Clinical Research Response: Preparing Europe for the next infectious diseases outbreak

Herman Goossens, MD, PhD
University of Antwerp, Belgium
University Medical Center of Utrecht, the Netherlands
“There are only two infectious disease situations that can be considered inevitable, serious pandemic threats: influenza and antimicrobial resistance”

Osterholm and Olshaker, 
Diedliest enemy: our war against killer germs, March 2017.
Clinical research responses to ID outbreaks are usually fragmented and too late.
PREPARE:
fast-forward clinical research during epidemics
to improve clinical management
Agenda

• PREPARE
  – Clinical studies
  – Pandemic preparedness and response to outbreaks
• ECRAID
PREPARE: Platform for European Preparedness Against (Re-)emerging Epidemics

2014-2021
Partners:
Academia, clinical trial networks, industry societies

Coordinator:
Herman Goossens
(University of Antwerp)

Deputy Coordinator:
Menno de Jong
(Academic Medical Center Amsterdam)

Our mission
To establish PREPARE as the European clinical research framework

• for harmonised large-scale clinical research studies on infectious diseases

• prepared to rapidly respond to any severe infectious disease outbreak

• providing real-time evidence for clinical management of patients and for informing public health responses

Funded by the European Union
WP1: EARL
Ethical, Administrative, Regulatory and Logistical aspects of PREPARE

Overarching aim

To identify and provide solutions to key structural (ethical, administrative, regulatory and logistical) bottlenecks as well as behavioural and cultural barriers to the rapid implementation of large multi-site clinical studies in Europe in response to severe ID outbreaks;
Overall architecture WP2-9

PATHOS
- European platform for patient oriented PATHOgenesis Studies

PRACTICE
- Platform for Harmonised and Rapid response Clinical Trials in Infectious diseases in Children and adults in Europe

PREDICT
- European Platform for REsearch and support on Diagnostics for Infectious disease Clinical Trials

CRISP: Clinical Research Information Sharing Platform

CREATE: Clinical Research Education And Training in Europe

Funded by the European Union
Clinical studies in PREPARE

Three observational studies: Multi-centre EuRopean study of MAjor Infectious Disease Syndromes (MERMAIDS) in primary care and hospitalized adult and pediatric patients, comprising:
- Sepsis-like syndrome (SLS) in infants and Acute respiratory infection (ARI) in children (PED-MERMAIDS)
- Acute Respiratory Infections in Adults (ARI)
- Arboviral compatible febrile illness

Two Adaptive platform design studies:
- European multi-centre double-blinded randomised placebo-controlled Interventional Trial on Influenza-Like-Illness (ILI) in Primary Care (ALIC4E)
- Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)
Primary Care Network:
Build on GRACE FP6 project

- 21 Networks
- 15 Countries
- 13 Languages
- 207 Primary care practices
Hospital Care Network:
Build on COMBACTE - ND4BB project and other networks

> 800 hospitals
> 600 diagnostic labs
> 40 European countries

Funded by the European Union
### COMBACTE / PREPARE Clinical Studies (September 2018)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Sponsor</th>
<th>Patients</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE-ICU</td>
<td>UM CU</td>
<td>ICU, VAP</td>
<td>Epi</td>
</tr>
<tr>
<td>ASPIRE-SSI</td>
<td>UM CU</td>
<td>Various</td>
<td>Epi</td>
</tr>
<tr>
<td>WP66 tbd</td>
<td>AZ/Mi</td>
<td>ICU</td>
<td>RCT</td>
</tr>
<tr>
<td>WP83</td>
<td>MedComp ICU</td>
<td>ICU</td>
<td>RCT</td>
</tr>
<tr>
<td>SATELITE</td>
<td>AZ/Mi</td>
<td>ICU</td>
<td>RCT</td>
</tr>
<tr>
<td>ANTICIPATE</td>
<td>DaV</td>
<td>Various</td>
<td>Epi</td>
</tr>
<tr>
<td>EURECA</td>
<td>SAS</td>
<td>Various</td>
<td>Epi</td>
</tr>
<tr>
<td>REVISIT</td>
<td>Pfizer</td>
<td>ICU+</td>
<td>RCT</td>
</tr>
<tr>
<td>REJUVENATE</td>
<td>Pfizer</td>
<td>ICU+</td>
<td>RCT</td>
</tr>
<tr>
<td>EVADE</td>
<td>AZ/Mi</td>
<td>ICU, VAP</td>
<td>RCT</td>
</tr>
<tr>
<td>WP46</td>
<td>AZ/Mi</td>
<td>ICU, VAP</td>
<td>RCT</td>
</tr>
<tr>
<td>WP65</td>
<td>AlCults</td>
<td>cUTI</td>
<td>RCT</td>
</tr>
<tr>
<td>WP66</td>
<td>AlCults</td>
<td>cUTI</td>
<td>RCT</td>
</tr>
<tr>
<td>RESCUING</td>
<td>ICS-HUB</td>
<td>cUTI</td>
<td>Epi</td>
</tr>
<tr>
<td>WP1</td>
<td>UniLeeds</td>
<td></td>
<td>Epi</td>
</tr>
<tr>
<td>WP2</td>
<td>UniLeeds</td>
<td></td>
<td>Epi</td>
</tr>
<tr>
<td>PREPARE</td>
<td>U of Oxford</td>
<td>ARBO</td>
<td>Epi</td>
</tr>
<tr>
<td>MERMAIDS</td>
<td>U of Oxford</td>
<td>ARI</td>
<td>Epi</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>UM CU</td>
<td>ICU</td>
<td>adaptRCT</td>
</tr>
<tr>
<td>CREDIBLE-CR</td>
<td>Shionogi</td>
<td></td>
<td>RCT</td>
</tr>
<tr>
<td>MK-7653A</td>
<td>RESTORE-IMI2</td>
<td>Merck</td>
<td>ICU</td>
</tr>
<tr>
<td>Collatin</td>
<td>NIH</td>
<td>ICU</td>
<td>RCT</td>
</tr>
<tr>
<td>BAC0006</td>
<td>BAC0006</td>
<td>Janssen</td>
<td>Epi</td>
</tr>
<tr>
<td>HAP/VAP</td>
<td>CTTI</td>
<td>HAP/VAP</td>
<td>Epi</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Sponsor</th>
<th>Patients</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shionogi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPARE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERMAIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td></td>
<td></td>
<td>adaptRCT</td>
</tr>
<tr>
<td>CREDIBLE-CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-7653A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAC0006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAP/VAP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total Patients Enrolled:** 11,858
# PREPARE Clinical studies  
(Number of patients 18/09/2018)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Sponsor</th>
<th>Patients</th>
<th>Type</th>
<th>Target</th>
<th>Number of patients included</th>
</tr>
</thead>
<tbody>
<tr>
<td>PED-MERMAIDS</td>
<td>U0x</td>
<td>SLS Infants</td>
<td>Epi</td>
<td>1,000</td>
<td>549</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARI children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERMAIDS</td>
<td>U0x</td>
<td>ARI adults</td>
<td>Epi</td>
<td>2,000</td>
<td>1,131</td>
</tr>
<tr>
<td>MERMAIDS</td>
<td>U0x</td>
<td>ARBO</td>
<td>Epi</td>
<td>1,500</td>
<td>581</td>
</tr>
<tr>
<td>ALIC4E</td>
<td>U0x</td>
<td>Primary care</td>
<td>APT</td>
<td>4,500</td>
<td>3,268 (Closed April 2018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>UMC</td>
<td>ICU</td>
<td>APT</td>
<td>4,000</td>
<td>22 randomized; 9 Informed consent</td>
</tr>
</tbody>
</table>
Platform Trials

• Adaptive trials
  – Focus on disease, not a particular Rx
  – Multiple interventions (arms)
  – ‘Perpetual’ enrollment
  – Often based on Bayes’ theorem
  – Tailor choices over time
  – Add and substitute arms in the event of a pandemic

• Focus on pre-approval space
  – Emphasis on efficiency with (very) small sample sizes
  – Different therapies “graduate” to next phase while trial continues

Berry et al JAMA 2015

Funded by the European Union
Agenda

• PREPARE
  – Clinical studies
  – Pandemic preparedness and response to outbreaks
• ECRAID
The outbreak research modes of PREPARE

0. Default Mode

1. Clinical Research Preparation Mode
   - Assessing operational readiness in the networks, identifying important knowledge and resource gaps and preparing clinical protocols.

2. Clinical Research Mobilisation Mode
   - Planning and implementing preparatory work necessary to achieve operational readiness in the networks to initiate a clinical research response to specific ID outbreak if and when needed.

3. Clinical Research Response Mode
   - Implementing clinical research projects in the networks tailored to the specific ID outbreak, and addressing the most important and urgent clinical research questions.

Executing the planned ‘inter-epidemic’ preparedness research activities according to the EC grant agreement.

Funded by the European Union
Overview of PREPARE’s process from receipt of trigger to delivery of a clinical research response to a (re-)emerging ID outbreak
**Overview of PREPARE response to outbreaks 2014-2018**

<table>
<thead>
<tr>
<th>Date</th>
<th>Outbreak</th>
<th>Trigger</th>
<th>Threat to Europe</th>
<th>Mode</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/04/2014</td>
<td>MERS-CoV</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Develop clinical protocols (collaboration with ISARIC).</td>
</tr>
<tr>
<td>08/08/2014</td>
<td>Ebola Virus</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Surveyed PREPARE affiliated European hospitals to assess Ebola preparedness and capacity; Develop clinical protocols (collaboration with ISARIC).</td>
</tr>
<tr>
<td>09/09/2014</td>
<td>Enterovirus 68</td>
<td>PREPARE partner</td>
<td>Low</td>
<td>Mode 0</td>
<td>No action. (WP3 MERMAIDS-PEDS study under development and would be ready to respond (in infants) once clinical sites activated).</td>
</tr>
<tr>
<td>04/12/2015</td>
<td>Zika</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Adapted WP3 CRFs and developed maternal and neonatal CRFs (in collaboration with ISARIC)</td>
</tr>
<tr>
<td>15/09/2017</td>
<td>CHIV</td>
<td>PREPARE partner</td>
<td>Low</td>
<td>Mode 0</td>
<td>No action. (Current WP3 MERMAIDS-ARBO study ready to respond in active sites).</td>
</tr>
<tr>
<td>11/01/2018</td>
<td>Influenza A H3N2</td>
<td>PREPARE Core Group</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Assessment of operational readiness in PREPARE clinical WPs; communication brief outlining PREPARE position to address anxiety generated from media reporting.</td>
</tr>
</tbody>
</table>

* Threat determined by PREPARE OMC in response assessment
Real chikungunya virus (CHIV) scenario: timeframes for deciding on an Outbreak Research Mode.

15/09/2017 Trigger received from EVD Lab-net coordinator regarding a rising number of cases of autochthonous chikungunya virus (CHIV) in 3 European regions: Var, France; Lazio, Italy; Anzio, Italy (source: ECDC).

15/09/2017: Trigger validated, OMC met to initiate response assessment
ECDC risk assessment reviewed. No information on sequence comparison of virus was available. OMC agreed actions to progress response assessment.

9/10/2017: Response assessment complete: Mode 0 maintained.
Rationale for Mode 0: Emerging data confirmed that the CHIV outbreaks were of different strains. Further, the outbreaks were being brought under control with cases declining and seasonal activity of mosquitoes (CHIKV vector) was in decline. It was considered unlikely that these outbreaks might signal potential for re-emergence the following year: a viremic traveller in a region with competent mosquitoes typically introduces CHIV into that region and there is no primary animal reservoir in Europe.

11/10/2017: Outcome communicated with relevant stakeholders.
Initiatives of ORM Working Group

Rolling programme of tabletop simulation exercises to **develop**, **plan** and **rehearse** clinical research preparedness.

*May 2017, Lisbon*: multi-stakeholder consultation to refine and shape outbreak response plan

*Oct 2017, Brussels*: table-top simulation exercise
  - Chikungunya: observational study (with sampling)
  - Acute ARI: Primary care intervention study
  - Acute ARI: ICU intervention study

*May 2018, Berlin*: table simulation exercise:
  - Avian influenza (H5N9): new antiviral for evaluation in APTs

*March 2019: Dakar* joint meeting with ALERRT
Agenda

• PREPARE
  – Clinical studies
  – Pandemic preparedness and response to outbreaks

• ECRAID
The EU can take the lead on clinical trials in ID: Combining Clinical Research on AMR and EID

Antimicrobial resistance

- Fast completion of clinical studies;
- Largest need in bacterial infections (antibiotic resistance)

Emerging Infectious Diseases

- Rapid initiation of clinical studies;
- Mostly virus infections

Need for operational high quality large-scale clinical research infrastructure with European (and global) coverage:

ECRAID: European Clinical Research Alliance on Infectious Diseases

COMBACTE

Platform for European Preparedness Against Risks of Emergent Infectious Diseases (PREPARE)
<table>
<thead>
<tr>
<th><strong>Deadline:</strong></th>
<th>18 April 2018 (single stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available budget:</strong></td>
<td>€ 2 -3 million (100% funding)</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Type of Action:</strong></td>
<td>Coordination and Support Action (CSA)</td>
</tr>
</tbody>
</table>
ECRAID-Plan

Creation of a European wide sustainable clinical research network for infectious diseases
ECRAID-Plan: joint effort of EU funded research networks

(co-) coordinating institutions or legal entities of 12 other networks with highly complementary activities and roles to PREPARE and COMBACTE, are directly involved
ECRAID-Plan: Objectives

I. To develop the detailed business plan for ECRAID, based on COMBACTE and PREPARE.
   The ECRAID Business Plan will serve three main purposes:
   • Function as the central guiding document presenting the agreed strategy for the development of ECRAID;
   • Serve as a means to build awareness of and support for ECRAID amongst stakeholders;
   • Attract sufficient start-up funding/income to commence operations in ECRAID.

II. To align the ECRAID business plan to the activities, roles, mandates and ambitions of relevant other initiatives and organisations active in clinical research or complementary research on ID.

III. To build awareness of and create support for the ECRAID initiative amongst the broader group of stakeholders.
ECRAID-Plan: Ambition

The mission of ECRAID is to reduce the impact of infectious diseases (ID) on individual and population health by efficiently generating rigorous evidence to improve the diagnosis, prevention and treatment, and to better respond to ID threats.

Our vision is to establish a coordinated, permanent, European clinical research infrastructure for clinical research on ID
ECRAID-Plan: Components

- Ambition
- Services
- Operations
- Governance
- Financials

Internal Analyses
External Analyses

Reconciliation of EID and AMR
Interoperability of networks
Datasharing

Strategic themes
Innovation of clinical research

- **Perpetual observational studies**: In open-ended perpetual observational studies, a selected number of sites continuously “enrol” patients and collect outcomes for specific IDs or ID syndromes, in a selected number of sites and countries, while using local standard care procedures (e.g. diagnostics, treatment protocols).

- **Warm-base trials**: master study protocol for diagnosing and treating patients in a specific perpetual observational study would allow simultaneous evaluation of multiple new drugs for the ID. By focusing the warm base studies on prevalent infections or ID syndromes, executed in appropriately trained and experienced clinical sites, recruitment can be expected to follow a predictable pace. New products that move into clinical development, can then be added as a new study arm in an ongoing platform trial.

- **Adaptive Platform Trials**: allows the study of multiple therapies in an ongoing way, with therapies entering and leaving the platform on the basis of a decision algorithm using pre-specified thresholds for futility or effectiveness, with adaptive components such as Response Adaptive Randomization (RAR) to increase efficiency and increase the chances of study participants receiving the most promising intervention in the trial.
ECRAID: Our plan and timelines

High level Design

High Level design completed

Detailed Design of Business plan and operating model

Construct & Implement

2016
2017
2018
2019
2020
2021
2022

end of current funding PREPARE

end of current funding COMBACTE-Net

FUNDING THROUGH IMI2 FOR Dx PART (VALUE-Dx – 01.2.2019??)

FUNDING FOR ID STUDIES TO BE ACQUIRED FROM PUBLIC AND PRIVATE SECTOR

FUNDING THROUGH H2020 (ECRAID-Plan – 01.01.2019)

ECRAID: Our plan and timelines
What ECRAID could offer

• Clinical Trial Network for infectious diseases in hospital care and primary care, adults and children
• European coverage and globally embedded
• Faster and easier clinical research
• As a single-point of access into a high quality, business oriented clinical research network
• Rapid access to well trained clinicians and laboratory (specialized and routine) sites
• An active network, continuously including patients in platform trials, allowing rapid clinical research response in the event of an EID or pandemic threat
• Focus on services that alleviate the Ethical, Administrative, Regulatory and Logistical (EARL) barriers to clinical research and reduce timelines (lower costs, faster processes)
Hugely ambitious, but...

This is a **once-in-a-lifetime opportunity** to gear up the public and private resources already invested in COMBACTE, and PREPARE (and other projects that will be discussed today!).

If we don’t **collaborate**, we will fail and stand **accused of having turned our back** on the prospect of tackling pandemic infectious diseases, and effective investigations and treatments of infections for our citizens.
Thank you