



Protocol Amendment to Corticosteroid Domain-Specific Appendix Summary of Changes

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

REMAP-CAP Corticosteroid Domain-Specific Appendix Amendment Summary of Changes

Dated 16 October 2021

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1. BACKGROUND TO AMENDMENT

The Corticosteroid Domain-Specific Appendix Protocol document underwent an amendment in October 2023. The primary objective of this amendment is to make minor changes to provide clarification and context to the recruitment of pediatric patients to this domain of REMAP-CAP.

2. SUMMARY OF CHANGES

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Corticosteroid Domain-Specific Appendix Version 5 dated 09 November 2022	REMAP-CAP Corticosteroid Domain-Specific Appendix Version 5.1 dated 16 October 2023	Administrative change
Whole document	Version 5.0 9 th November 2022	Version 5.1 16 th October 2023	Minor administrative corrections to align new sections referenced in the text and with nomenclature across protocol documents. Updated appendix approval date by Chair
Throughout document	... aged \geq 28 days old.	... aged \geq 28 days old (corrected gestational age).	Clarification that age for infants refers to corrected gestational age.
Domain-specific working group members		Removed Wilma van Bentum Puijk and Ed Litton Added Djillali Annane	Updated to reflect changes to the domain-specific working group membership over time
Section 6.2.2	There are several interrelated and overlapping clinical questions regarding the role of corticosteroids in	There are several interrelated and overlapping clinical questions regarding the role of corticosteroids in	Section updated to clarify the rationale for

	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.	patients, both adults and children , with severe CAP. The first of these is whether patients who have septic shock as a complication of severe CAP benefit from corticosteroids. The second is whether patients with severe CAP who do not have septic shock benefit from corticosteroids. The third is whether patients with severe CAP due to influenza respond differently to corticosteroids. Fourth is whether there are differences across the age range, from children to adults, in their responsiveness to corticosteroids.	evaluating the use of corticosteroids in both adults and paediatric populations, including the ability to evaluate differential responsiveness to systemic corticosteroid therapy by age.
Section 6.2.5	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.	During the 2009 H1N1 influenza pandemic, among patients admitted to an ICU, approximately one third of patients received corticosteroids (Falagas et al., 2010) as either a primary therapy or as a rescue therapy for patients with severe ARDS (Kumar et al., 2009, Dominguez-Cherit et al., 2009). In children the use of corticosteroids ranged between 9 and 21% (Muthuri et al., 2014). This widespread use occurred despite the absence of any evidence from RCTs regarding the effectiveness of corticosteroids in CAP secondary to influenza.	Background section updated to provide greater context regarding the use of corticosteroids in paediatric populations.
Section 6.2.5	Corticosteroids have now become a standard of care for severe COVID-19 pneumonia as a result of high quality	Corticosteroids have now become a standard of care for severe COVID-19 pneumonia in both adults and children as a result of high quality RCT evidence and such	Background updated to make reference to the current standard of care

	RCT evidence and such evidence is now needed for severe influenza pneumonia.	(although it should be noted there were no RCTs of corticosteroids in children). Such evidence is now needed for severe influenza pneumonia for both adults and children.	for paediatric patients (as well as adults) with COVID-19.
Section 6.2.7	<p>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.</p>	<p>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.</p> <p>For children, there are minimal safety data in children less than three months, and for longer courses (greater</p>	Updated to reflect available safety information regarding the use of systemic corticosteroids in young paediatric patients.

		than five days) of corticosteroids. In the premature infant population, there is a possibility of neurodevelopmental issues from courses of dexamethasone. The risks of prolonged exposure to corticosteroids include the possibility of myopathy, increased rates of infection, and the possibility of neurodevelopmental concerns in the very young population.	
Section 7	* In children – dexamethasone 0.15 mg/kg (max 6mg/day) for 10 days	* In children – dexamethasone 0.15 mg/kg (max 6mg/day) for a maximum of 10 days	Minor clarification that the fixed duration of dexamethasone is for a maximum of 10 days (while the patient remains admitted to hospital)
Section 8.3.5	Patients allocated to the fixed duration dexamethasone intervention, will have dexamethasone, IV or enteral 6 mg daily for 10 days while in hospital. Administration is to commence immediately after the allocation status is revealed at the time of enrollment on study day 1. The choice of enteral or IV administration is at the discretion of the treating clinician based on the patient's ability to take enteral medication and illness severity including likely gastric absorption rates. In children the dose of	Patients allocated to the fixed duration dexamethasone intervention, will have dexamethasone, IV or enteral 6 mg daily for 10 days while in hospital. Administration is to commence immediately after the allocation status is revealed at the time of enrollment on study day 1. The choice of enteral or IV administration is at the discretion of the treating clinician based on the patient's ability to take enteral medication and illness severity including likely gastric absorption rates. In children the dose of	Minor clarification that the fixed duration of dexamethasone is for a maximum of 10 days (while the patient remains admitted to hospital).

	<p>dexamethasone will be 0.15 mg/kg (max 6mg/day) for 10 days while in hospital. In pregnancy dexamethasone should be replaced by oral prednisolone 40mg once daily or IV hydrocortisone 50mg every 6 hours for 10 days while in hospital. From completion of the 10-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone or dexamethasone, for this episode of CAP and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone or dexamethasone, after completion of the 10-day course is permitted only for the treatment of new illnesses that develop in the course of a patient's hospital stay, such as asthma, airway swelling or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration after day 10 is documented.</p>	<p>dexamethasone will be 0.15 mg/kg (max 6mg/day) for a maximum of 10 days while in hospital. It is expected that most children will spend less than 10 days in hospital and therefore duration of therapy will be shorter. In pregnancy dexamethasone should be replaced by oral prednisolone 40mg once daily or IV hydrocortisone 50mg every 6 hours for 10 days while in hospital. From completion of the 10-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone or dexamethasone, for this episode of CAP and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone or dexamethasone, after completion of the 10-day course is permitted only for the treatment of new illnesses that develop in the course of a patient's hospital stay, such as asthma, airway swelling or treatment of an allergic reaction. In particular longer courses of corticosteroids should be avoided in very young infants. All use of systemic corticosteroids is recorded and the reason for any administration after day 10 is documented.</p>	<p>Minor additions to explain that the expected course of corticosteroids is likely to be less than 10 days. This is important in the context of the recommendation that prolonged courses of corticosteroids should be avoided in young infants.</p>
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