REMAP-CAP

Confirming Eligibility Training

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Chief Investigator: Prof Anthony Gordon

Study Coordination Centre:

Intensive Care National Audit & Research Centre

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Imperial College London

ecraid

UMC Utrecht

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icnarc intensive care national audit & research centre

25 Years and counting

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Coordinating Centre / Trial Management Team

- **Trial coordinated by Imperial College London**
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REMAP-CAP

Introduction to REMAP-CAP

- A Randomised, Embedded, Multi-factorial, Adaptive Platform trial for Community-Acquired Pneumonia.
- REMAP-CAP is currently open in ICUs and wards testing treatments for COVID-19, CAP and Influenza.
- Adults and children admitted to hospital acutely unwell with confirmed influenza will be recruited to the trial.

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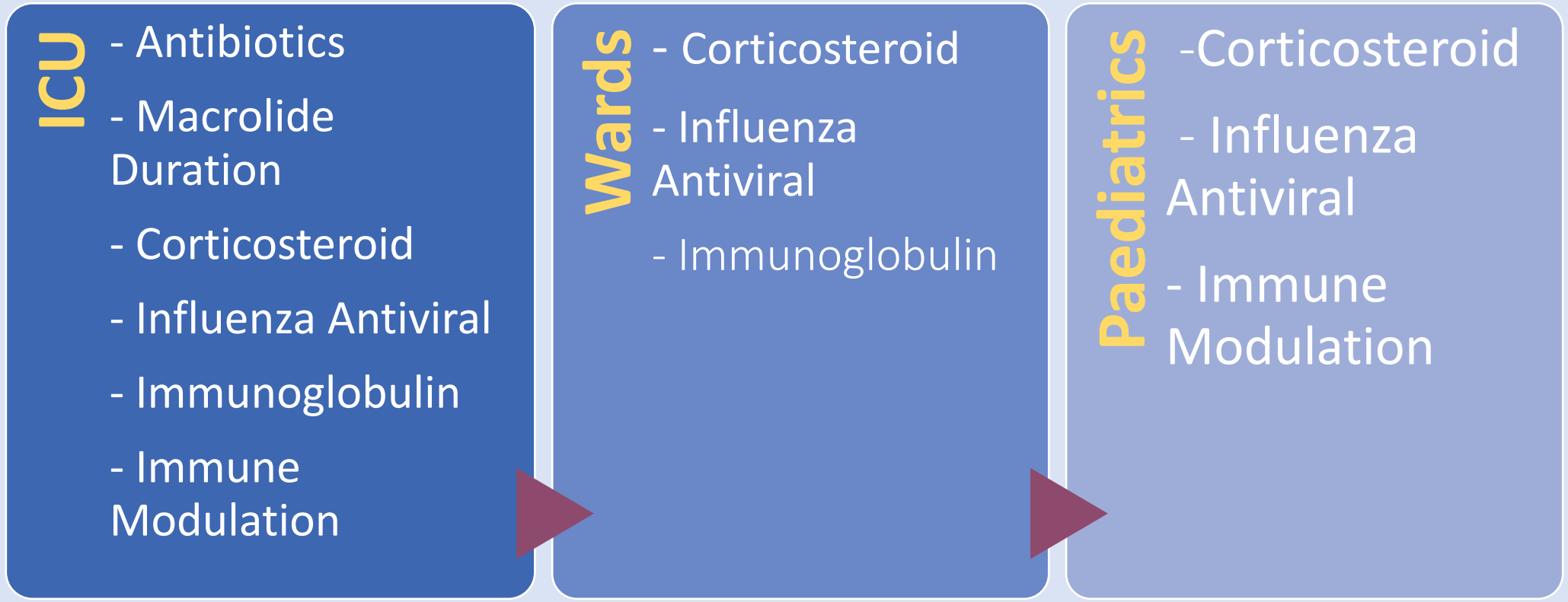
Current open domains and stratum



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Confirming Eligibility

- As per MHRA requirements only a **clinician (or a role that has prescribing rights)** is able to confirm whether a patient is eligible for the trial.
- The clinician confirming eligibility is required to be listed on the delegation log and must have completed a training log for this **eligibility assessors training** so that the study has oversight of those who have received training and are qualified to confirm eligibility.
- Eligibility should be confirmed for the trial and for specific domains. This needs to be documented in the medical records.
- This can be in the form of completing an **'eligibility statement' template** (signed/dated) or a direct entry in the patient medical records.

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CAP/FLU platform inclusion criteria

- Adult or paediatric patient (28 days or older) hospitalised with an acute illness due to a lower respiratory tract infection.

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CAP/FLU platform exclusion criteria

1. More than 14 days has elapsed since admission to hospital
2. If receiving organ failure support in an ICU, more than 48 hours has elapsed since admission to ICU
3. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
4. Previous participation in this REMAP within the last 90 days
5. Expected to be discharged from this hospital admission within the next 24 hours

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Influenza Antiviral domain

Inclusion

- Influenza infection has been confirmed by microbiological testing.

Exclusion

- Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors
- Patient has already received one or more doses of baloxavir
- Patient is already receiving, or a clinical decision has been made to commence, an antiviral active against influenza other than oseltamivir or baloxavir, or both.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

If in Moderate State

- More than 96 hours has elapsed since hospital admission

If in Severe state

- More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU

Intervention Specific Exclusions

- Known hypersensitivity to oseltamivir or baloxavir
- Known or suspected pregnancy will result in exclusion from interventions that include baloxavir

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Corticosteroid domain

Inclusion – If in moderate state

- Patient is receiving some form of supplemental oxygen (simple facemask, low or high flow nasal oxygen, or non-invasive ventilation)

Exclusion

- Known hypersensitivity to any corticosteroid
- Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jirovecii or COVID19 pneumonia
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- **If in Severe state**
- More than 24 hours have elapsed since ICU admission; if the patient has already been assigned a treatment in another domain in the Moderate State, exclusion will occur if more than 24 hours has elapsed since commencement of sustained organ failure support in an ICU.

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Immune Modulation domain (ICU only)

Inclusion

- ≥2 years
- Confirmed influenza
- In the opinion of the treating clinician, the primary contributor to the patient's Severe Illness State is a respiratory tract infection

Exclusion:

- Confirmed COVID-19
- Immunosuppression
- A neutrophil count <1.0 x 109 / L
- **Confirmed or strongly-suspected** active mycobacterial infection or invasive fungal infection
- Pregnancy - baricitinib (& tocilizumab-for now)
- Renal failure – baricitinib (eGFR <15ml/min/1.73m2 (or <30 if <9years) or RRT)
- Patient has already received any dose of one or more of tocilizumab (or another IL-6 receptor antagonist) or baricitinib (or another JAK inhibitor) during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

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Immunoglobulin domain (adults only)

Inclusion

- SARS-CoV-2 infection is confirmed by microbiological testing
- Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, corresponding to the APACHE II definitions (Knaus et al., 1985), extended to take into account equivalent forms of immunosuppressant therapy that post-date the APACHE II definitions.

Exclusion

- Patient has already received treatment with any non-trial prescribed polyclonal antibody therapy (hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this acute illness.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- Known hypersensitivity/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving high titre plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

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Antibiotic domain (ICU adult only)

Inclusion

- Admitted to ICU

Exclusion

- Received more than 48 hours of intravenous antibiotic treatment for this index illness
- More than 24 hours has elapsed since ICU admission
- Known hypersensitivity to all of the study drugs in the site randomization schedule
- A specific antibiotic choice is indicated, for example:
- Suspected or proven concomitant infection such as meningitis
- Suspected or proven infection with resistant bacteria where agents being trialled would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection.
- Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count 4 preceding weeks).
- Suspected melioidosis
- Specific microbiological information available to guide specific antibacterial therapy
- The treating clinician believes that participation in the domain would not be in the best interests of the patient.

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Antibiotic domain (ICU adult only) - continued

Intervention Specific Exclusions

- Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin
- Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone and ceftaroline.
- Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline.
- Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention.
- Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline.
- Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin and ceftaroline interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.

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Macrolide domain (ICU only)

Inclusion

- Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic Domain.

Exclusion

- Agreement to participate in this domain has been declined or has not been requested before the end of study day 5.
- There is microbiological confirmation or the clinician strongly suspects Legionella or any other form of atypical pneumonia.
- Macrolide antibiotics have already been discontinued for more than 36 hours.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient.

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Good Clinical Practice (GCP)

- International, ethical and scientific quality standard to which all research involving human participants is conducted
- Comprised of 13 core principles & applies to all clinical investigations that could affect safety and well-being of human participants, providing international assurance that:
  - Data and reported results of clinical investigations are credible and accurate
  - Rights, safety and confidentiality of participants in clinical research are respected and protected
- You are encouraged to obtain GCP certification, such as that available through NIHR: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm

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Principles of Good Clinical Practice (GCP)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval/favourable opinion.

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Principles of Good Clinical Practice (GCP)

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. ***This principle applied to all records referenced in this guideline, irrespective of the type of media used.***
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice(GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

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