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

Pandemic Stratum

PREPARE Platform foR European Preparedness Against (Re-)emerging Epidemics

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Pandemic Appendix to Core Protocol

- **Pandemic strata** designed as a sleeping strata
  - Activated by the REMAP-CAP trial steering committee 13 March 2020
- Activation of Pandemic Strata results in a number of changes to:
    - Eligibility criteria
    - Primary end-point
    - Statistical model
    - Frequency of RAR
    - New pandemic-specific domains

Changes to eligibility

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Does the patient have clinically suspected or proven pandemic infection

- Clinically suspected = treating clinician believes that pandemic infection is a likely diagnosis
- That testing is being done is not sufficient, must think pandemic infection is likely
- Response to this question drives a number of changes to eligibility, CRF, randomization, and primary end-point.
- Suspected or proven hospital-acquired pandemic infection are eligible

Changes to eligibility

The following platform eligibility criteria do not apply for patients with clinically suspected or proven pandemic infection:

- Is the patient a resident of a nursing home or long-term care facility
- Prior to this illness was the patient known to be an inpatient in any healthcare facility within the last 30 days
- Does the patient have signs and/or symptoms that are consistent with lower respiratory tract infection
- Does the patient have radiological evidence of new onset infiltrate of infective origin
- Time window from hospital admission to ICU admission

Questions are still asked, software processes responses

Changes to eligibility

Platform inclusion criteria:

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection

Platform exclusion criteria:

1. Death deemed imminent within next 24 hours
2. Patient expected to be discharged from hospital today or tomorrow
3. >14 days have elapsed while admitted to hospital with symptoms of acute illness due to suspected/proven pandemic infection
4. Previous participation in this REMAP within the last 90 days

Changes to eligibility

Patients may now be eligible in both Moderate and Severe disease states:

- Severe State = receiving organ support in ICU
- Moderate State =
  - In ICU but not receiving organ support
  - Not in ICU

Patients may receive allocations while in Moderate state and later receive an allocation to other domains if then progress to Severe state.

Patients in Severe state cannot receive additional allocations if they become Moderate.

Changes to eligibility

- Location of the patient at time of screening
  - ICU or non-ICU location
- Whether the patient has received invasive mechanical ventilation in ICU during this acute hospital admission
  - For patients being assessed for Moderate State
- Where was pandemic infection acquired
  - In hospital or in the community
  - If in hospital, have signs or symptoms of pandemic infection been present for less than 14 days
- Ability to receive allocations in additional domains for Moderate patients who transition to the Severe state

Changed definitions

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ICU

- During a pandemic an ICU is defined as an area that is capable of providing ICU-level care:
  - NIV with a sealed mask, invasive mechanical ventilation, or vasopressors via continuous infusion
  - Existing wards which provide sealed mask NIV which do not have expanded capabilities do not qualify

- May be a physical ICU or an area not usually designated as an ICU which has been re-purposed

Changed definitions

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ICU Admission

- For patients admitted to a location that is not usually designated as an ICU, admission is the time of first administration of qualifying organ support
  - Mechanical ventilation
  - Non-invasive ventilation (including HFNO)
  - Vasopressors or inotropes via continuous infusion

- If the patient is not in a physical ICU, do not commence the eligibility process until patient has a qualifying organ failure support

Changed definitions

REMAP-CAP

ICU Discharge

- For patients admitted to a location that is not usually designated as an ICU, discharge is the time at which a patient leaves an area that is able to provide ICU level care
- Time and date of first and last organ support also documented
  - Mechanical ventilation
  - Non-invasive ventilation
  - Continuous infusion of vasopressor or inotropes
  - HFNP with $FiO2 \geq 0.4$
  - ECMO

Primary end-point

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Days alive and not receiving organ support in ICU at Day 21

- Censored at hospital discharge (no need to follow-up after hospital discharge until usual D90)
- It is VITAL that D21 endpoint is entered as soon as possible after the end of study day 21

- D90 follow up still required
- D180 follow up not required for patients with suspected or proven pandemic infection

CRF changes

- Baseline
  - Whether the patient is a healthcare worker who has had direct contact with patients with suspected/confirmed COVID-19 within the last 21 days.
  - Whether the patient is in a physical ICU or area not usually designated as an ICU at eligibility
  - Additional physiological measurements

- Micro CRF
  - Results of microbiological testing for SARS-CoV-2 (during this acute respiratory illness, up until 72 hours after eligibility)

CRF changes

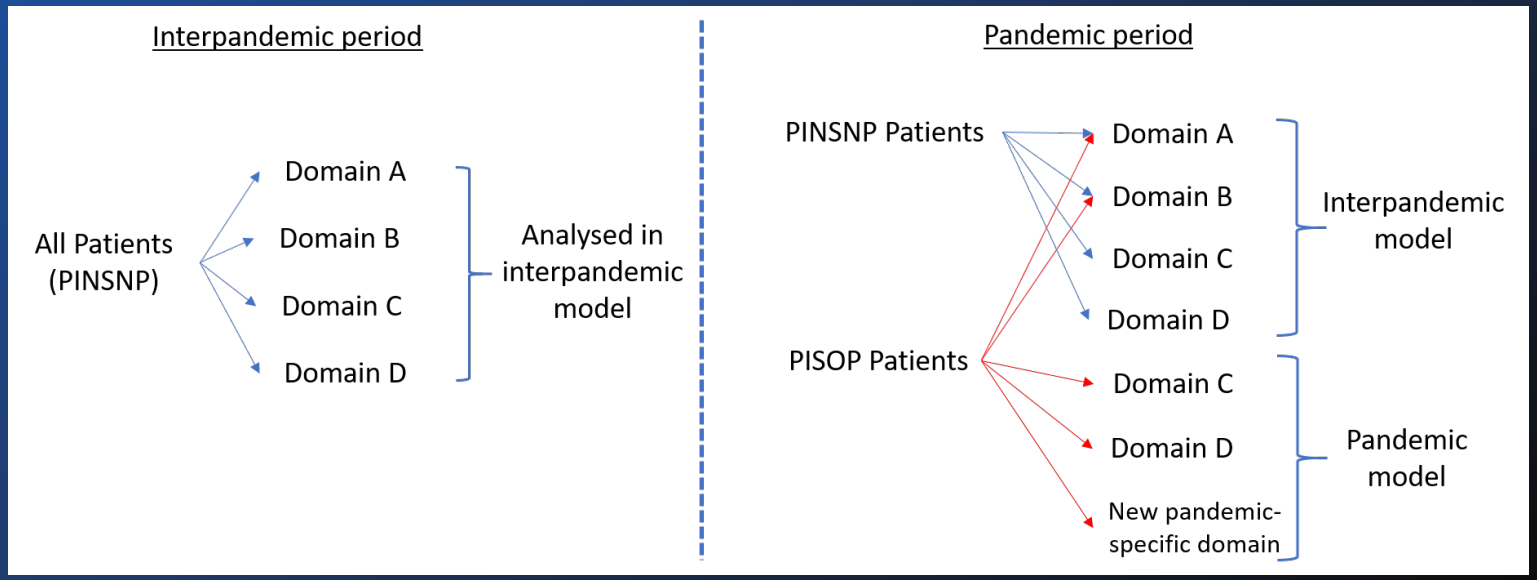
- Daily data
  - Location of patient on each study day (physical ICU, or area not usually designated as an ICU)
  - Corticosteroid administration for all patients with suspected or proven infection
- Medication administration
  - Updated to collect administration of antiviral and immunomodulatory agents that may be active against SARS-CoV-2

CRF changes

- Discharge
  - Date and time of first and last organ support in ICU
  - Co-enrolment in another study (study name, participant ID, and allocation if known)
- Day 21
  - Date and time of ICU discharge and any ICU readmissions prior to day 21
  - Hospital discharge date and status (prior to day 21)

Statistical Model

- Domains considered relevant to the pandemic are analyzed using a separate statistical model
- RAR occurs separately for patients with and without pandemic infection



PISOP patients = Pandemic Infection Suspected or Proven
PINSNP patients = Pandemic Infection Neither Suspected Nor Proven

Analysis and RAR during pandemic

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- Statistical model evaluates all pandemic domains
- Evaluates patients who are confirmed COVID-19 and not confirmed COVID-19 separately with borrowing between stratum, as appropriate
- Reduction in statistical trigger from 0.99 to 0.95 probability of superiority
- RAR driven off confirmed COVID-19 for future suspected and confirmed patients
- Assesses safety in suspected patients who turn out to be non-COVID patients

Current Domains in pandemic model

- Corticosteroid strategy
  - Sites can choose different set of interventions for pandemic and non-pandemic patients
- Macrolide duration
  - Important given French uncontrolled case-series
  - Only accessible if allocated to a beta-lactam + macrolide combination in antibiotic domain
- Can still get assignment for antibiotics and influenza antiviral, analyzed in non-pandemic statistical model

COVID-19 Specific Domains

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- COVID-19 Antiviral Domain
  - No antiviral for COVID-19 (no placebo)
  - Lopinavir/ritonavir (“Kaletra”)
  - Hydroxychloroquine
- COVID-19 Immune Modulation Domain
  - No immune modulation for COVID-19 (no placebo)
  - Interferon-β-1a
  - Anakinra (Interleukin-1 receptor antagonist)
  - Tocilizumab
  - Sarilumab

COVID-19 Specific Domains

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- Therapeutic anticoagulation
  - Local standard thromboprophylaxis
  - Therapeutic anticoagulation with LMWH or UFH
- Immunoglobulin
  - No immunoglobulin intended to neutralize COVID-19
  - Convalescent plasma for COVID-19
- Simvastatin
  - No simvastatin
  - Simvastatin

COVID-19 Collaboration

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Coordinating with other studies for COVID-19

- ASCOT trial in ANZ (antivirals)
- CATCO in Canada (antivirals)
  - Possible randomisation in REMAP-CAP antiviral domain if in control arm of ASCOT / CATCO
- LOVIT trial (vitamin C)
- ATTACC trial (therapeutic anticoagulation)

Consent processes during pandemic

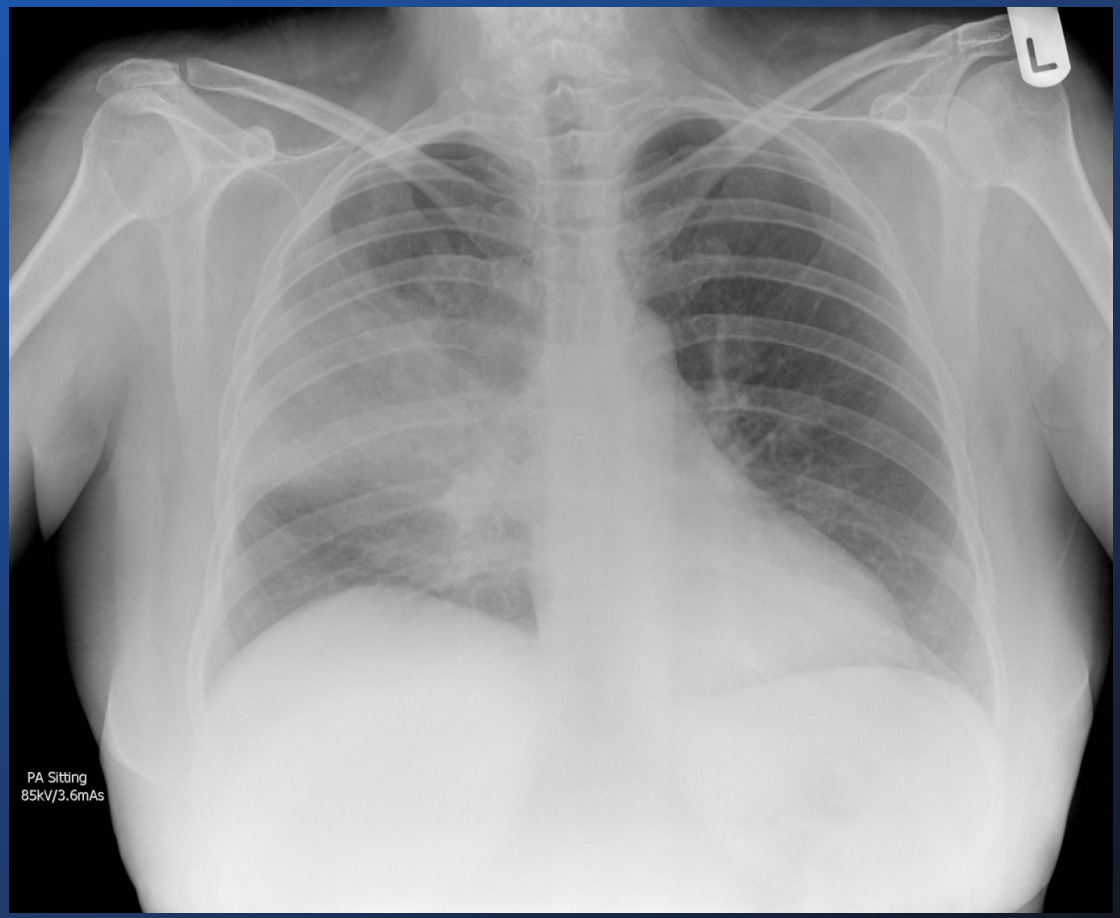
- Have requested permission to use phone / electronic confirmation of agreement to participate from person responsible

- Considering asking for permission to allow verbal consent from participant if competent to consent

Role of DSMB

- Granted more flexibility
- Can ask for additional analyses that might be relevant
- Permitted to contact public health authorities direct with any information that they believe is important to public health response to COVID-19

Questions?



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For **C**ommunity-**A**cquired **P**neumonia