

Building a European clinical research alliance to respond to emerging infectious diseases

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PREPARE, COMBACTE LAB-Net and VALUE-Dx
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ECRAID-Plan
Coordinator, University Medical Center Utrecht

Hope you will see the light in the tunnel at the end of my talk!



“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.

1. PREPARE:

*Preparing Europe for Infectious
Diseases outbreaks and
pandemics*

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



Overall architecture



CRISP: Clinical Research Information Sharing Platform

CREATE: Clinical Research Education And Training in Europe

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**)



Funded by the
European Union



Adaptive Platform Trials



Many advantages:

- 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
- Emphasis on efficiency with (very) small sample sizes
- Different therapies “graduate” to next phase while trial continues



Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

Christopher C Butler, Alike W van der Velden, Emily Bongard, Benjamin R Saville, Jane Holmes, Samuel Coenen, Johanna Cook, Nick A Francis, Roger J Lewis, Maciek Godycki-Cwirko, Carl Llor, Sławomir Chlabicz, Christos Lionis, Bohumil Seifert, Pär-Daniel Sundvall, Annelies Colliers, Rune Aabenhus, Lars Bjerrum, Nicolay Jonassen Harbin, Morten Lindbæk, Dominik Glinz, Heiner C Bucher, Bernadett Kovács, Ruta Radzeviciene Jurgute, Pia Touboul Lundgren, Paul Little, Andrew W Murphy, An De Sutter, Peter Openshaw, Menno D de Jong, Jason T Connor, Veerle Matheeussen, Margareta Ieven, Herman Goossens, Theo J Verheij

The Lancet, in press

- **Funding:**
 - EU FP7 PREPARE WP 5 program
 - Australian NHMRC 'OPTIMISE' program (\$6M)
 - New Zealand NRC (\$2M)
 - Applications submitted elsewhere
- **Simultaneously test:**
 - Different anti-microbial strategies
 - Different host immunomodulation strategies
 - Different ventilation strategies
- **Separate RAR and stopping rules for multiple subgroups**
- **Patients are preferentially assigned to the best performing arm**
 - Allocation is random, but not 50:50
 - Odds of assignment proportional to odds of success

The outbreak research modes of PREPARE



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

Default Mode

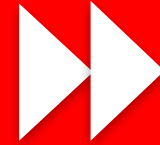
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generic

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

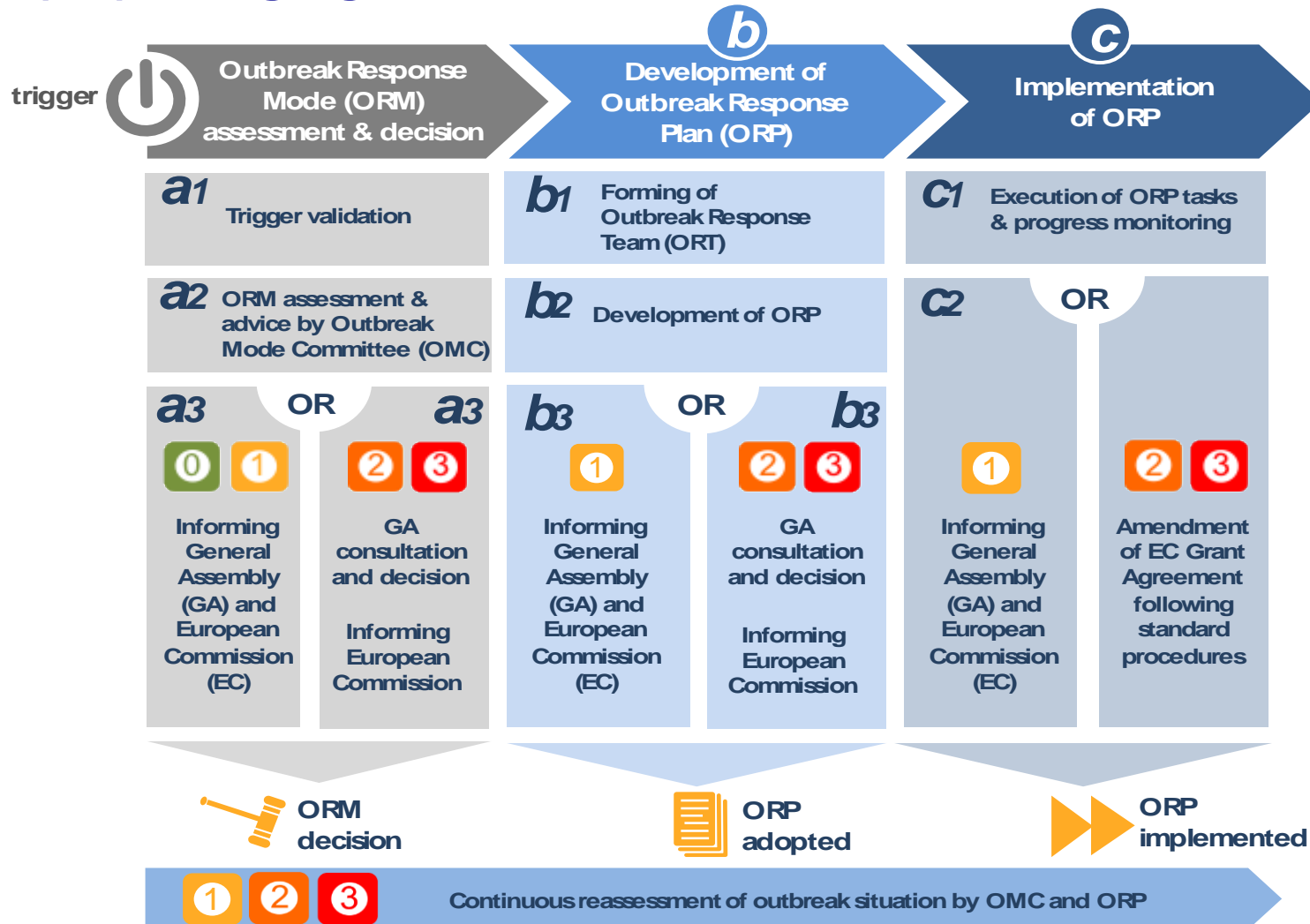
Assessing operational readiness in the networks, identifying important knowledge and resource gaps and preparing clinical protocols.

tailored to specific (potential) infectious disease outbreak

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



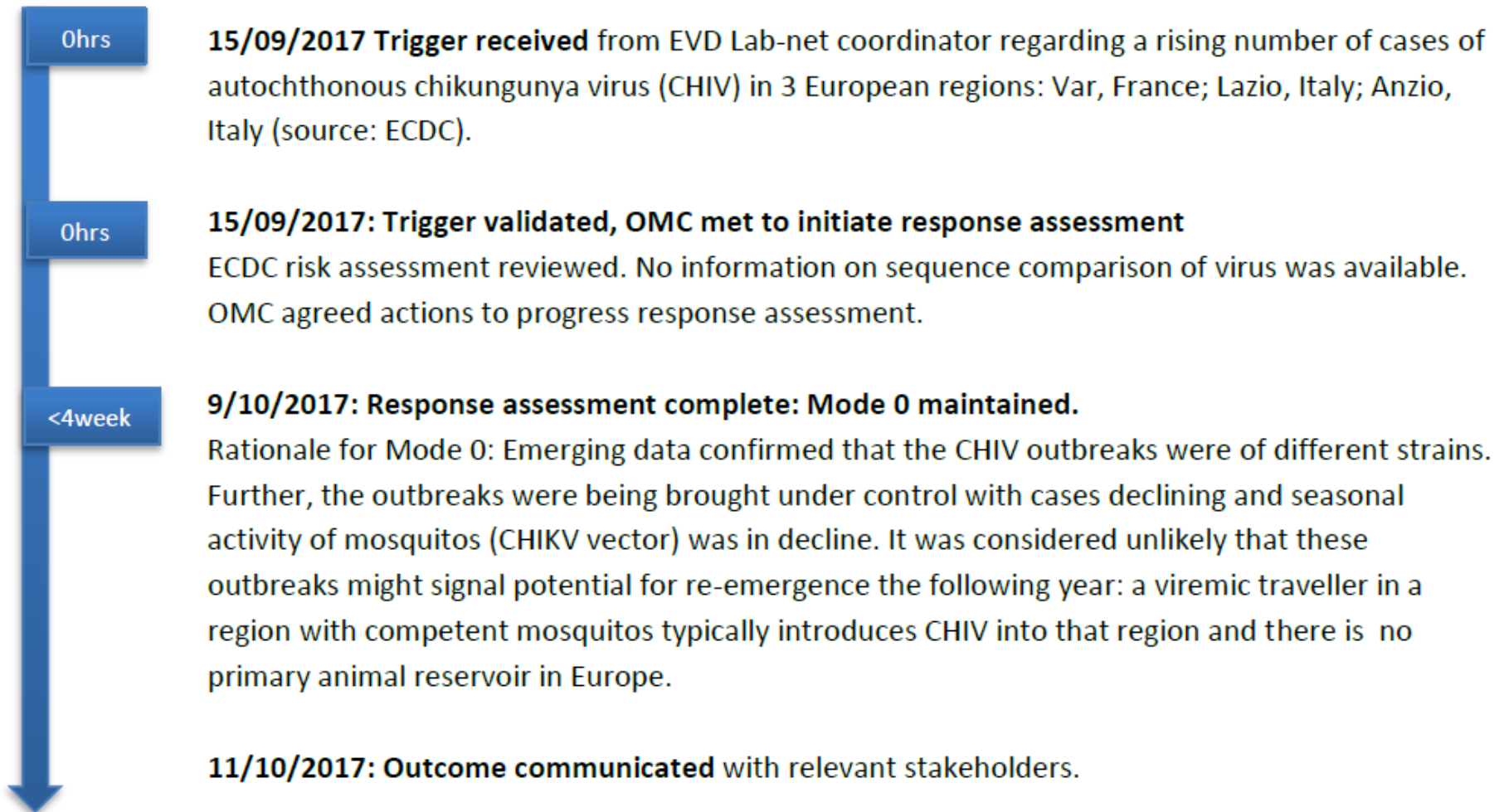
Date	Outbreak	Trigger	Threat to Europe*	Mode	Activities
28/04/2014	MERS-CoV	PREPARE partner	Limited	Mode 1	Develop clinical protocols (collaboration with ISARIC).
08/08/2014	Ebola Virus	PREPARE partner	Limited	Mode 1	Surveyed PREPARE affiliated European hospitals to assess Ebola preparedness and capacity; 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

Funded by the
European Union



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



2. COMBACTE:

*Clinical research on antimicrobial
resistance*

Pursuing Novel Antibacterials: New Drugs for Bad Bugs (ND4BB)

**COMBACTE: Combatting Antibiotic
Resistance in Europe**

COMBACTE: Combatting Bacterial Resistance in Europe

Four consortia:



Create a self-sustaining antibacterial development network

- Expanding research and laboratory networks
- Optimal alignment of clinical trials with investigator sites
- Obtain clinical and epidemiological data

Increase efficiency of antimicrobial drug development

- Align clinical trials with cutting edge molecular methodologies and trial design
- Deliver clinical trials with various candidate compounds from pharmaceutical companies



The four pillars of COMBACTE



CLIN-Net

Clinical investigator network

Improve the efficiency of clinical study execution



LAB-Net

Laboratory surveillance network

Optimize diagnostics in clinical studies

STAT-Net

Improvements in trial design

Develop more efficient study designs & better methods for data analysis



EPI-NET

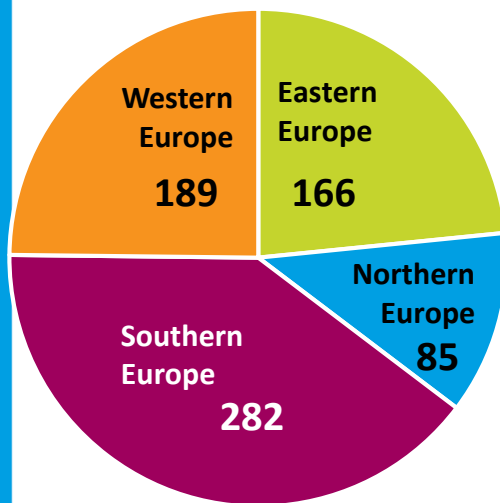
Epidemiology support for ND4BB & beyond

Improve information on AMR in Europe from existing surveillance systems

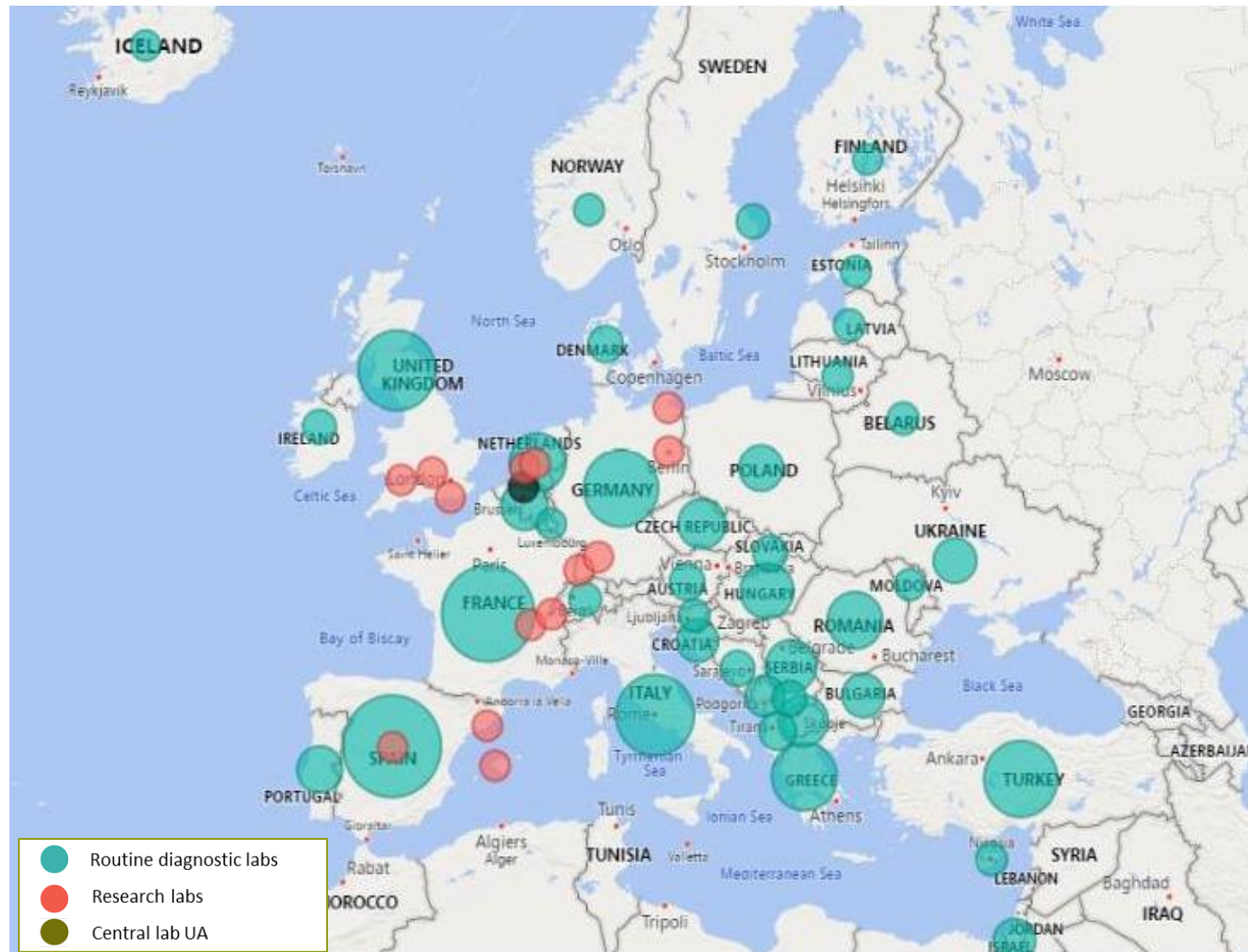


LAB-Net Network

- 762 routine diagnostic labs
- 1133 lab contacts
- 14 research labs
- 41 European countries



Distribution of the number of laboratories in LAB-Net per region in Europe as per WHO definitions



LAB-Net Goes Global

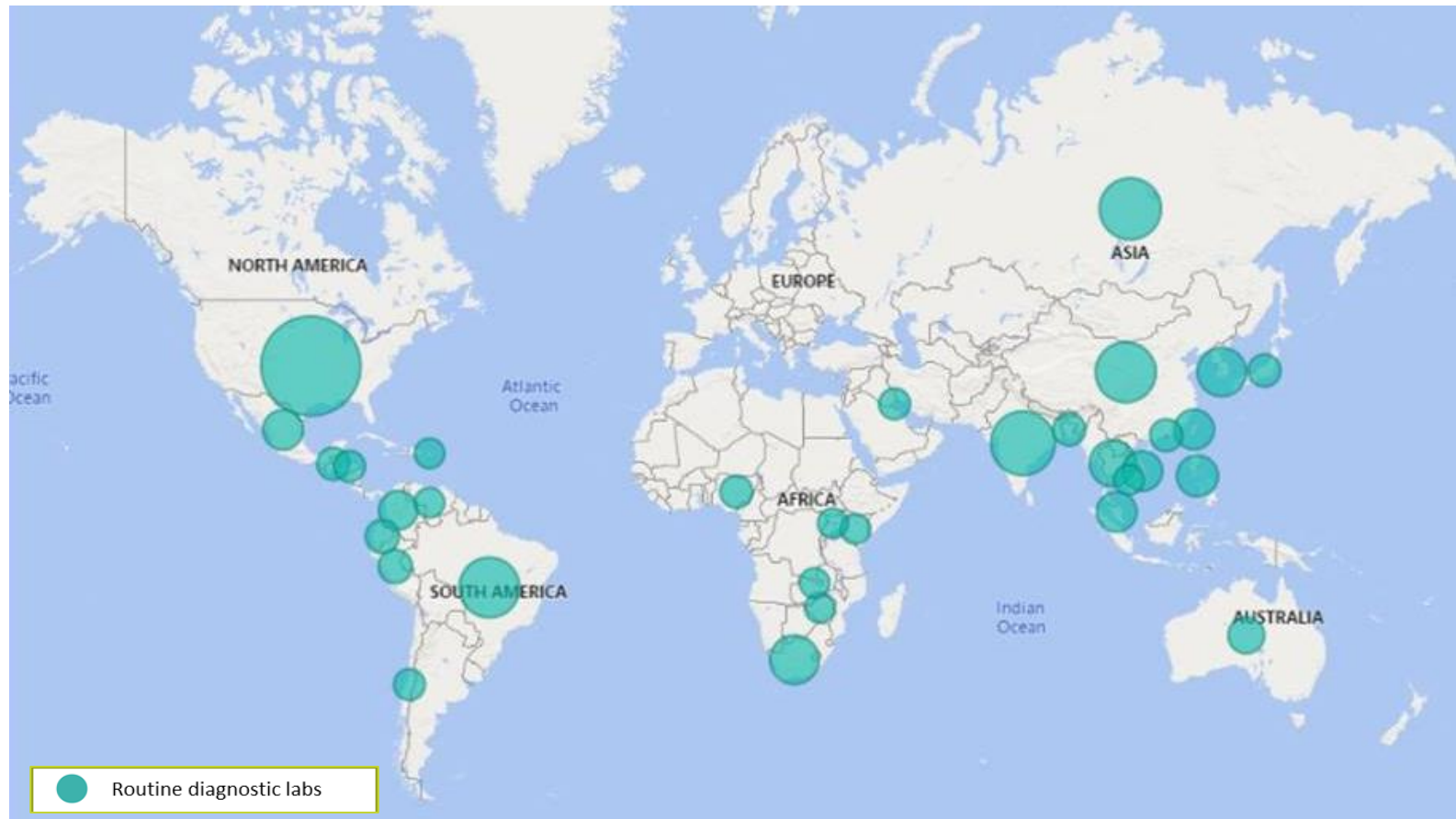
GLOBAL STUDIES

CREDIBLE-CR

NeoAMR

PediCAP

- 327 labs in 32 non-European countries



Overview of non-European laboratories collaborating with the LAB-Net network

*As of November 2019

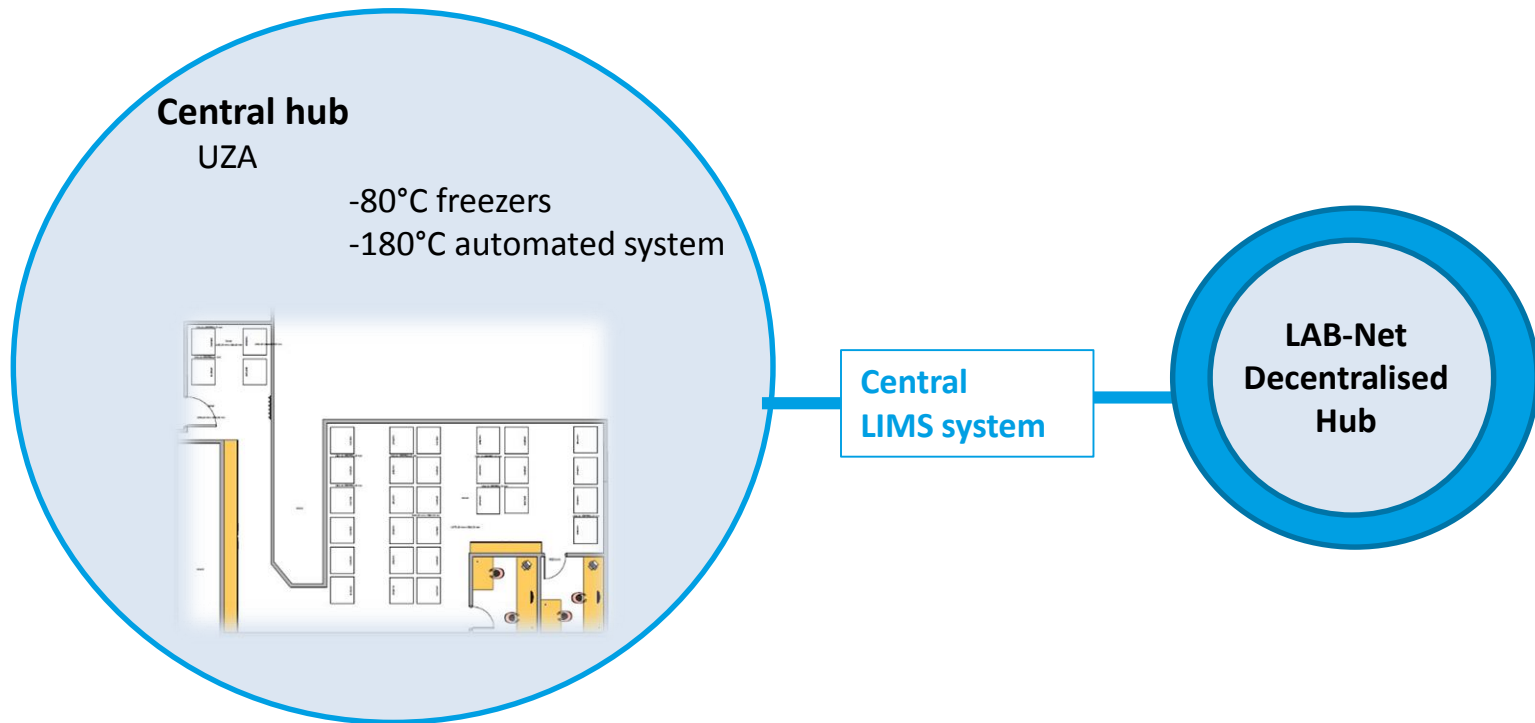
Study specific activities (COMBACTE-NET and beyond)

- LAB-Net is involved in multiple studies and actively participates in all aspects of these studies

		Clinical Protocol	CRO selection	Dx test selection	Questionnaire	Site selection	Local lab Manual	Sample kits and study materials	Local lab training	EOA panel	Biobanking	Central lab	Research lab
COMBACTE-NET	ASPIRE-ICU												
	ASPIRE-SSI												
	SAATELLITE												
	MEDI4893 PhaseIII												
	ANTICIPATE												
	EXPECT-2												
COMBACTE-MAGNET	HONEST-PREPS												
	ASPIRE-ICU												
COMBACTE-CARE	EVADE												
	EURECA												
	REJUVENATE												
COMBACTE-CDI	REVISIT												
	WP1												
	WP2												
NON-COMBACTE STUDIES	WP3												
	CREDIBLE-CR												
	NeoOBS												
	PediCAP												
	OVERCOME												
	RESTORE-IMI-2												
	ARBO-MERMAIDS												
	ARI-MERMAIDS												
	PED-MERMAIDS												
	ALIC ⁴ E												

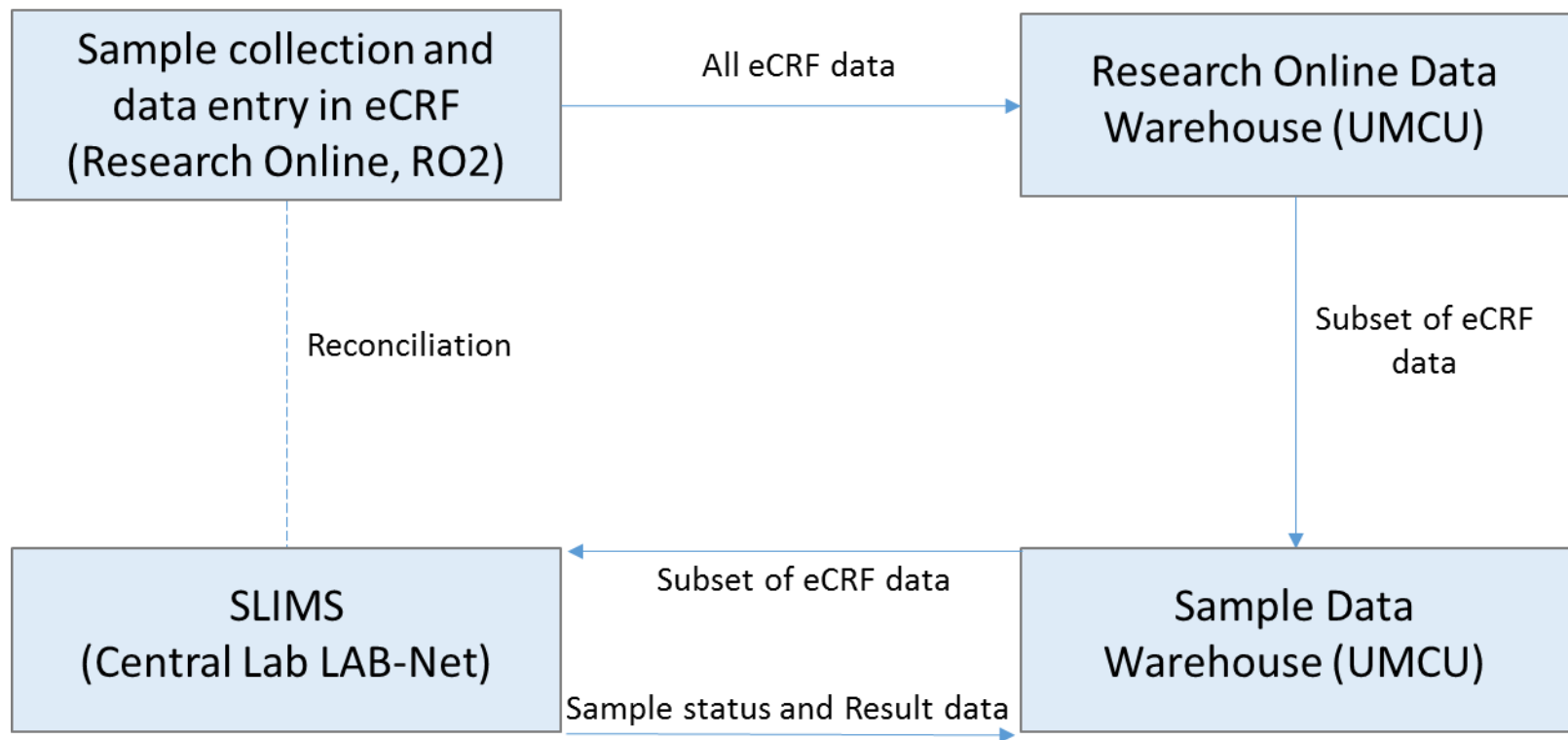
LAB-Net involved in task
 LAB-Net involved in task in 2019

LAB-Net biobanking infrastructure

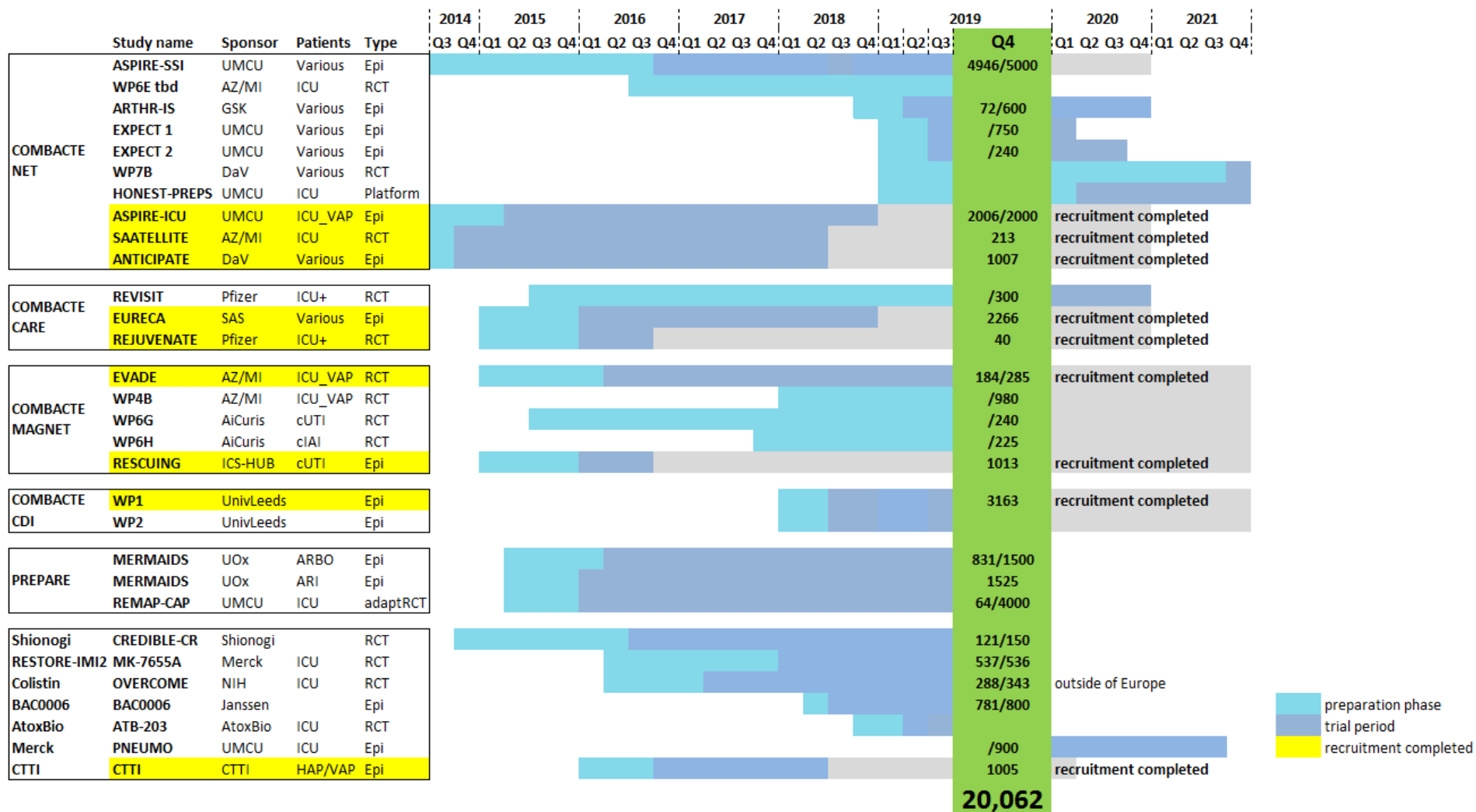


LAB-Net biobanking data flow

concept developed for EXPECT-2 study



COMBACTE, PREPARE and other Clinical studies



20,062 patients enrolled

European Clinical Trial Networks



**Primary
care**



**Hospital
care + Labs**



**Pediatric
care**



**Long Term
Care**

>200 primary care
practises in >20
European countries



- ✓ Recruited over 20,000 patients into clinical studies on ARTI
- ✓ Randomised 3,268 participants in a response-adaptive platform trial of a drug for a CA-ARTI

Chris Butler



>850 hospitals and
>750 labs in >40
European countries



- ✓ To date, this network is managing 19 trials, including phase I – III trials for 6 new compounds against multi-resistant bacteria, and recruited over 14,000 patients.

**Marc Bonten (Clin)
Herman Goossens (Lab)**

90 paediatric
clinical sites in 18
countries



- ✓ Active a.o in ZIKACTION, PREPARE, C4C (IMI2)

Carlo Giaquinto

Nursing homes and
rehabilitation
centres in 11
countries in Europe
and Israel with more
than 14,000 LTCF
beds

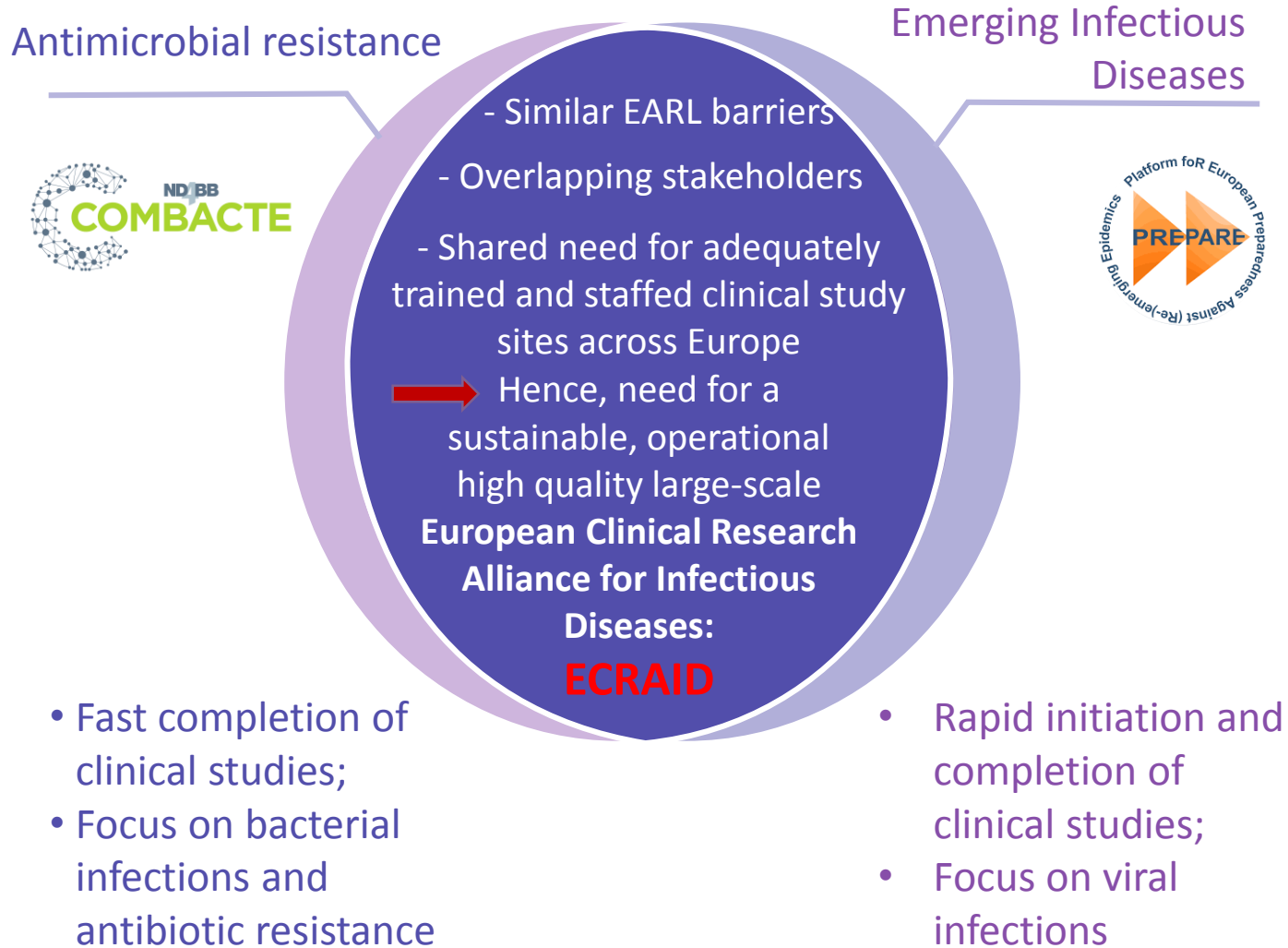
- ✓ Experience in clinical trials on antibiotic use, influenza epidemiology and vaccines, microbiome and more.

**Evelina Tacconelli
Mical Paul**

3. ECRAID:

***European Clinical Research
Alliance on Infectious Diseases***

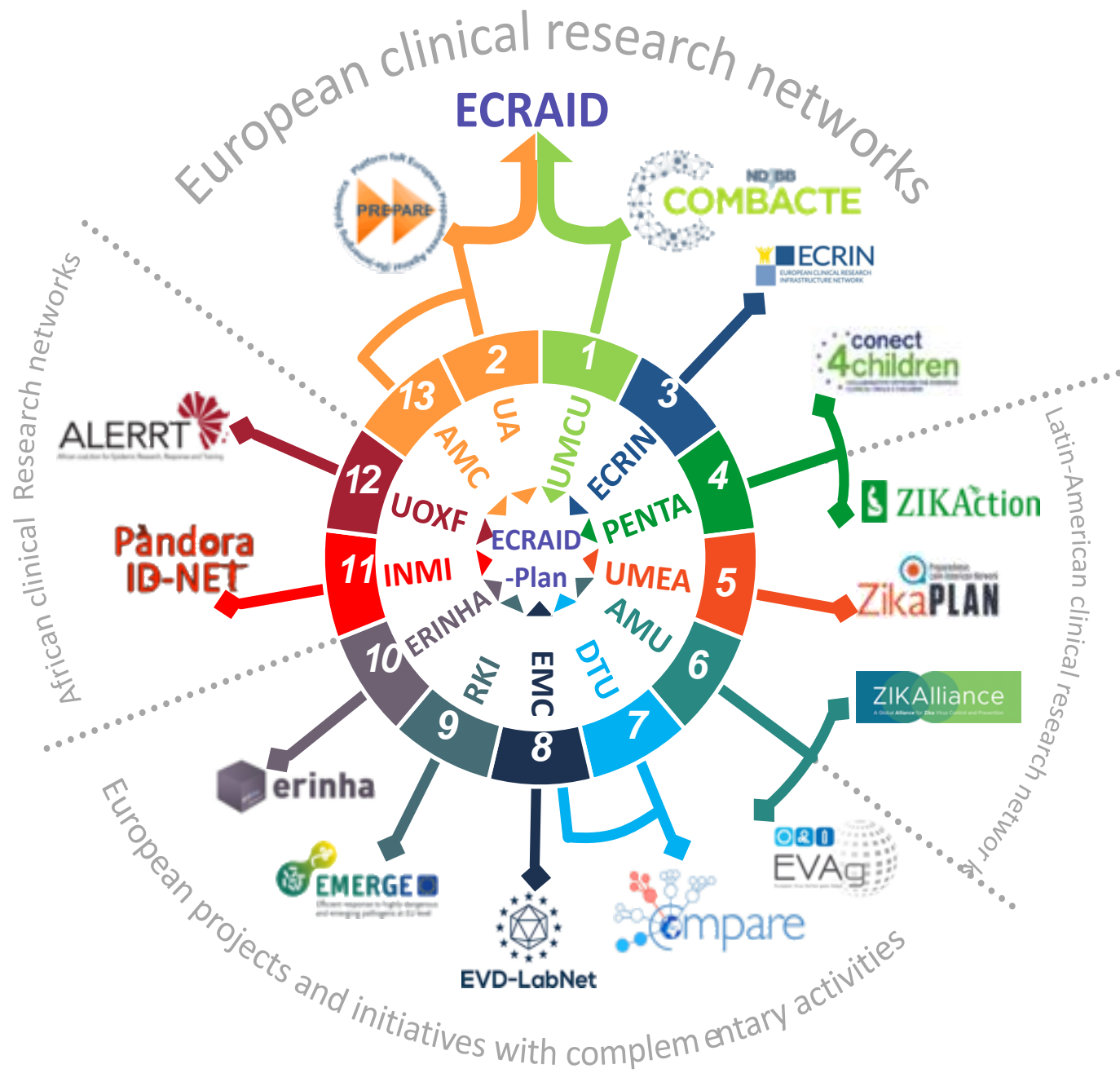
Leveraging EU/IMI investments in clinical research on AMR and EID



ECRAID-Plan: 1.1.2019 – 31.12.2020.

**3 Million
EURO**

*Direct
involvement
of relevant
other EU
funded
projects,
networks and
organisations*



ECRAID-Plan is funded by the European Commission under Grant Agreement 825715

Objectives

Overall goal:

Developing the detailed business plan for ECRAID, building on the high-level design developed in 2016 by the ECRAID Working Group

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

***Kick-off 17
January 2019***

“We expect the ECRAID-Plan to come up with a business plan that offers concrete solutions and prepares Europe to better deal with antimicrobial resistance and large infectious diseases outbreaks”
–EU commissioner Carlos Moedas,

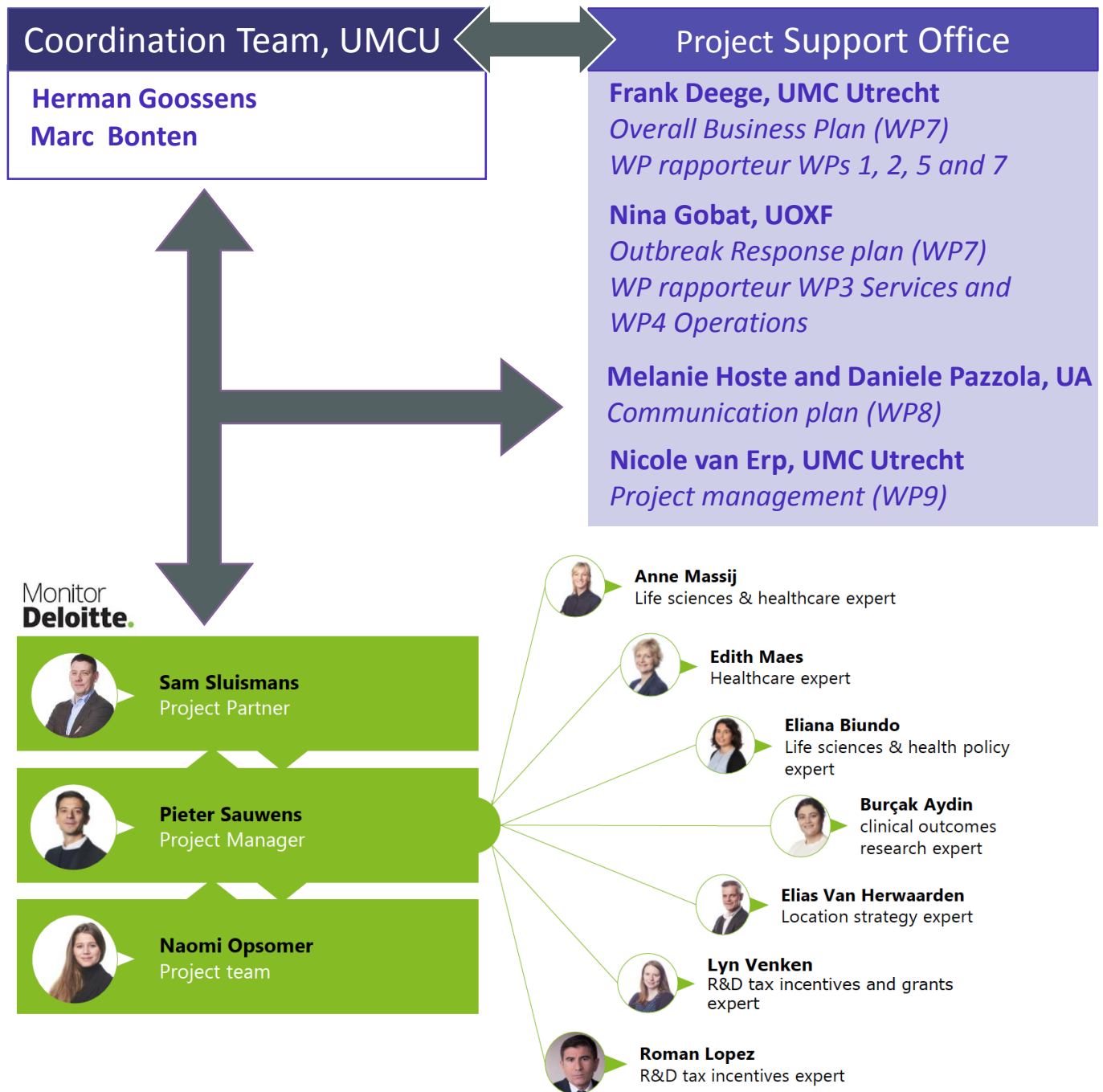


“an inspiring vision of a pan-European infrastructure for patients and communities, bringing public health, clinical and laboratory, science, innovation and society together.” – Sir Jeremy Farrar.



ECRAID-Plan

Project management structure



4. VALUE-Dx:

Setting the scene for public-private collaborations in diagnostics of infectious diseases

VALUE-Dx

Setting the scene for public-private
collaborations in diagnostics of
infectious diseases



Objectives of VALUE-Dx

Helping to build the economic case for rapid diagnostics as a public good in the fight against AMR

1. To design a health-economic framework (HEF) to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients.

2. To establish a sustainable European Standardised Care Network adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics.

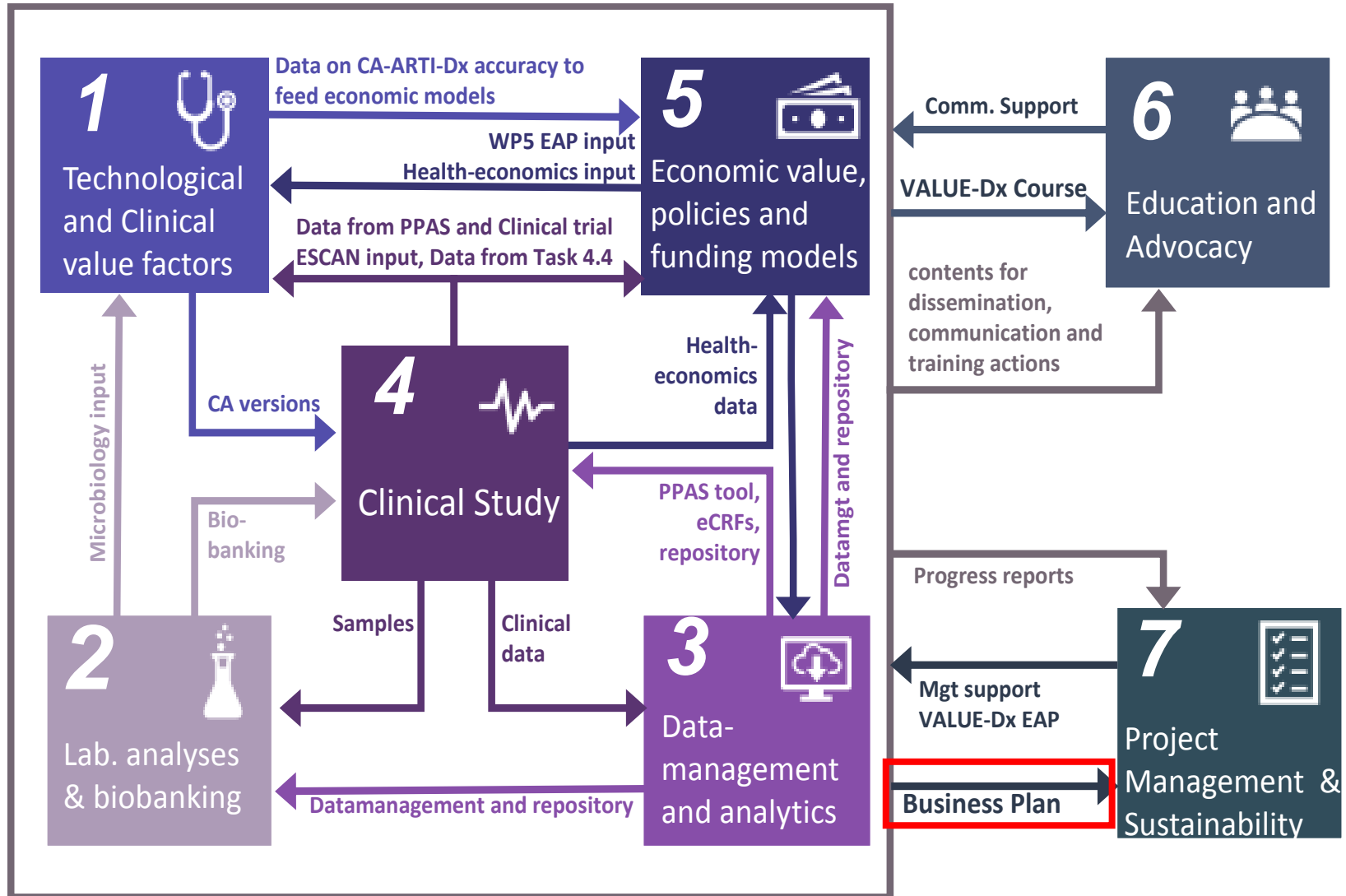
3. To design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of Community-Acquired Acute Respiratory Tract Infections (CA-ARTIs)

4. To explore, define and attempt to resolve the psychological, ethical and social barriers which prevent the more widespread adoption of diagnostics delivering healthcare to the population.

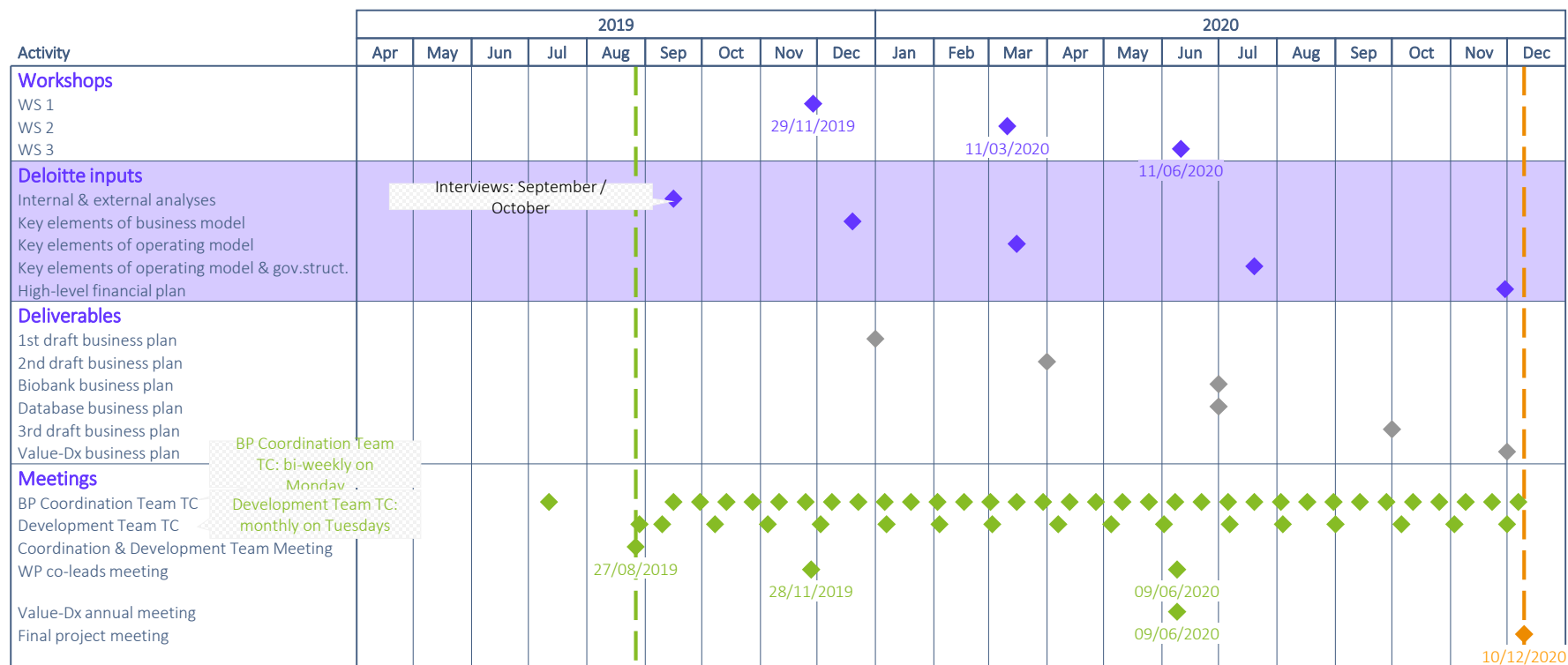
The VALUE-Dx Consortium



Interaction between the Work Packages



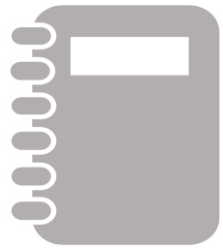
PROJECT TIMELINE & STATUS UPDATE



Together with ECRAID: present coherent overall Business Plan

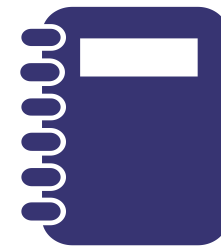
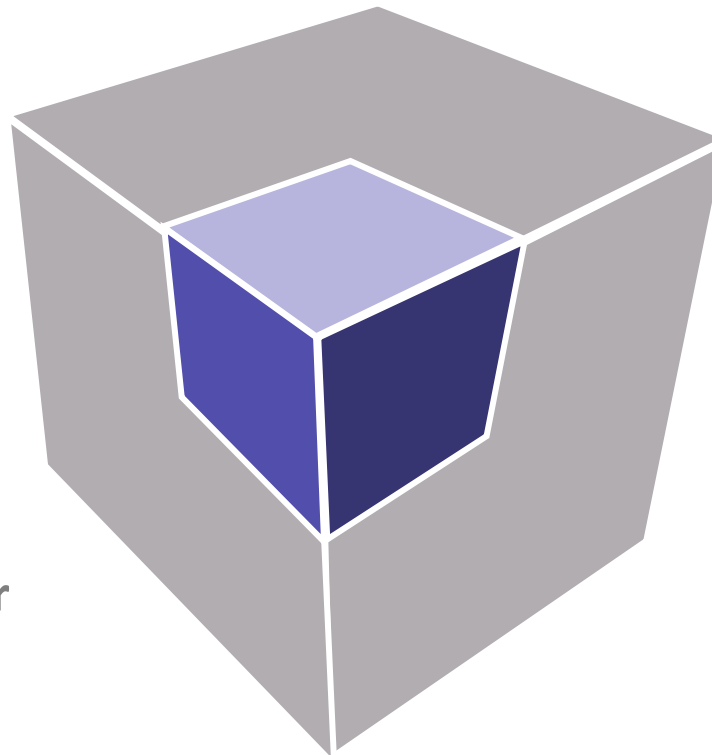
- Work in progress -

Integration of sustainability plans of ECRAID-Plan and VALUE-Dx



ECRAID-plan sustainability plan

- ✓ Building infrastructure for clinical trials of Infectious Diseases in all clinical care settings



VALUE-Dx sustainability plan

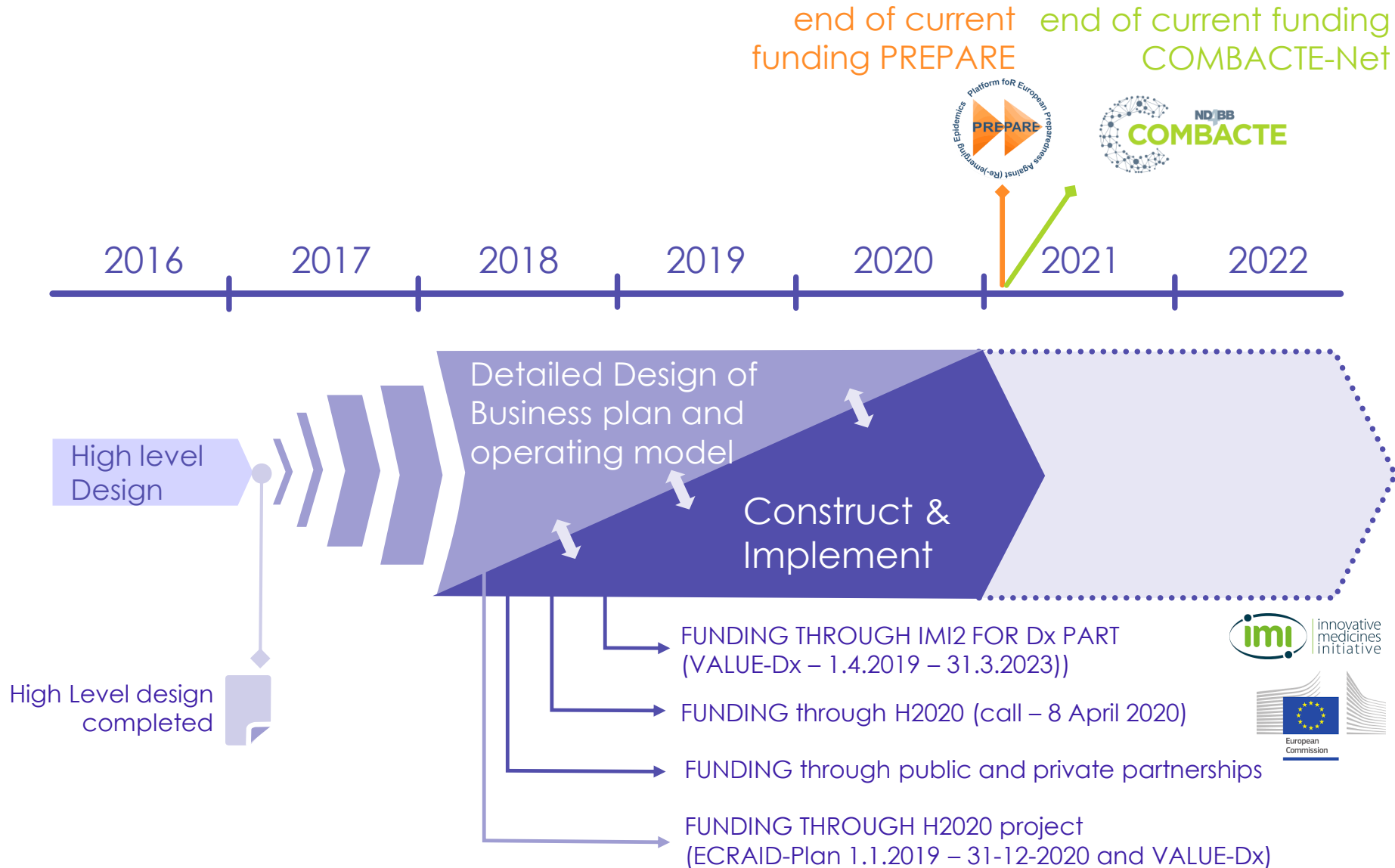
- ✓ Building infrastructure for clinical trials and labs on diagnostics of Infectious Diseases
- ✓ Building biobank
- ✓ Building database

What ECRAID could offer

- ✓ Clinical Trial Network for infectious diseases in hospital care and primary care, adults and children
- ✓ Rapid access to target European patient populations
- ✓ Globally embedded
- ✓ Single-point of access into a high quality, business oriented clinical research network
- ✓ Focus on services that alleviate the Ethical, Administrative, Regulatory and Logistical (EARL) barriers to clinical research (faster start-up, reduce timelines, lower costs)
- ✓ Direct access to leading expertise on Infectious Diseases
- ✓ An active network, continuously including patients in platform trials, allowing rapid clinical research response in the event of an EID or pandemic threat



ECRAID: Our plan and timelines



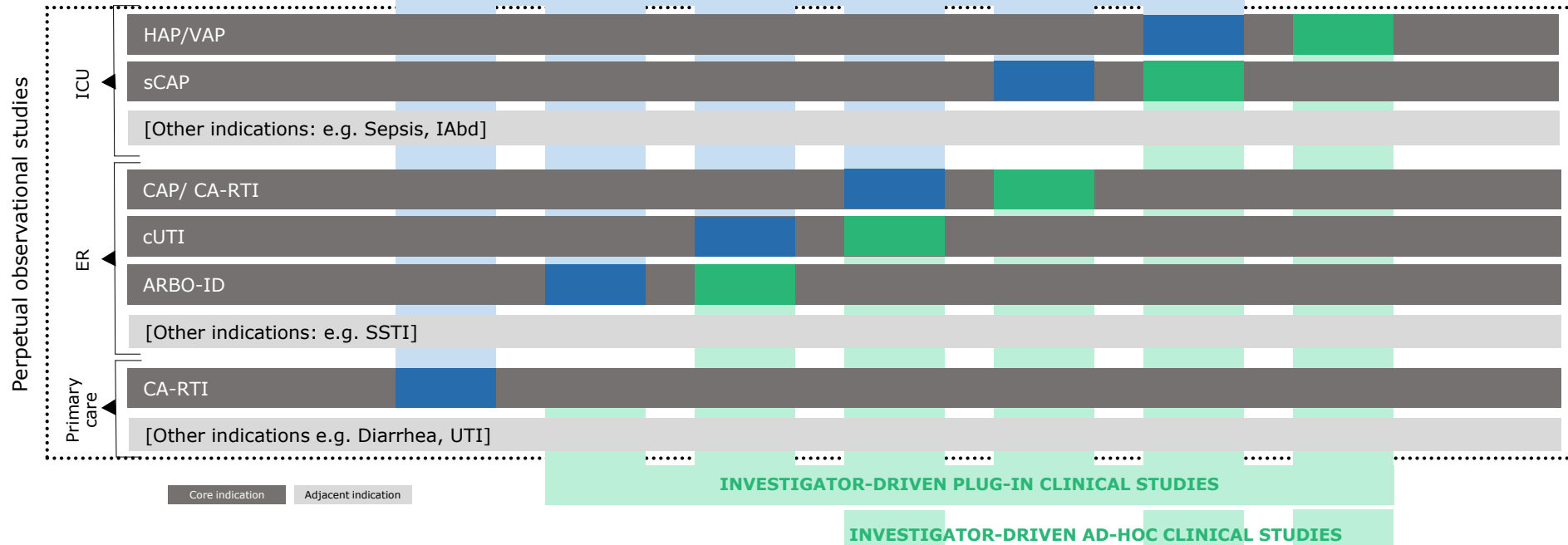
CURRENT THINKING FOR A NEW H2020 PROPOSAL: A SINGLE-ACCESS CLINICAL RESEARCH NETWORK FOR PREPAREDNESS AND RESPONSE TO INFECTIOUS DISEASES OUTBREAKS, REDUCING THE IMPACT OF INFECTIOUS DISEASES ON INDIVIDUAL AND POPULATION HEALTH

A PLATFORM FOR INNOVATIVE TECHNOLOGIES

INDUSTRY-DRIVEN AD-HOC CLINICAL STUDIES

A PLATFORM FOR IMPROVED PREPAREDNESS AND RESPONSE

INDUSTRY-DRIVEN PLUG-IN CLINICAL STUDIES



Legend: HAP = Hospital Acquired Pneumonia; VAP = Ventilator Associated Pneumonia; IAbd – Intra-Abdominal diseases; CAP = Community Acquired Pneumonia; CA-ARTI = Community Acquired Respiratory Tract Infections; cUTI – Complicated Urinary Tract Infections; ARBO-ID = Arthropod-Borne Infectious Diseases

Thank you

