemic steroids	↓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 was late failure (>72 hours) ↑with prednisolone
(Meijvis et al., 2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	↓hospital LOS
(Chen et al., 2011)	Meta-analysis (6 RCTs, n=437), CAP	↑resolution of symptoms ↑clinical stability ↓rate of relapse
(Nie et al., 2012)	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall ↓mortality in severe CAP
(Shafiq et al., 2013)	Meta-analysis (8 RCTs, n=1119), CAP	↓hospital LOS, No change in mortality
(Cheng et al., 2014)	Meta-analysis (4 RCTs, n=264), severe CAP	↓hospital LOS, ↓mortality
(Torres et al., 2015)	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	↓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	↓time to clinical stability
(Siemieniuk et al., 2015)	Meta-analysis (12 RCTs, n= 1974), CAP	↓all-cause mortality, ↓mechanical ventilation and ↓ARDS, ↓time to clinical stability, ↓duration of hospitalization
(Wan et al., 2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, ↓ARDS

6.2.5. 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 the particularly severely lung injured group (i.e. ARDS) of patients with severe CAP in the ICU. Meduri, et al, 1998 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) However, this study was very small and it is also important to note that there were differences in baseline characteristics between groups. (Meduri et al., 1998) A subsequent larger 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 significantly associated with 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 equipoise exists to randomize severe CAP patients who develop ARDS to receive corticosteroids (or not).

6.2.6.Corticosteroids in severe CAP secondary to influenza

It has been noted that almost one third of patients admitted to an ICU with 2009 H1N1 pandemic influenza 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 there being little evidence of the efficacy and safety 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)) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection. (Zhang et al., 2015) However, it is likely that severity of illness will be a confounding factor in observational studies that evaluate this question and it is always uncertain if confounding due to this course has been adjusted for adequately. There

have been no RCTs examining the effects of corticosteroids (versus no corticosteroids) in patients who are critically ill due to CAP caused by influenza. A particular feature of this REMAP trial is that it can respond to event such as pandemics, a Pandemic Influenza DSA for corticosteroids will address this question.

6.2.7. The need for a large trial to definitively address the role of corticosteroids in severe CAP is a priority.

Although the recent RCTs and meta-analyses have increased our knowledge regarding the potential usefulness and safety of corticosteroids in severe CAP, more studies are needed to clarify the effect of corticosteroids on mortality. Moreover, it is possible that there may be differential treatment effect in defined sub-groups of patients (i.e. shocked or not). Reliable treatment recommendations can only be raised only when large multi-center RCTs are conducted with sufficient statistical power to detect a difference in mortality. (Cheng et al., 2014)

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of hydrocortisone for the treatment of severe CAP.

The interventions that will be compared are:

- Hydrocortisone IV, 50 milligrams every 6 hours for up-to 7 days
- No hydrocortisone

We hypothesize that the probability of all-cause mortality at 90 days will be different in patients who are randomized to receive corticosteroids.

We hypothesize that the treatment effect of corticosteroids 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 corticosteroids is different depending on the duration of concomitant treatment with a macrolide. This is an intervention by intervention interaction between this domain and the Macrolide Duration Domain.

We hypothesize that the treatment effect of corticosteroids is different depending on the concomitant antibiotic that is administered. This is an intervention by intervention interaction between this domain and the Antibiotic Domain.

8. TRIAL DESIGN

This domain will be conducted as part of a REMAP trial for severe CAP (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. Population

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the REMAP-level inclusion and none of the REMAP-level exclusion criteria (see Core Protocol Section 7.4). Patients who are eligible for the REMAP may have conditions that may exclude them from the Corticosteroid Domain.

8.2.1. Exclusion criteria from this domain

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 other than CAP (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* pneumonia
- Have received an immunomodulatory dose of systemic corticosteroid therapy in the 24 hours prior to the time of enrollment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.3. Interventions

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

1. Hydrocortisone IV, 50 mg every 6 hours for up-to 7 days.
2. No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo)

8.3.1. Timing to initiation of corticosteroids

In patients randomized to receive hydrocortisone, administration should commence immediately after the allocation status is revealed, which is at the time of enrollment. The scientific validity of the study and patient welfare, as a consequence of Response Adaptive Randomization (RAR), is enhanced by immediate commencement of treatment according to the patient's allocation status as this maximizes separation between interventions.

8.3.2. Duration of administration of corticosteroids

Hydrocortisone will be prescribed for 7 days at the time of enrollment or until discharge from hospital, if hospital discharge occurs before 7 days have elapsed. For patients who are discharged from the ICU before 7 days, it is the responsibility of ICU staff to prescribe hydrocortisone for administration for a total of 7 days. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the study drug after discharge from the ICU.

8.4. Concomitant care

Administration of corticosteroids to patients who are enrolled in this domain and allocated to not receive corticosteroids for the 7 days after enrollment is a protocol violation.

8.4.1. Implications of allocation status for eligibility in other domains

Randomization in this domain has no influence on eligibility to other domains in this REMAP.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-cause mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

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 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

No additional domain-specific data will be collected for this domain. Refer to Core Protocol Section 8.9 for data collection fields and processes.

9.2. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for discontinuation criteria for the participation in REMAP-CAP.

9.3. Blinding

9.3.1. Blinding

Hydrocortisone will be administered on an open-label basis. All appropriate measures, such as notes on paper medication charts or entries into an electronic prescribing system will be used to prevent inadvertent administration of systemic corticosteroids to patients who are randomized to not receive hydrocortisone.

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 capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 7.8.6 to 7.8.9.

10.2. Strata

Both analysis of the treatment effect and the RAR will utilize the stratum of shock in this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is as specified to be Randomization with Immediate Reveal and Initiation (see Section 7.8.3.4 in Core Protocol).

10.4. Interactions with interventions in other domains

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

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

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

10.5. Post-trial Sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of the domain. Sub-groups of interest include:

- The causative organism, in patients from whom a microbiological diagnosis for the qualifying pneumonia has been made on the basis of culture or other investigations (nucleic acid

testing, urinary antigen testing) based on tests taken before or within 72 hours of admission to hospital.

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, 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. Please refer to Core Protocol Section (8.13) for information about safety monitoring and reporting.

11.3. Domain-specific consent issues

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, although there is limited evidence of effectiveness, there remains no high-quality evidence that the use of hydrocortisone improves mortality. 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 but that such treatment decisions would reflect the choice of clinicians making a treatment decision in the absence of high quality evidence.

Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain.

12.GOVERNANCE ISSUES

12.1. Funding of domain

The REMAP trial is funded in Australia by an Australian National Health and Medical Research Council project grant (APP1101719), in Europe by a European Union 7th Framework Programme for Research and Technological Development grant (602525) and in New Zealand by a Health Research Council New Zealand Programme grant (16/631).

12.2. Funding of domain interventions

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.

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