Clinical research response during the COVID-19 pandemic: Lessons learned and how to prepare for the next pandemic

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History of the Clinical Trial Networks and Trials

History (1)

- **1991: PENTA**
  - Global Pediatic research network with its foundation in HIV and Ped ID.
  - The PENTA Foundation was set up in May 2004 as PENTA coordinating centre, to support activities aimed at carrying out research on HIV and Pediatric Infections.
  - The portfolio today includes a global range of research activities in Pediatric Infections from basic science to observational studies and innovative clinical trials

History (2)

- **2006: GRACE** (“Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe”)
  - FP6 project.
  - The first Primary Care CTN for Infectious Diseases.
  - Sustainability achieved through successive EU project funding (e.g., R-GNOSIS, PREPARE, RECOVER, VALUE-Dx).

History (3)

- **2016: the “Australian model”**
  - Vision: a single, permanent, European infrastructure for clinical research on Infectious Diseases.
  - ECRAID = COMBACTE (AMR) + PREPARE (Pandemic Preparedness and Response).
  - PREPARE: Perpetual observational studies (MERMAIDS) and Adaptive Platform Trials in Primary Care (ALIC^{4}E) and Hospital Care (REMAP-CAP).

History (4)

- **2020: the “EU model”**
  - COVID-19 pandemic very rapidly resulted in RTD funding of:
    - Existing clinical studies and CTN of PREPARE, i.e. MERMAIDS and REMAP-CAP (= RECOVER project, which was the Outbreak Response Mode 3 of PREPARE);
    - New projects and CTN, i.e. EU-RESPONSE and VACCELERATE.

Landscape of CTN in Europe anno 2024

- **Primary Care**
  - GRACE founded CTN, integrated in the Ecraid Foundation
- **Hospital Care**
  - PENTA / C4C Pediatric CTN
  - The COMBACTE/PREPARE CTN, integrated in the Ecraid Foundation
  - EU-RESPONSE CTN
  - VACCELERATE CTN
- **Long-term Care**
  - ESCMID-ESGIE founded LOTTA-Net CTN, integrated in the ECRAID Foundation

Lessons learned

Lessons learned

- The most successful international trials where those with established structures and procedures to facilitate a rapid, large scale clinical research response in the event of a pandemic (e.g., REMAP-CAP, RECOVERY).
- EU funding for COVID-19 clinical research response proved to be flexible and very rapidly available.
- No coordination between Member States and lack of consensus on clinical research priorities.
- Insufficient political support for EU funded clinical studies and no top-down prioritisation.
- Competition between European-wide and national studies, the latter often setting priorities supporting trials studying drugs that, for instance, received a lot of media attention.
- Some clinical investigators were more interested in setting-up their own trials and did not see the general interest to participate in EU-funded or international clinical studies.
- Resources and infrastructures were not optimally used.
- Clinical research not sufficiently embedded into practice.
- Protocols and (particularly) contract agreements took too long, particularly for new sites.
- Fast knowledge production, but insufficient time to analyse the data and publish papers.

As a result, most of the trials conducted in Europe did not reach their target number of inclusions and, therefore, failed to deliver solid conclusions, which led to many redundant studies and very little impact on patient management.

Thaminy et al, Report “Lessons learned from the EC-funded PREPARE and RECOVER consortia”

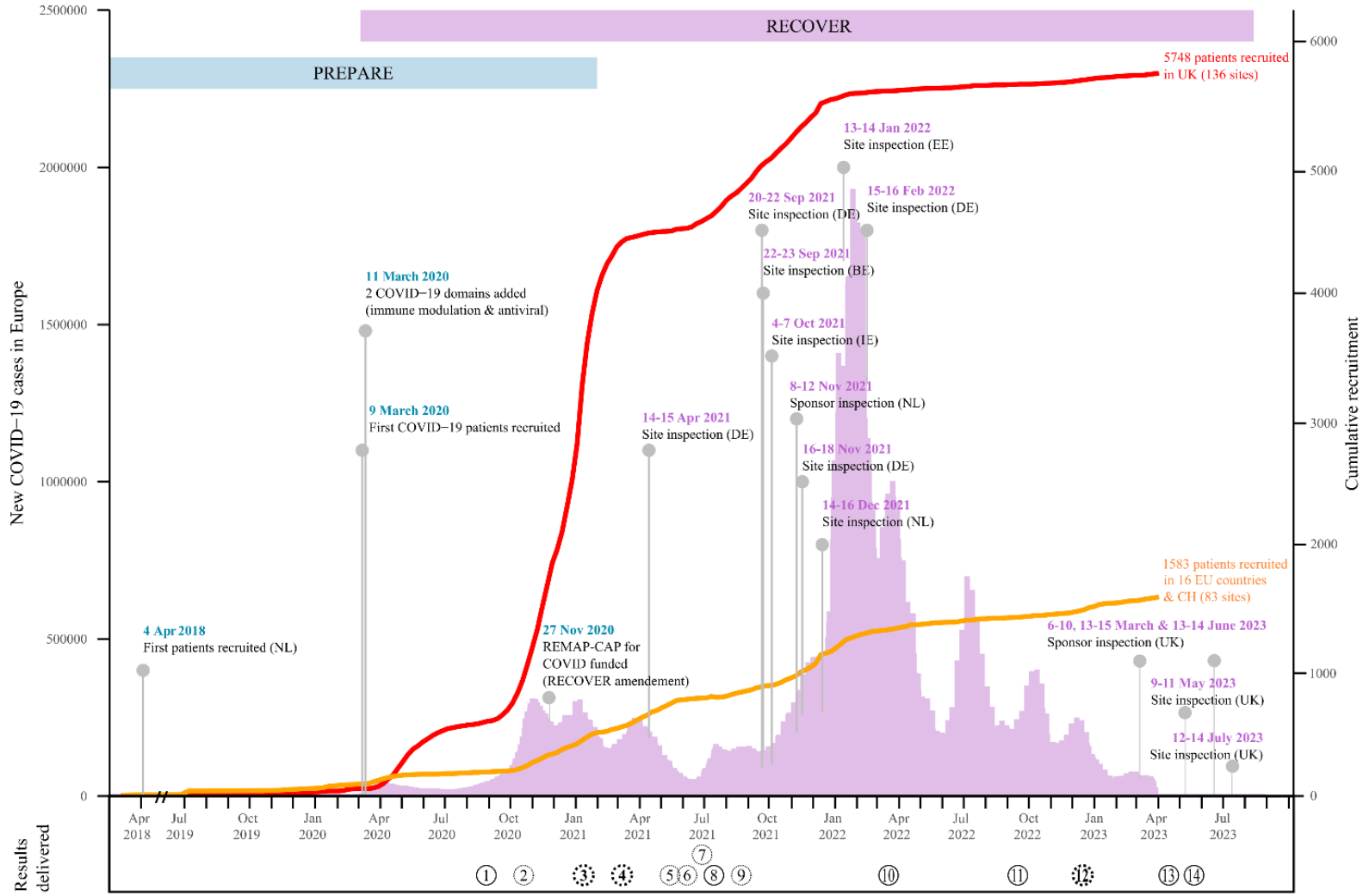
Lessons learned from two Adaptive Platform Trials

- **REMAP-CAP** was an established international multi-centre clinical trial with an explicit pandemic response function ready to fire up quickly when a pandemic strikes, and an established global governance structure.

- **RECOVERY** was a national health system with an embedded research infrastructure, an existing concept of ‘urgent public health research’, sustainable funding and centralized powers to prioritize research.

Goossens et al, LID, December 2021

REMAP-CAP trial



Health
Food Chain Safety
Environment

Lessons learned (1)

- Both the EU and UK had established structures and procedures to facilitate a rapid, large scale clinical research response in the event of a pandemic, resulting in two highly successful platform trials (REMAP-CAP and RECOVERY).
  - As a result, RECOVERY and REMAP-CAP were ready to include COVID-19 patients within 40 and 33 days, respectively, after the outbreak was declared a PHEIC, and enrolled their first COVID-19 patient within two and six days, respectively, after the protocol was approved.

- Although REMAP-CAP was designed years before the pandemic started, it faced major challenges in motivating study sites to participate in an international study in anticipation of a future pandemic.
  - As a result, at the time of pandemic onset REMAP-CAP was active in only 26 study sites in Europe.

- The UPH status and the presence of staff, infrastructure and additional financing for national health research priorities through NIHR in NHS hospitals was a major stimulus for sites to participate in clinical trials in the UK.
  - As a result, although RECOVERY was only initiated after the pandemic started, the protocol was deployed very fast.

Lessons learned (2)

- In EU countries REMAP-CAP had to compete with many national studies, some of them supported by national research funding.

- These national funding bodies often set priorities supporting trials studying drugs that received a lot of media attention.
  - As a result, we witnessed a massive concentration of clinical research efforts for these drugs, which impaired enrolment of patients in trials evaluating other potential treatments. Unfortunately, most of these clinical trials did not reach their target number of inclusions and, therefore, failed to deliver solid conclusions.

- In the UK, the GCP-requirement for labelling investigational medicines was waived for repurposed drugs tested in COVID-19. Such a waiver was not granted in the EU.
  - As a result, logistic complexity, costs, and timelines increased substantially in the EU because of additional contracts and shipment of drugs.

- There were large differences in approval times of Institutional Review Boards (IRB) between EU countries.
  - As a result, fast-track approval of study protocols in the initial phase of the pandemic ranged between 1 week (UK and some EU countries) to 12 months (on average 3 months in the EU).

How to prepare for the next pandemic

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1. Create structures and partnership that facilitate prioritization of clinical research.
2. Simplify clinical trial delivery.
3. Develop digital models and procedures for data collection and sharing.
4. Develop a mechanism to rapidly leverage pandemic funding and to liaise EU funding with national funding.
5. Invest in clinical trial networks, platform trials and master protocols.
6. Embed EU pandemic clinical research response in global response.

Goossens et al, LID, December 2021

1. Create structures and partnership that facilitate prioritization of clinical research

- An **authority** should be created to oversee pandemic preparation, clinical research response and to prioritise clinical studies (*HERA*).
- A **partnership** should be developed between the EU Member States and the European Commission to agree on aligned goals of clinical research in response to pandemics (*Launched in 2025*).

Both require a comprehensive and lean strategy, dedicated leadership, and political commitment.

4. Develop a mechanism to rapidly leverage pandemic funding and to liaise EU funding with national funding

- In response to COVID-19 substantial research funding was quickly made available through competitive calls in the ongoing EU research framework programme Horizon2020 to support clinical research.

- However, these EU research programmes were disconnected from clinical research funding of Member States.

- Therefore, an **Outbreak Funding Mechanism (OFM)** should be in place to rapidly leverage EU funding and to liaise this funding with national public funding programmes.

5. Invest in clinical trial networks, platform trials and master protocols

- During this pandemic the best evidence was provided by **platform trials**, such as REMAP-CAP and RECOVERY. Success was explained by existing structures, that could coalesce around a common goal, and an accepted mechanism for decision making.

- These platform trials have been especially useful in enabling simultaneous, sequential evaluation of multiple treatment regimes, **resulting in highly efficient trials** with fewer patients and shorter time to interpretable results.

- It is obvious that such trials should be **prepared during inter-pandemic periods**, because success depends on existing infrastructures and governance.

A Europe that cares, prepares and protects

Health Priorities for the Belgian Council Presidency

A Europe that Prepares:

Policy area on strengthening the European ecosystem for public clinical trial platforms

"It will reflect on whether in the event of a new health emergency, the EU will be able to rely on: (i) the right tools and procedures to deal with the crisis; (ii) **the financial means** to effectively secure adequate resources; (iii) the structures and institutions to develop coordinated, multi-level response strategies; (iv) the means and advice to speak with authority and legitimacy to the general public; and (v) sufficient intelligence to collect data and relevant information, and translate it into actionable insights.
In this context, the Presidency will also look to expand the EU's capacity to conduct large scale clinical trials.
The Presidency will work on the development of concrete actions **for strengthening the European ecosystem for public clinical trial platforms**".

A Europe that cares, prepares and protects, December 2023, page 3

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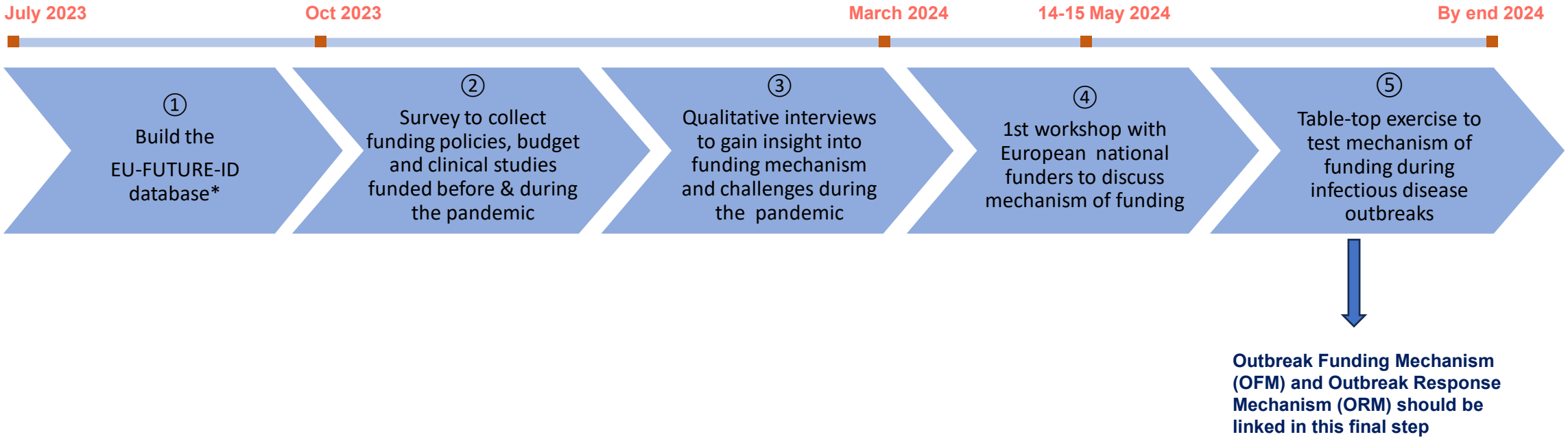
Programme

- **14 May:**
  - **Morning**: closed pre-workshop meeting to harmonise/align the CTNs and projects, including Outbreak Response Mechanism (CoMeCT, C4C, ECRAID-Base, ECRAID-Prime, EU-RESPONSE, PENTA, VACCELERATE)
  - **Afternoon**: meeting with national funders, CTNs, EC services
    - Minister Frank Vandenbroucke: welcoming;
    - Christian Drosten: potential threats for the next pandemic;
    - Herman Goossens: Lessons learned of clinical research response during COVID-19 and how to prepare for the next pandemic;
    - Ulla Narhi: new Sub-Group of the HERA Board on preparedness and response;
    - Presentations of warm-base laboratory and CTNs.
- **15 May / Morning:**
  - Safia Thaminy: presentation of preliminary results of the survey and interviews;
  - Case studies: Belgium, Germany, Norway, UK;
  - Discussion on coordination of funding of clinical research during future ID outbreaks.

Preparations for the Workshop started in July 2023



*EU-FUTURE-ID database : EUropean FUnders of clinical studies, Trials and Urgent REsearch for Infectious Disease outbreaks