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

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“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.

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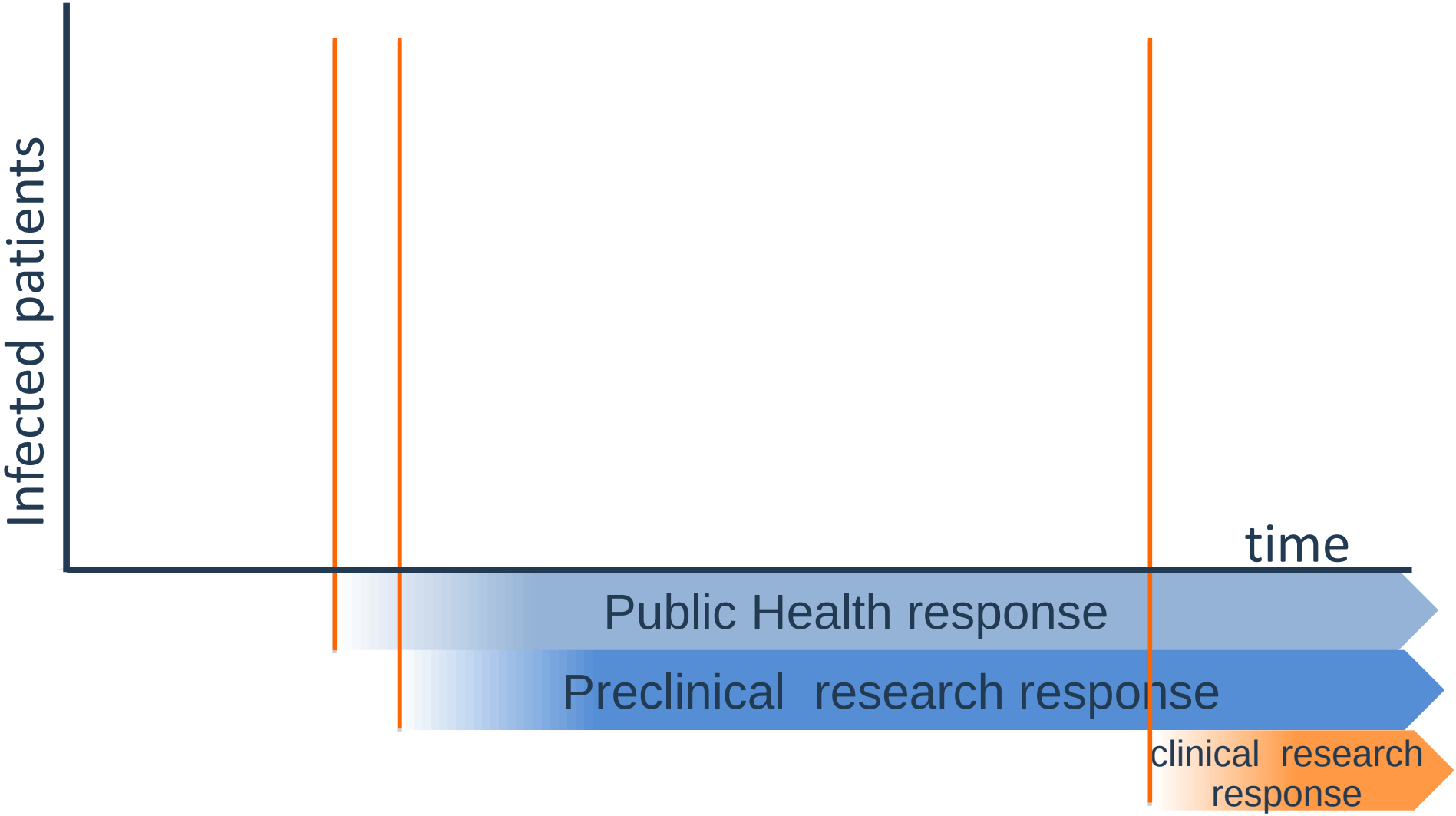
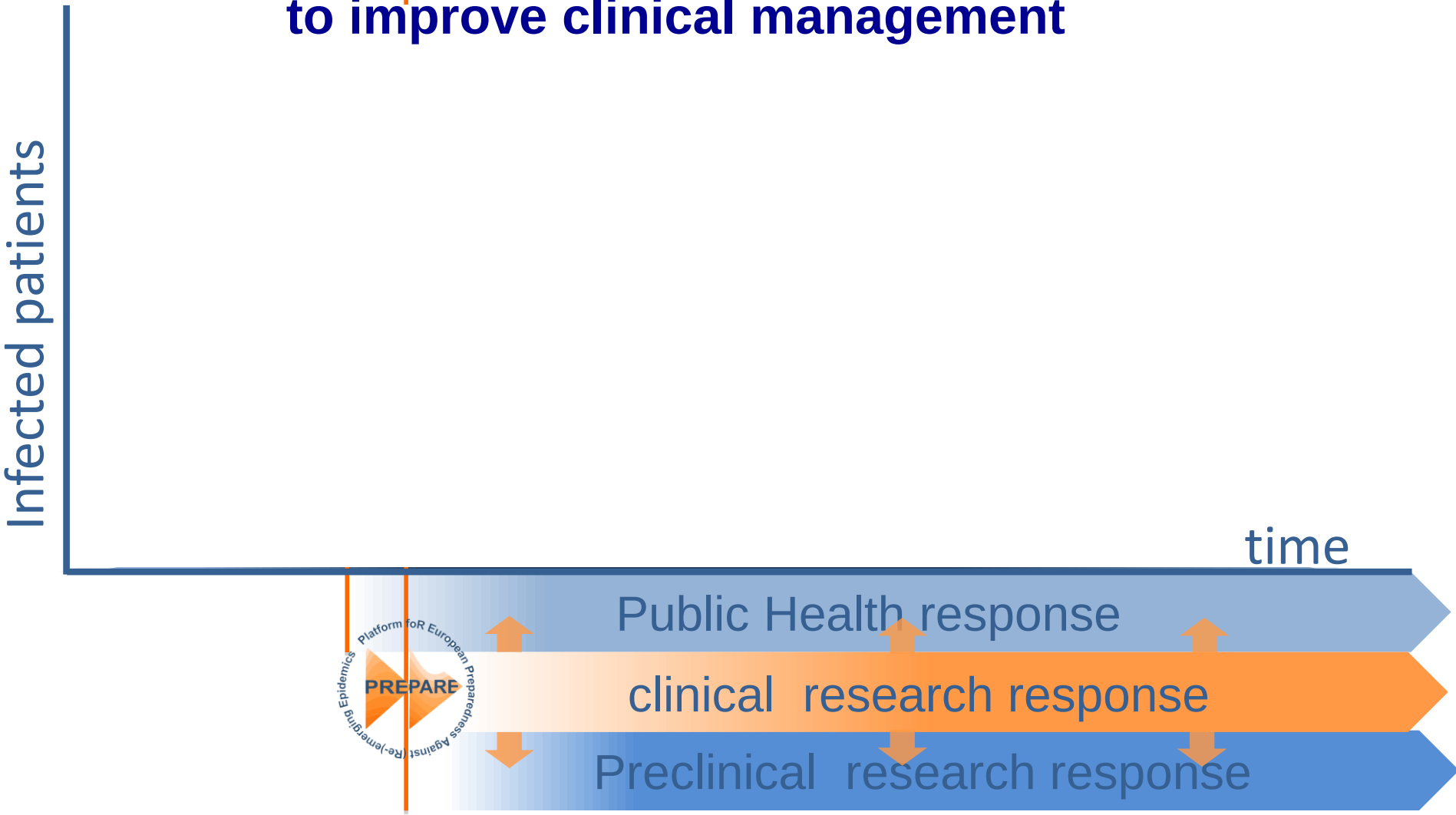
Clinical research responses to ID outbreaks are usually fragmented and too late



PREPARE:

fast-forward clinical research during epidemics to improve clinical management



Agenda

- PREPARE
  - Clinical studies
  - Pandemic preparedness and response to outbreaks
- ECRAID

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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

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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;



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Overall architecture WP2-9

CRISP: Clinical Research Information Sharing Platform

CREATE: Clinical Research Education And Training in Europe

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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

MERMAIDS
Multi-centre EuRopean study of MAjor Infectious Disease Syndromes

Two Adaptive platform design studies:

- European multi-centre double-blinded randomised placebo-controlled Interventional Trial on Influenza-Like-Illness (ILI) in Primary Care (**ALIC4E**)

ALIC4E

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

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

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Primary Care Network:
Build on GRACE FP6 project

21 Networks
15 Countries
13 Languages
207 Primary care practices

TRACE
Translational Research on Antimicrobial resistance and Community-acquired infections in Europe

GRACE
Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe

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Hospital Care Network:

Build on COMBACTE - ND4BB project and other networks

> 800 hospitals

> 600 diagnostic labs

> 40 European countries

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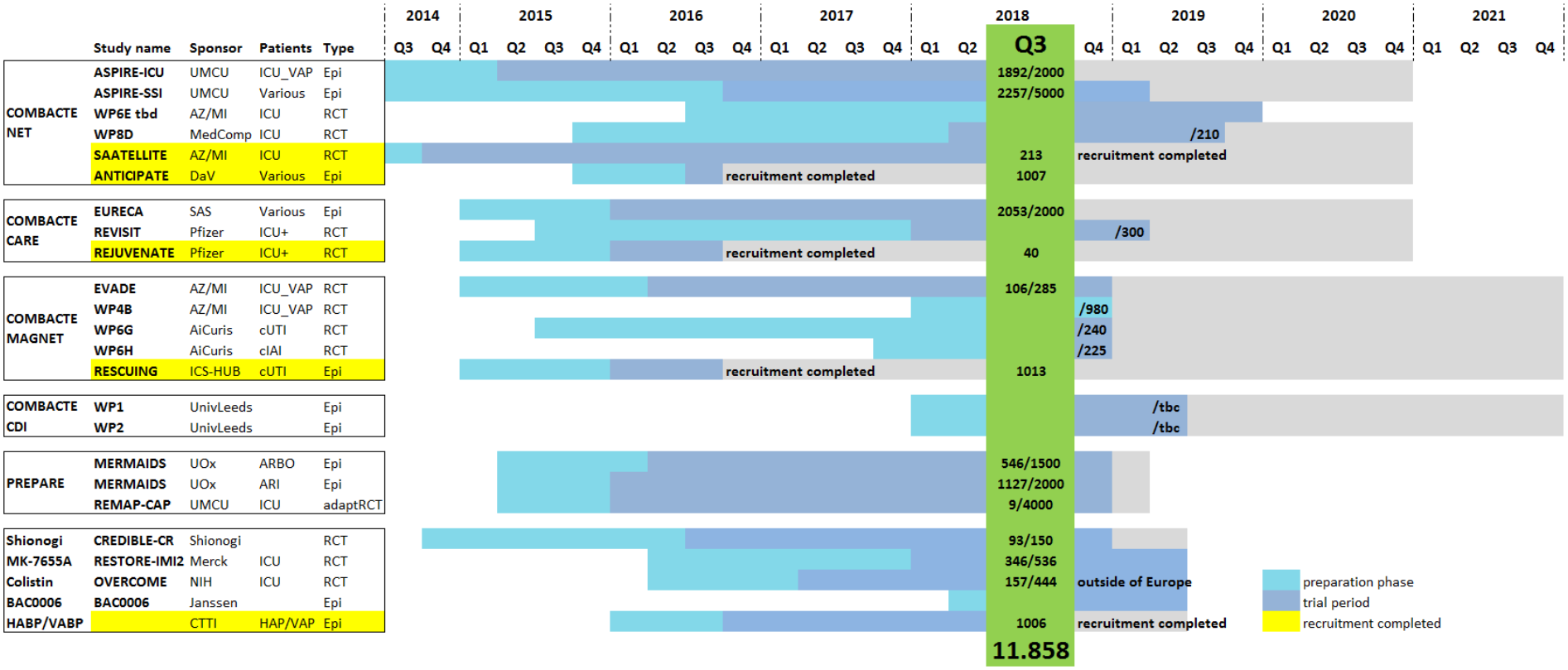
COMBACTE / PREPARE Clinical studies (September 2018)



11,858 patients enrolled

PREPARE Clinical studies
(Number of patients 18/09/2018)

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

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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 Respiratory Tract Infection
- **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

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The outbreak research modes of PREPARE

Executing the planned 'inter-epidemic' preparedness research activities according to the EC grant agreement

Default Mode

0

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.

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.

1 **Clinical Research Preparation Mode**

Assessing operational readiness in the networks, identifying important knowledge and resource gaps and preparing clinical protocols.

generic

tailored to specific (potential) infectious disease outbreak

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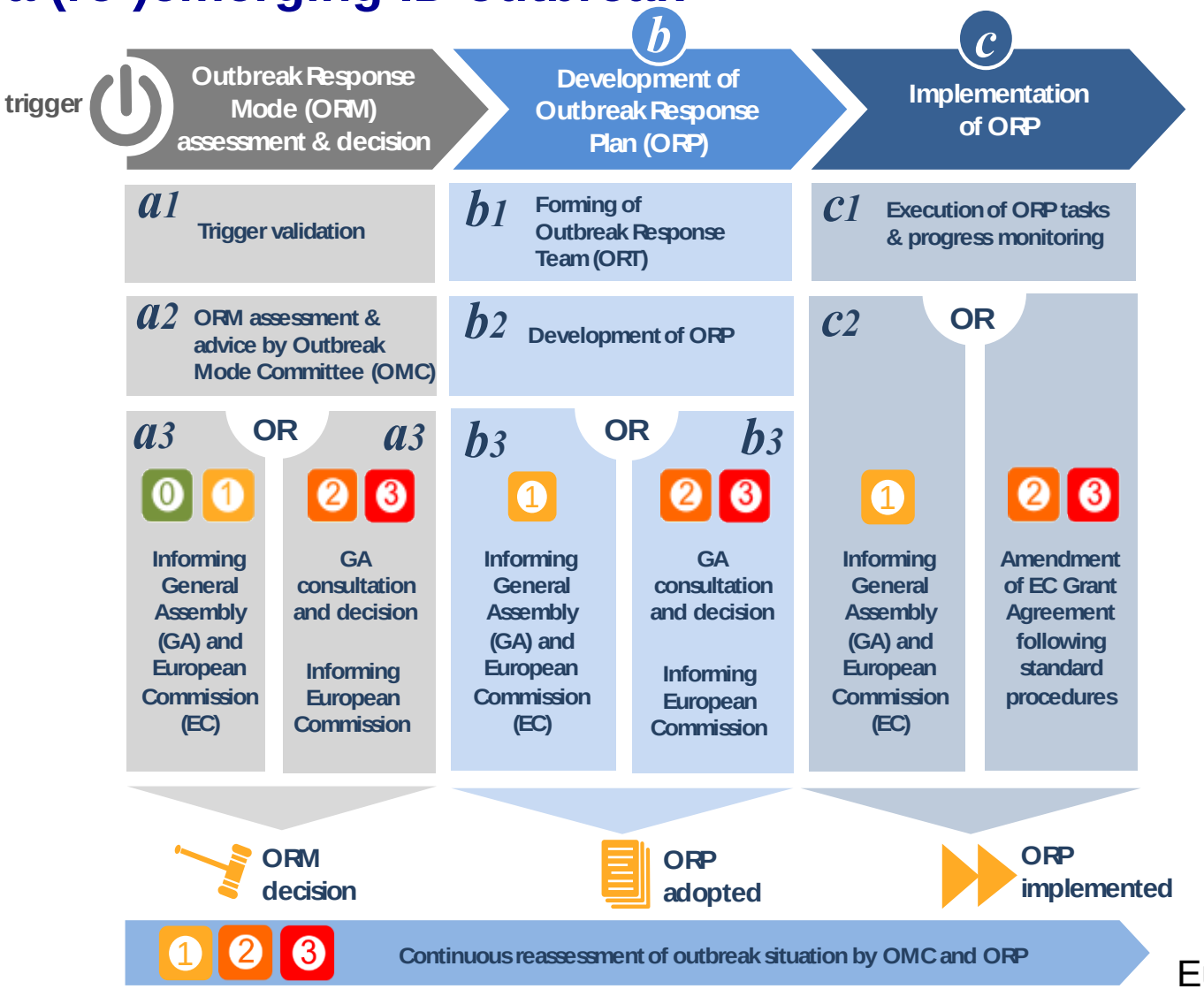
Overview of PREPARE's process from receipt of trigger to delivery of a clinical research response to a (re-)emerging ID outbreak



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Overview of PREPARE response to outbreaks 2014-2018

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

* Threat determined by PREPARE OMC in response assessment

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Real chikungunya virus (CHIV) scenario: timeframes for deciding on an Outbreak Research Mode.

0hrs

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).

0hrs

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.

<4week

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 mosquitos (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 mosquitos 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

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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 resisitance)

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

ECRAID: European Clinical Research Alliance on Infectious Diseases

Emerging Infectious Diseases

- Rapid initiation of clinical studies;
- Mostly virus infections

ND4BB COMBACTE

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

H2020 call

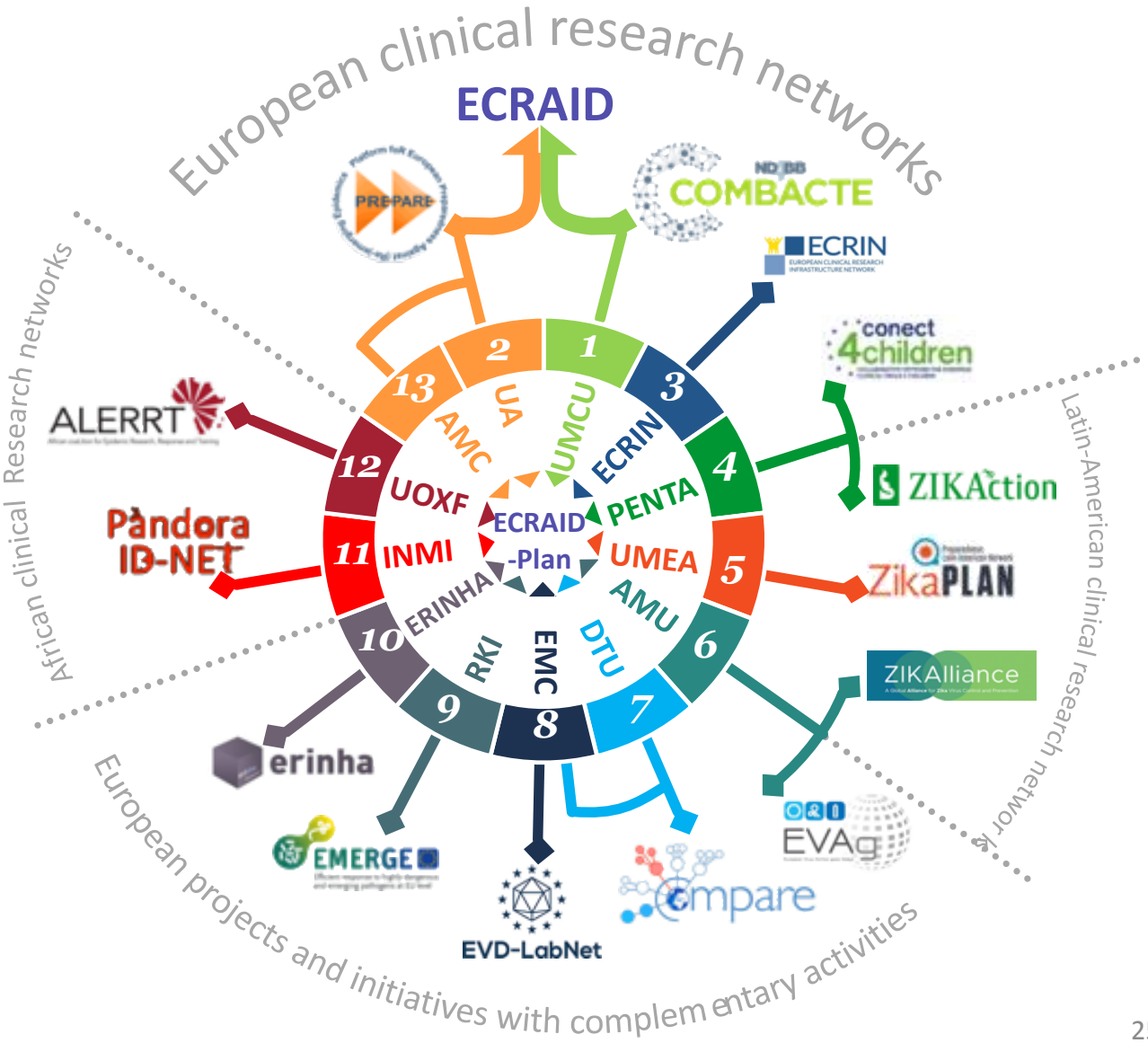
Creation of a European wide sustainable clinical research network for infectious diseases

Deadline:	**18 April 2018 (single stage)**
Available budget:	**€ 2 -3 million (100% funding)**
Duration:	**2 years**
Type of Action:	**Coordination and Support Action (CSA)**


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 directely 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.

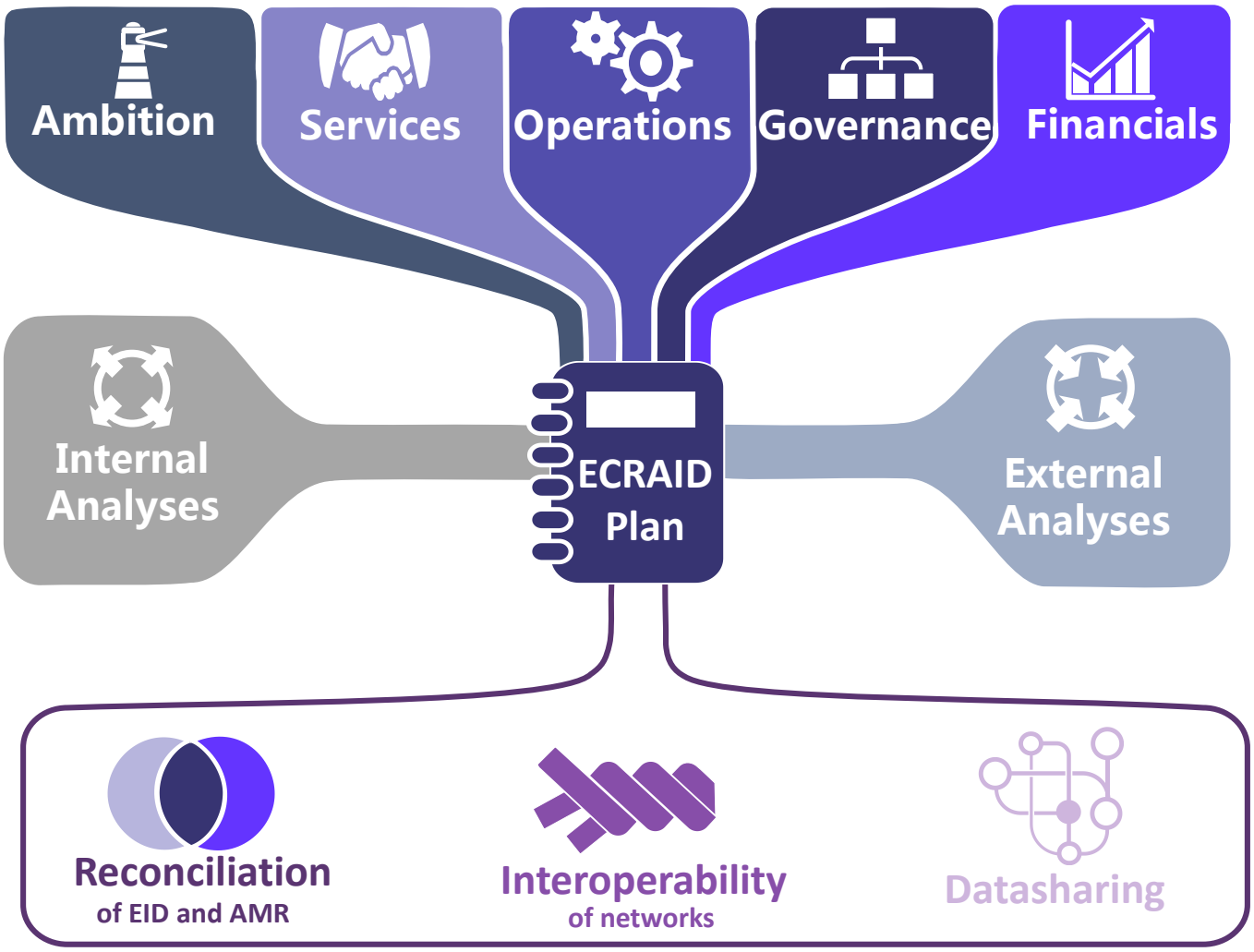
III. To build awareness of and create support for the ECRAID initiative amongst the broader group of stakeholders.

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



Strategic themes

ECRAID-Plan: Services

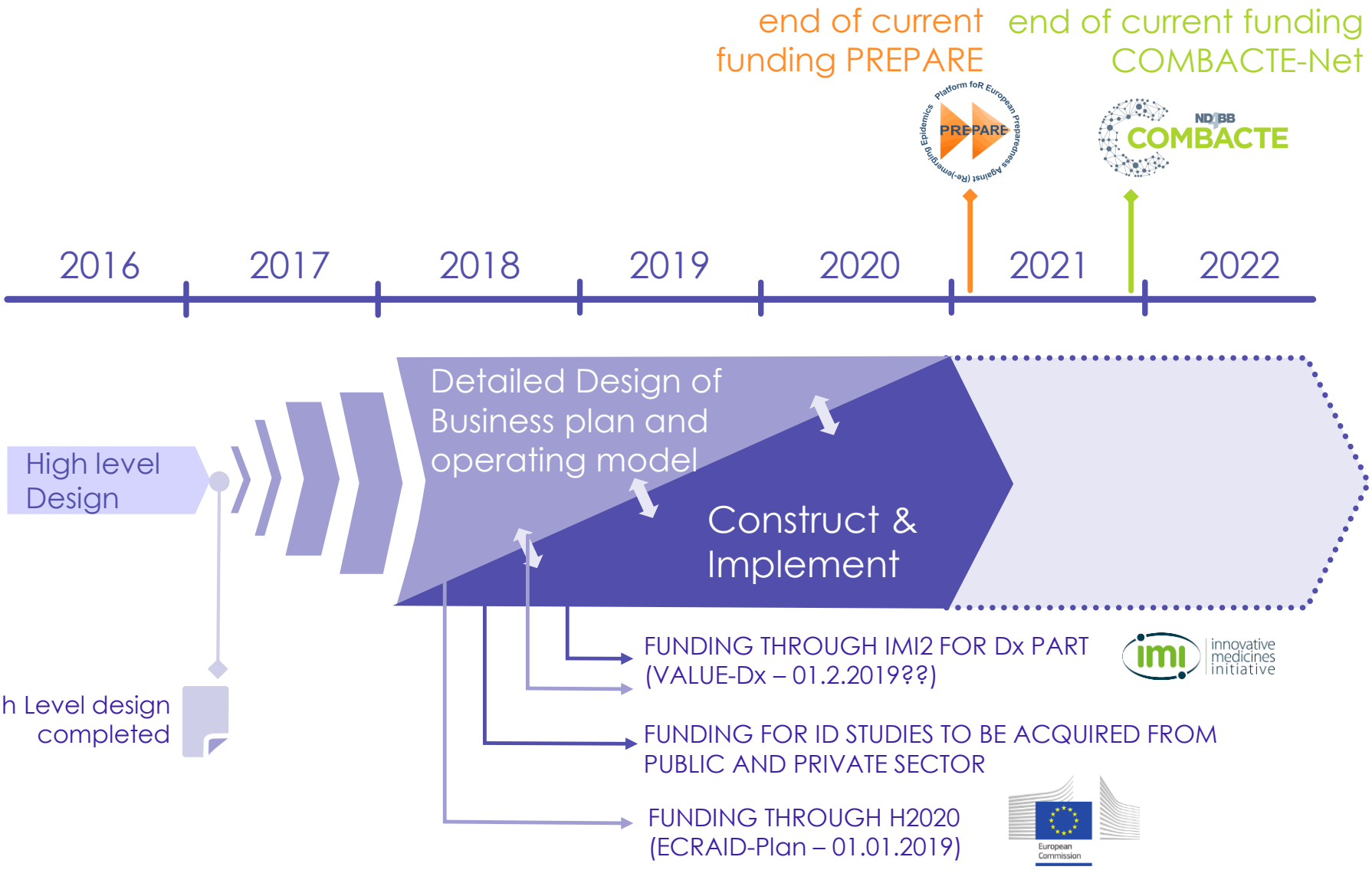
Innovation of clinical research

- *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



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