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

# REMAP-CAP in Europe

## an adaptive platform trial for severe CAP and hospitalized patients with COVID-19

**Designed for the pandemic**

REMAP-CAP is an adaptive platform trial (APT) that is funded since 2014 to be pre-planned, pre-approved, and practiced to treat patients with severe Community Acquired Pneumonia (sCAP). It was designed specifically to adapt during a pandemic. As a result of the continued global spread of COVID-19, the REMAP-CAP Pandemic Strata was activated in March 2020. REMAP-CAP builds on the combined input of the world's leading ICU trial networks and experts in infectious disease, immunology, critical care, emergency medicine, Bayesian statistics, and clinical trial execution.

**Designed to generate answers quickly**

APTs are a smarter, more flexible way of doing randomized controlled trials (RCTs). In RCTs there is downtime between testing sequential interventions, leading to loss of efficiency, a lack of understanding of interactions between treatments or across subgroups of patients; and a lack of flexibility to adapt to changes during a pandemic.

In REMAP-CAP randomization can be done in the absence of dedicated research staff. The eligibility module of the eCRF guides the bedside clinician, allowing enrollment of a patient within minutes.
The trial is designed to provide answers to many questions rapidly.

- The platform is multifactorial: each patient can be randomized to multiple treatments. It can evaluate interactions, e.g. is anakinra potentiated by high dose heparin?
- It uses frequent interim analyses: a question is concluded as soon as there is sufficient information to support a conclusion. Analyses can occur up to weekly dependent on recruitment rates.
- It detects superiority, inferiority, or equivalence of interventions within the platform.

**Designed to be flexible**

Sites and regions can choose the domains and interventions from the 'menu' of current options, and don't need to adopt all domains or interventions. New potential treatments can enter the study as soon as they are available.

**Co-enrollment**

REMAP-CAP can co-enroll with most other studies. Because of the multifactorial design of REMAP-CAP, patients can still be included even if participation in another trial would result in ineligibility for a specific REMAP-CAP domain.

**Current domains and interventions**

Before the pandemic, interventions to treat patients with sCAP were grouped under four domains:

- Antibiotic Domain (five alternative antibiotic strategies)
- Macrolide Domain (extended versus short course)
- Corticosteroid Domain (three alternative hydrocortisone strategies)
- Influenza Antiviral Domain (Influenza patients only; three alternative oseltamivir strategies)

These are still active in patients in ICU, but new domains have been added to treat hospitalized COVID-19 patients. We distinguish severely ill patients (organ support) and moderately ill patients (no organ support). Not all interventions are available for moderately ill patients, reflecting the earlier stage of disease and the potential difference in risk/benefit ratio:

- COVID-19 Antiviral therapy (no antiviral, lopinavir/ritonavir)
- COVID-19 Immune modulation (no modulator, interferon-beta, anakinra, tocilizumab*, sarilumab*)

- COVID-19 **Immunoglobulin** (no immunoglobulin, convalescent plasma)
- COVID-19 **Anti-coagulation** (Standard practice thromboprophylaxis, therapeutic anticoagulation)
- COVID-19 **Statin therapy** (no simvastatin, simvastatin)
- COVID-19 **Antiplatelet** (no antiplatelet, Aspirin, P2Y12 inhibitor)
- **Vitamin C** (no intervention, high dose vitamin C iv) – also available for sCAP patients
- **Ventilation domain*** (clinician preferred, guideline recommended) – also available for sCAP patients

* = not available for moderately ill patients (no organ support).

Each qualifying patient is randomly assigned to **one intervention within each domain** that is active for the participating site. The set of interventions across the domains assigned to a specific patient makes up the **treatment regimen**. All hospitalized COVID-19 patients are eligible for the study (ward and ICU). *More COVID-19 domains are under development*.

**Who can join the #remapcapfamily?**

We welcome sites from all types of hospitals and backgrounds, but will evaluate the capability of each site to participate in the trial. Though REMAP-CAP is pragmatic (open-label, embedded in daily care), running the trial still requires a knowledgeable and dedicated team. CRFs, SAE/SUSAR forms etcetera have to be completed and, for some domains, study medication has to be managed. Sampling is included but not compulsory. Within participating hospitals, **collaboration** between all physicians taking care of patients with respiratory infections, and between ward and ICU research teams, is essential.

Central Ethical approval will be obtained for every site participating in the overarching REMAP-CAP platform in Europe. Each site can choose which domains and interventions they want to adopt; and if they want to include severely ill and/or moderately ill patients. For each domain, sites need to choose at least two interventions to allow randomization. Additionally, one of those must be the control arm (usually the "standard of care" arm). The platform is very flexible, and we provide **a tailor-made study** that matches the interest and capabilities of each participating site.

**Though the "machinery" of REMAP-CAP is complex, this is all handled "behind the scenes", and for participating sites the delivery is not more complex than a regular RCT investigating the same treatments. Online randomization is instant and eCRFs can be completed within office hours.**

**Financial aspects**

Each site participating in REMAP-CAP will receive a **start-up fee** to cover participation in training and set-up of activities, printing of materials like posters, folders and instructions, etcetera. A **per-patient fee** will be paid to participating sites which will depend on the number of domains a patient receives an allocation status for. Payments for sampling will be made separately, in addition to this fee.

Medications considered to be part of daily care, for which comparative effectiveness research is undertaken in REMAP-CAP, won't be reimbursed or provided to sites. This includes medications like heparin and antibiotics. Registered medications investigated as new treatments for COVID- 19 will be reimbursed and, where possible, supplied to the site.

**Please contact us for more information or with any questions at eu.remapcap@umcutrecht.nl or have a look at www.remapcap.org or find us on twitter (@remap_cap)**

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