European Clinical Trial Network for Infectious Diseases

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MedTech Europe
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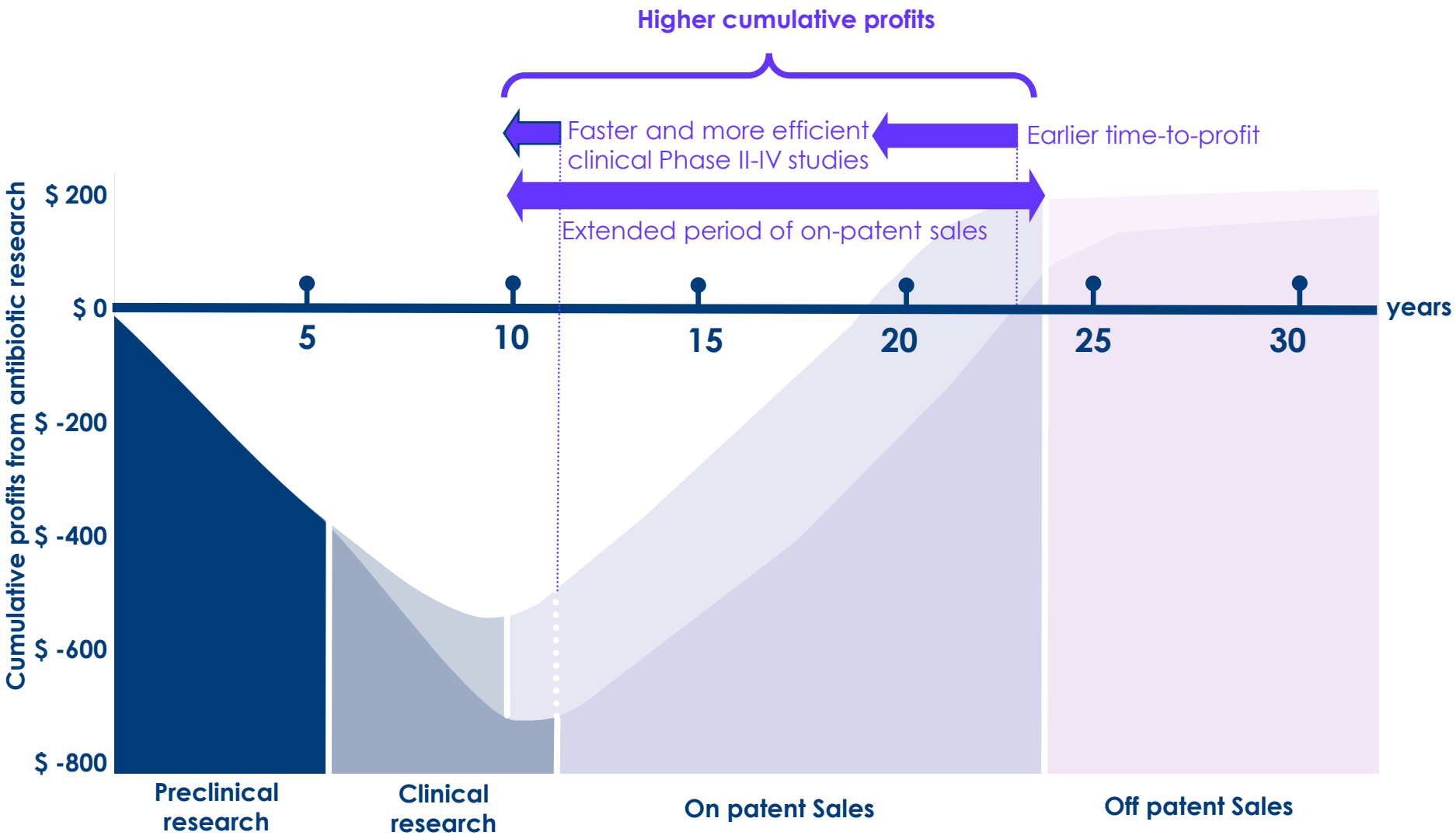
Agenda

- AMR clinical trials: COMBACTE
- Pandemic clinical trials: PREPARE
- European Clinical Research Alliance for Infectious Diseases: ECRAID
- Concluding remarks

Antimicrobial Resistance

Increasing the incentive for industry to invest in antibiotics pipeline



Adapted from Review on Antimicrobial Resistance (O'Neill, 2015)


ND4BB
COMBACTE

Europe: AMR programme

New Drugs for Bad Bugs:

- Part of the Action Plan against the increased threats from AMR
- Launched by the European Commission in Nov 2011
- Vision: delivering a pipeline of new antibacterial agents to patients

Innovative Medicines Initiative:

- Largest public-private (EU-EFPIA) partnership in life science R&D
- Speed up the development of better and safer medicines for patients
- IMI-1: part of EU FP7, 2008 - 2014, 2 billion Euro
- IMI-2: part of EU H2020, 2014 – 2024, 3.3 billion Euro

EFPIA: European Federation of Pharmaceutical Industries and Associations

New Drugs for Bad Bugs ND4BB

Cross-project communication & collaboration

TRANSLOCATION
Research penetration and efflux Gram-negatives Data Hub and Learning from R&D experience

ENABLE
Discovery & Development of new drugs combatting Gram-negative infections

COMBACTE
- Enabling clinical collaboration & refining clinical trial design
- Clinical development of compounds for Gram- positives

COMBACTE CARE
Clinical development of antibacterial agents for Gram-negative, antibiotic resistant pathogens

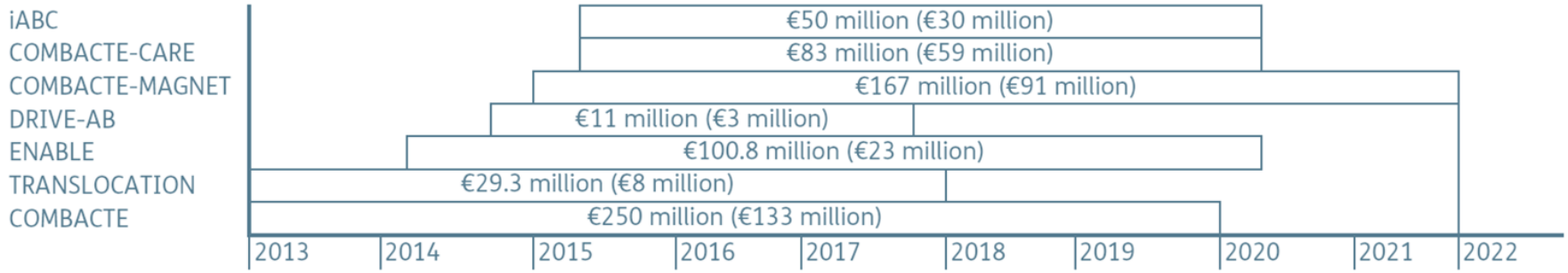
COMBACTE MAGNET
Systemic molecules against healthcare-associated infections

iABC
Inhaled antibact-erials in bronchiec-tasis and cystic fibrosis

DRIVE-AB
Driving reinvestment in R&D & responsible use of antibiotics

ND4BB Information Centre
All data generated is submitted and made accessible to all partners

Drug discovery
Drug development Gram-negatives
Drug development Gram-positives
Economics and Stewardship



References: Kostyanev et al. J Antimicrob Chemother. 2016 Feb;71(2):290-5.

COMBACTE: Combatting Bacterial Resistance in Europe

Three consortia:

- 2011 - 2021
- Managing entitiy: University Medical Center Utrecht (Marc Bonten)

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 mehodologies and trial design
- Deliver clinical trials with various candidate compounds from pharmaceutical companies

COMBACTE network infrastructure

827
hospitals

583
laboratories

42
countries

The 4 pillars of the COMBACTE projects

CLIN-Net
High-quality clinical research network in all European countries with certification criteria and GCP Training program
Lead: University Medical Center Utrecht, M. Bonten

LAB-Net
High-quality laboratory network in all European countries with assessment of existing laboratory methods, quality assessment system, specimens and strains repository
Lead: University of Antwerp, H. Goossens

STAT-Net
Network to improve clinical trials delivery, perform advanced biostatistical and PK/PD modelling studies, evaluate novel clinical design strategies using modern biostatistical concepts
Lead: University of Geneva, S. Harbarth

EPI-Net
Network to identify and map existing surveillance systems, to establish frameworks for data collection to support antibacterial drug development
Lead: University of Tübingen, E. Tacconelli

Contribution of LAB-Net to clinical studies

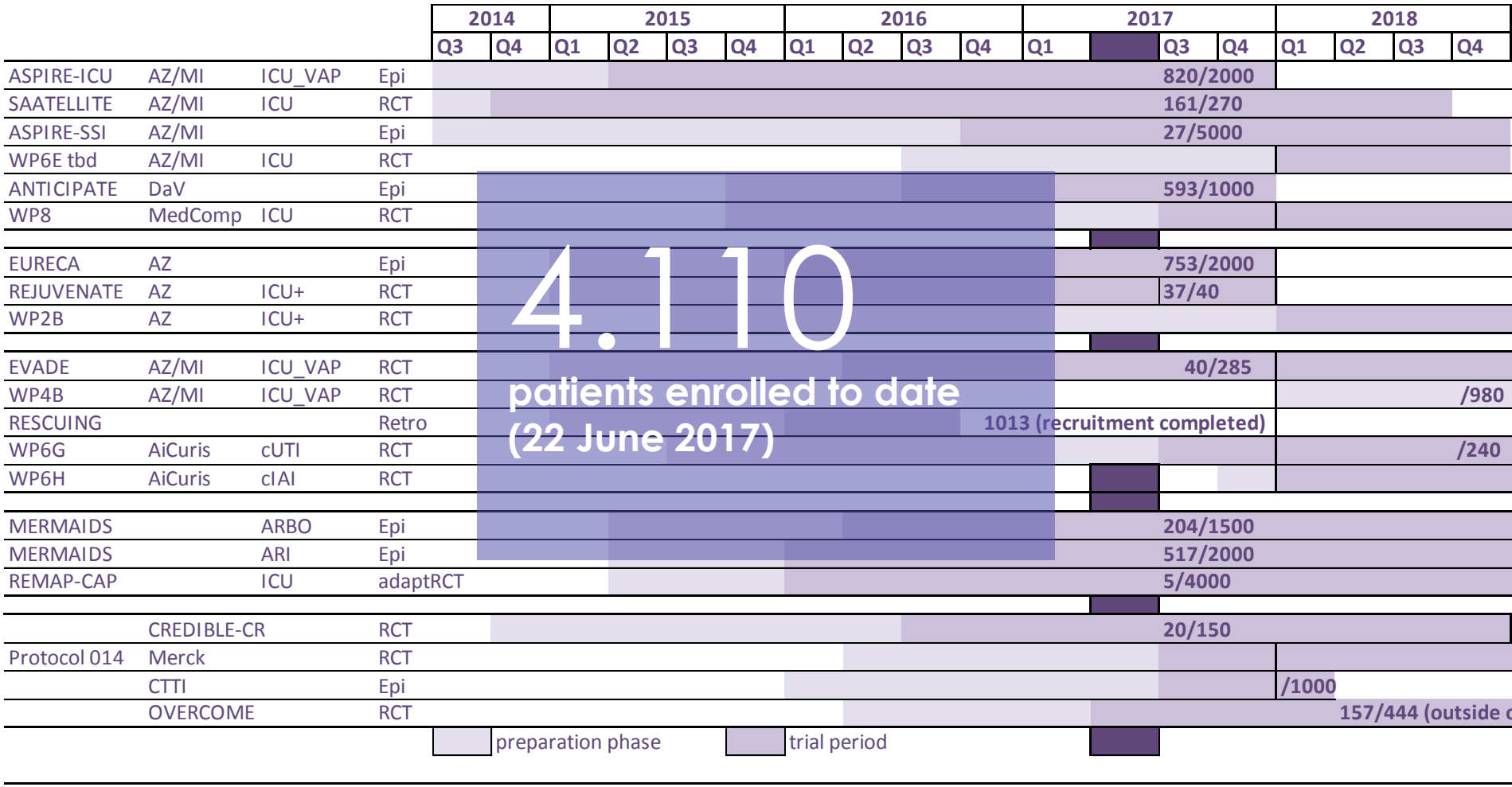
				Clinical Protocol	CRO selection	Dx test selection	Questionnaire	Site selection	Local lab Manual	Sample kits	Local lab training	EQA panel	Biobanking	Central lab	Research lab
COMBACTE-NET	WP6A	ASPIRE-ICU	Observational		NA							NA			
	WP6A	ASPIRE-SSI	Observational		NA							NA			
	WP6B	SAATELLITE	Phase II									NA			
	WP6E	ICU_VAP	Phase III		FU	FU	FU	FU	FU	FU	FU	NA	FU		
	WP7	ANTICIPATE	Observational		NA							NA			
	WP8	705	Phase III		FU					FU		NA	FU	FU	FU
COMBACTE-MAGNET	WP3A	ASPIRE-ICU	Observational		NA							NA			
	WP4A	EVADE	Phase II									NA			
COMBACTE-CARE	WP1A	EURECA	Observational		NA					NA					
	WP2A	REJUVENATE	Phase II		NA	NA			NA	NA	NA	NA	NA	NA	NA
	WP2B	WP2B	Phase III			FU				FU			FU	FU	FU
NON-COMBACTE		CREDIBLE-CR	Phase III												NA
		iBEST	Phase II			NA						NA			
		OVERCOME	Observational	FU	FU	FU	FU	FU	FU	FU	FU	FU	FU	FU	FU
	PREPARE WP3	ARBO-MERMAIDS	Observational		NA	NA					NA	NA			
	PREPARE WP3	ARI-MERMAIDS	Observational		NA	NA					NA	NA			
	PREPARE WP3	PED-MERMAIDS	Observational		NA	NA					NA	NA			
	PREPARE WP4	ALIC^{4}E	Observational		NA	NA					NA	NA			

	LAB-Net involved in task		LAB-Net not invoved in task
NA	Task not applicable for the study	FU	Future study, tasks not defined yet

LAB-Net actively participates in all aspects of clinical studies:

- Selection of CRO, sites, Dx tests
- Preparation of protocols, lab manuals, questionnaires, sample kits and EQA panel
- Lab training
- Includes biobank, central lab and research labs

Clinical trials



4.110

patients enrolled to date (22 June 2017)

Lessons learned in clinical trials of COMBACTE

Challenge of (ID) trials:	Lessons learned in COMBACTE trials:
complex & expensive	start-up issues and delays in pt. recruitment
take ages	unclear distribution of tasks (same CT model)
need competent teams	CRO difficulties to build sustainable competent team
one-off trial network and one-off trial team	little interaction between pharma and investigators
long lines of communication	high demands on microbiology support; yet often poor communication between the lab and clinical staff, lab not on board from the beginning or not present at SIV, no lab manual
	suboptimal training

Rapid diagnostics to aid patient enrollment

- Real value and huge need: narrow-spectrum drugs (antibiotics, monoclonals) will benefit immediately
- 4/9 intervention trials in COMBACTE require rapid diagnostis test
- Good microbiology support essential for the success of many COMBACTE trials

A *P. aeruginosa* - Focused VAP Programme

- Standard non-inferiority Phase 3 study[1]
  - Need 336/arm or 672 evaluable patients total
- If only 10% yield *P. aeruginosa*,
  - We need 6,720 patients … for ONE trial!

[1]Assumes 80% success rates, 10% margin, and 90% power.

Courtesy: John Rex

Needs of pharmaceutical companies to aid enrollment of patients in clinical trials

- Identification of one or more bacterial species in a clinical specimen
- Detect resistant organisms in a clinical specimen
- Detect resistant genes (in isolates or even in a clinical specimen)

This need creates a schism between pharmaceutical and diagnostic companies: Pharma perspective

- Pharma interested in tests that target a limited number of organisms (e.g. *Pseudomonas* or *Acinetobacter* or MRSA) in a specific sample (e.g. in ETA), that can be used for targeting the patient (RUO for ex-US clinical studies or IUO)
- tests with different requirements:
  - Detection of infection: sufficient to detect cutoff levels that correlate with infection (sensitivity less critical)
  - Detection of colonization: detection of any number of organisms (very high sensitivity required)

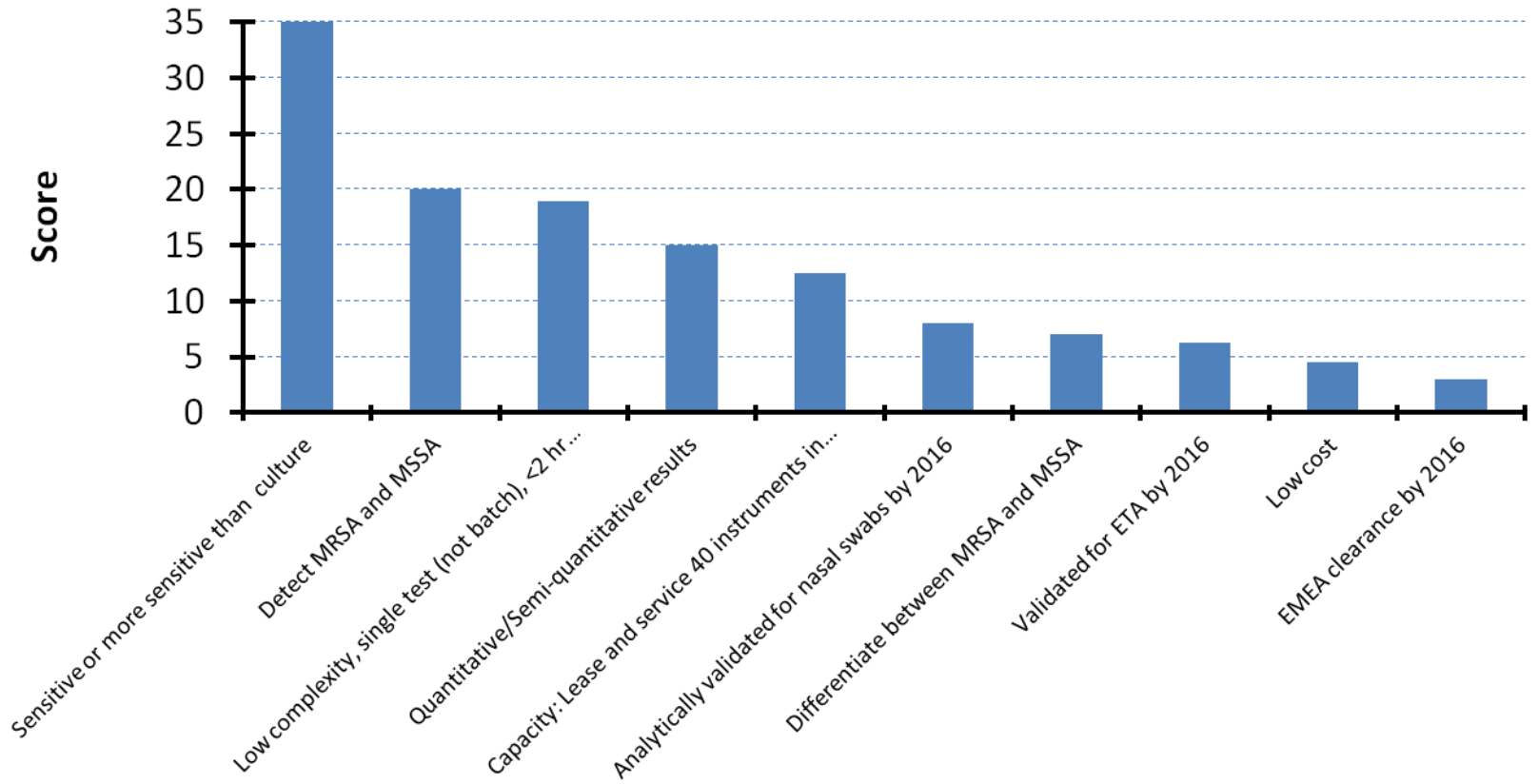
This need creates a schism between pharmaceutical and diagnostic companies: Diagnostic company perspective

- Diagnostic company only interested in developing multi-plexed tests with broad range of targets at affordable price
- tests that can be cleared for use (US-IVD or CE-IVD)
- Wide range of clinical applications

Examples of clinical trials in IMI where rapid diagnostics are needed

- Phase II RCT with anti-a-toxin staphylococcal antibody MEDI4893 for prevention of HABP/VABP (MedImmune):
  - Diagnostic test needed: rapid detection of *S. aureus* in ETA
- Phase II RCT trial with anti-pseudomonas antibodies MEDI3902 for prevention of HABP/VABP (MedImmune)
  - Diagnostic test needed: rapid detection of *P. aeruginosa* in ETA

S. aureus ETA Rapid Dx Weighting



Rapid Diagnostic for POCT for *Pseudomonas aeruginosa* colonization in endotracheal aspirates in patients on a mechanical ventilator

Required diagnostic specifications:

- High sensitivity (<10^2 cfu/mL) to identify patients as they become colonized (versus infected/pneumonia)
- High specificity also desired
- Validated for endotracheal aspirate samples (ETA)
- Minimal hands on time (<30 min) for specimen processing
- Rapid turn-around time for result (<2 hr)
- Test can be run on demand without need for batching
- Test can be performed outside of microbiology (ICU or step down unit)
- Low cost (<$40)

- Supply up to 100 instruments to sites across Western Europe
- Service and Technical support for the instruments and assay kits
- Supply ~x,xxx tests between 2016 and 2020

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CEPHEID ANNOUNCES DIAGNOSTIC COLLABORATION WITH MEDIMMUNE AND COMBACTE TO FACILITATE CLINICAL TRIALS OF NEW MONOCLONAL ANTIBODIES TO PREVENT SERIOUS INFECTIOUS DISEASES

GeneXpert Systems and Xpert Tests Expected to Enhance Efficiency of Clinical Trials

SUNNYVALE, CALIF. — January 13, 2016 —Cepheid (Nasdaq: CPHD) today announced a collaboration with MedImmune, the global biologics research and development arm of AstraZeneca, and COMBACTE, a European public/private partnership set up to promote the development of new drugs in the anti-infectives field, to develop a series of rapid diagnostic tests to identify *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) in respiratory secretions of mechanically ventilated patients. These tests will be used to help identify patients for MedImmune's MEDI4893 and MEDI3902 clinical programs, which are being conducted within the COMBACTE consortium to explore the use of biologics in preventing ventilator associated pneumonia (VAP) infections in intensive-care-unit (ICU) patients.

More examples (not exhaustive!)

- Phase III RCT of minocycline in subjects with HABP/VABP caused by *Acinetobacter baumannii complex* (Medicines Company)
  - Diagnostic test needed: rapid detection of *A. baumanii* in ETA
- Phase III Randomized trial with S-649266 for the treatment of severe Infections caused by Carbapenem-resistant Gram-negative bacteria (Shionogi)
  - Diagnostic test needed: rapid detection of CR-organisms and/or Carbapenemase genes

Lessons learned on role of diagnostics

to aid patient enrollment in COMBACTE clinical trials with narrow-spectrum drugs (4/9 intervention trials)

Unclear function and performance characteristics	How will test be used? What are required performance characteristics to aid patient enrolment?
Schism between pharma and diagnostic companies	RAPP-ID: Pharma: rapid triage test targeting limited number of organisms in a specific sample Diagnostic companies: broad range tests
Unclear exploitation	How is the test developed into labeled product? Who will pay for the test?
Regulatory blind-spots	Potential regulatory needs discussed too late and/or conflicting feed-back
Demand of pharma to perform test outside of microbiology lab	Purchasing and logistical challenges Challenges to organise, track and train HCW Maintenance, Q-controls and test support Miscommunication between pharma, diagnostic company, micro lab, and CRO

Collection of materials at the Laboratory of Medical Microbiology of the University Antwerp from EU studies

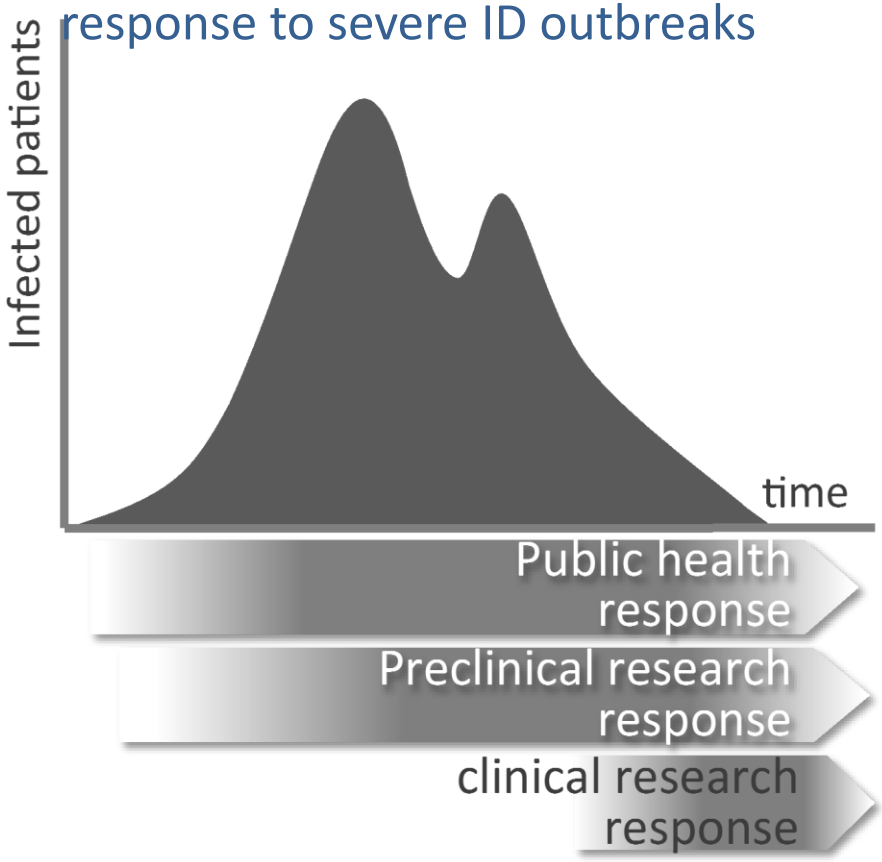
	At UA			ICF	Agreement on use after study
Studies	**Samples (not considering multiple aliquots)**	**DNA extracts**	**Strains**		
GRACE	13.305	9.199	784	yes	yes
MOSAR			12.222		
SATURN	5.273		27.539		
R-GNOSIS	6.218			some studies	
Kosovo study	1.711		1.466	no	
ASPIRE-ICU	37.400		1.500	Yes	Yes
ASPIRE-SSI	24.118		5.000	Yes	Yes
SAATELLITE	3.234		1.293	Yes	
ANTICIPATE	1.500			Yes	
EURECA			800	Yes	
EVADE	3.444		1.377	Yes	
Total	**57.318**	**9.199**	**45.501**		

Hundreds of thousands of individuals have freely donated samples in exchange for the promise of advancing medical research.
But most of these samples are …. sitting unused in lab freezers.

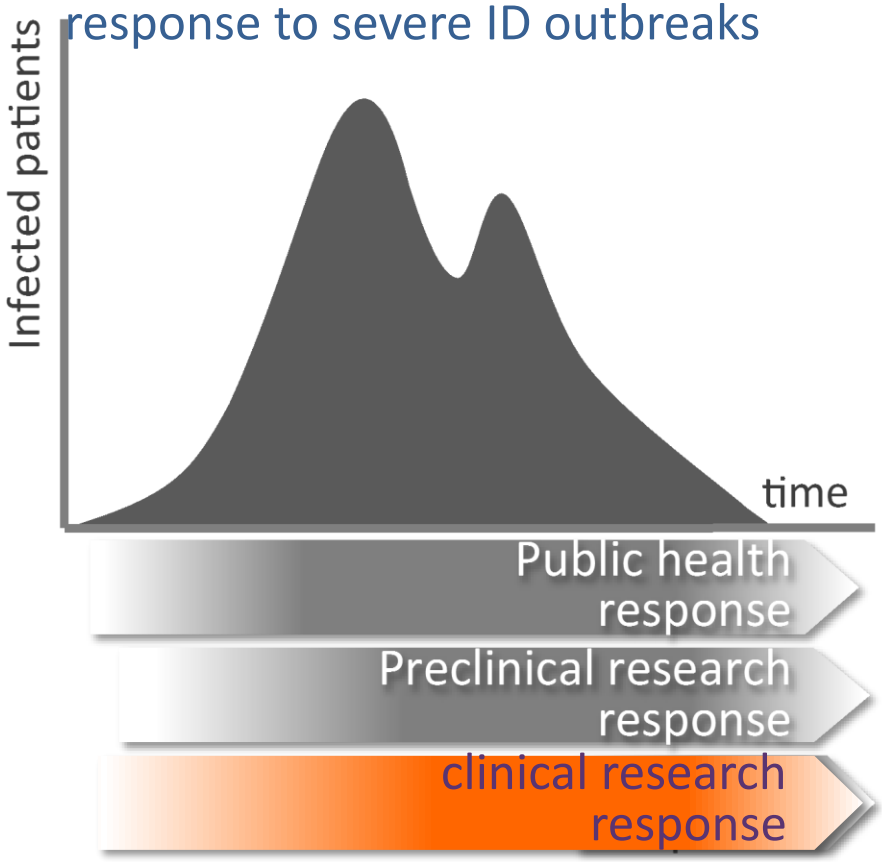
Pandemic disease research

Increasing the incentive to invest in clinical research response to severe ID outbreaks

Current situation: delayed, isolated and fragmented clinical research response to severe ID outbreaks



Future situation: rapid, integrated and harmonised clinical research response to severe ID outbreaks



Europe: Pandemic Preparedness

PREPARE Platform fo**R E**uropean **P**reparedness **A**gainst (**R**e-)emerging **E**pidemics

2014-2019

Partners:

Academia, clinical 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

Clinical trials 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**)

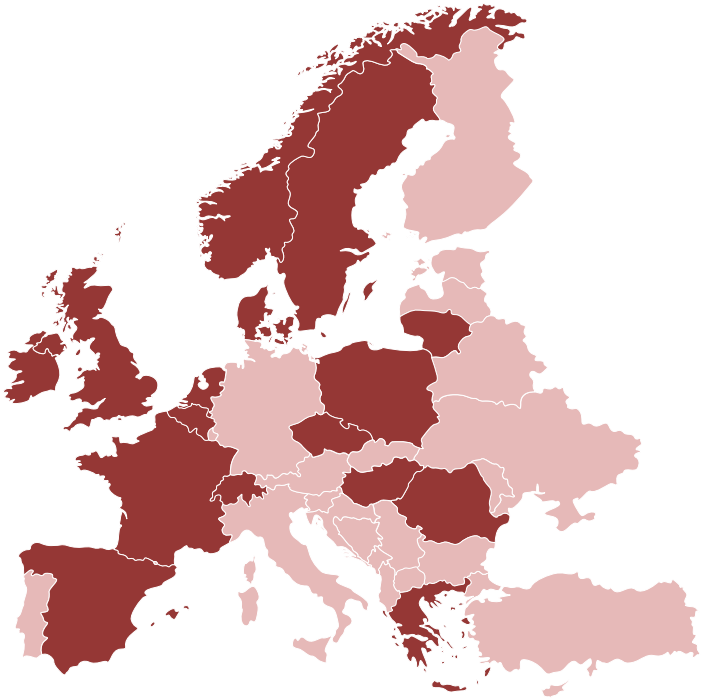
ALIC4E

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

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

Funded by the European Union

Primary Care Network



600 Primary care sites

19 European countries

>20 000 patients included in 16 countries in GRACE study

>1100 particpants in R-GNOSIS study

> 1700 participants in PREPARE ALIC⁴E study

Funded by the European Union

ECRAID:

European Clinical Research Alliance on Infectious Diseases

= a paradigm shift of Clinical Research on Infectious Diseases in Europe, build on AMR and pandemic disease research

ECRAID build on COMBACTE and PREPARE

Antimicrobial resistance

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

Need for operational high quality large-scale clinical trial research infrastructure with European coverage

Similar non-scientific barriers

Overlapping stakeholders

Emerging Infectious Diseases

- Rapid initiation and completion of clinical studies;
- Mostly virus infections

Public sector support: Kobé Communique

G7 Health Ministers' Meeting
11-12 September 2016

References: 1) Shiozaki et al. Lancet. 2016;388 (10051):1262-3. 2) Kobe Communiqué by G7 Kobe Health Ministers' Meeting. Sep 11-12, 2016.

"we encourage governments to consider the need for establishing a global clinical studies network on drug resistance that provides access to a large clinical research infrastructure for the design, coordination and conducting of clinical trials and studies in cooperation with the existing global experts networks to ensure the common benefit of the outcomes"

Private sector support: Industry Roadmap for Progress on Combating Antimicrobial Resistance

20 September 2016

"… we commit to:
*Support the creation of open and **sustainable clinical trial networks globally**, with our expertise and experience. As proposed by the AMR Review, this would build on work started in Europe and US with the goal of improving the speed and efficiency of conducting clinical trials"*

Reference: Industry Roadmap for Progress on Combating Antimicrobial Resistance. Sep 20, 2016

ECRAID Working Group

Coordination Team

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Coordinator PREPARE

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University of Tuebingen

Our purpose and vision

Our purpose is to reduce the impact of infectious diseases on individual and population health.

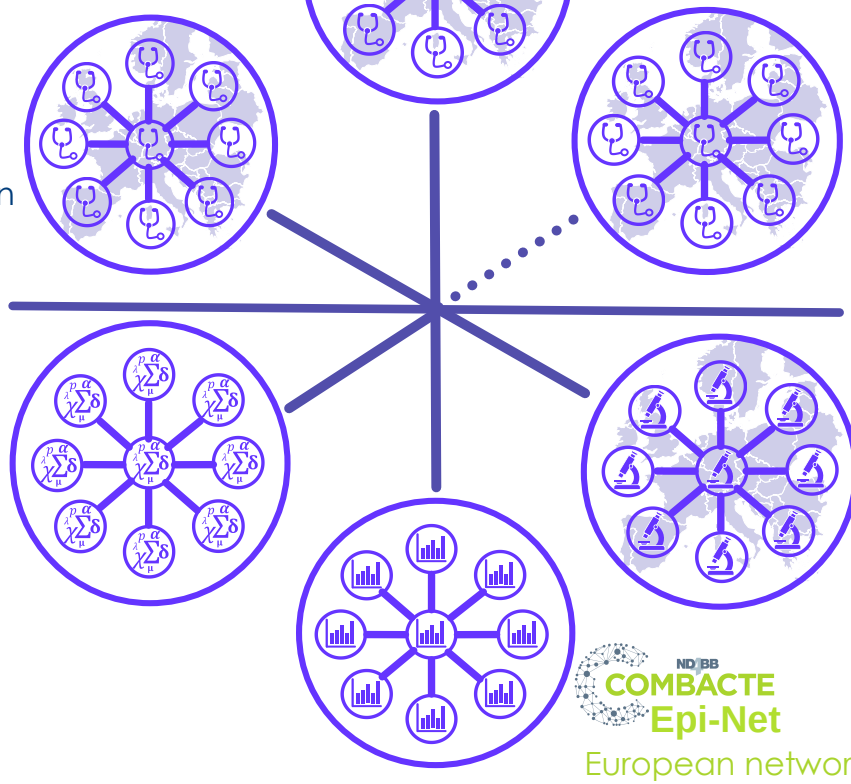
Our vision is to efficiently generate rigorous evidence for new or improved diagnosis, prevention and treatment of infections and to better respond to infectious disease threats. This is facilitated by a European multidisciplinary clinical research network and innovative research approaches.

ECRAID: added value

Building on EU consortia COMBACTE and PREPARE, ECRAID is:

- A multidisciplinary network of dedicated experts in medical microbiology and infectious disease
- An active European clinical trial research network
  - Continuously running multiple indication based master-protocol driven trials with:
    - Experienced and trained research staff
    - Capacity to efficiently add new study arms
    - Access to the right patient populations and research groups
    - Efficient and high quality data collection
  - Capacity and capability to run additional trials
- Linked to global initiatives

Inclusive, multidisciplinary network



ND BB COMBACTE Clin-Net

827 hospitals in 42 European countries.

600 Primary care sites in 19 European countries

Network of 90 paediatric clinical sites in 18 countries

ND BB COMBACTE Stat-Net

European network of experts in statistical research on IDs

ND BB COMBACTE Lab-Net

583 microbiology labs in 42 European countries

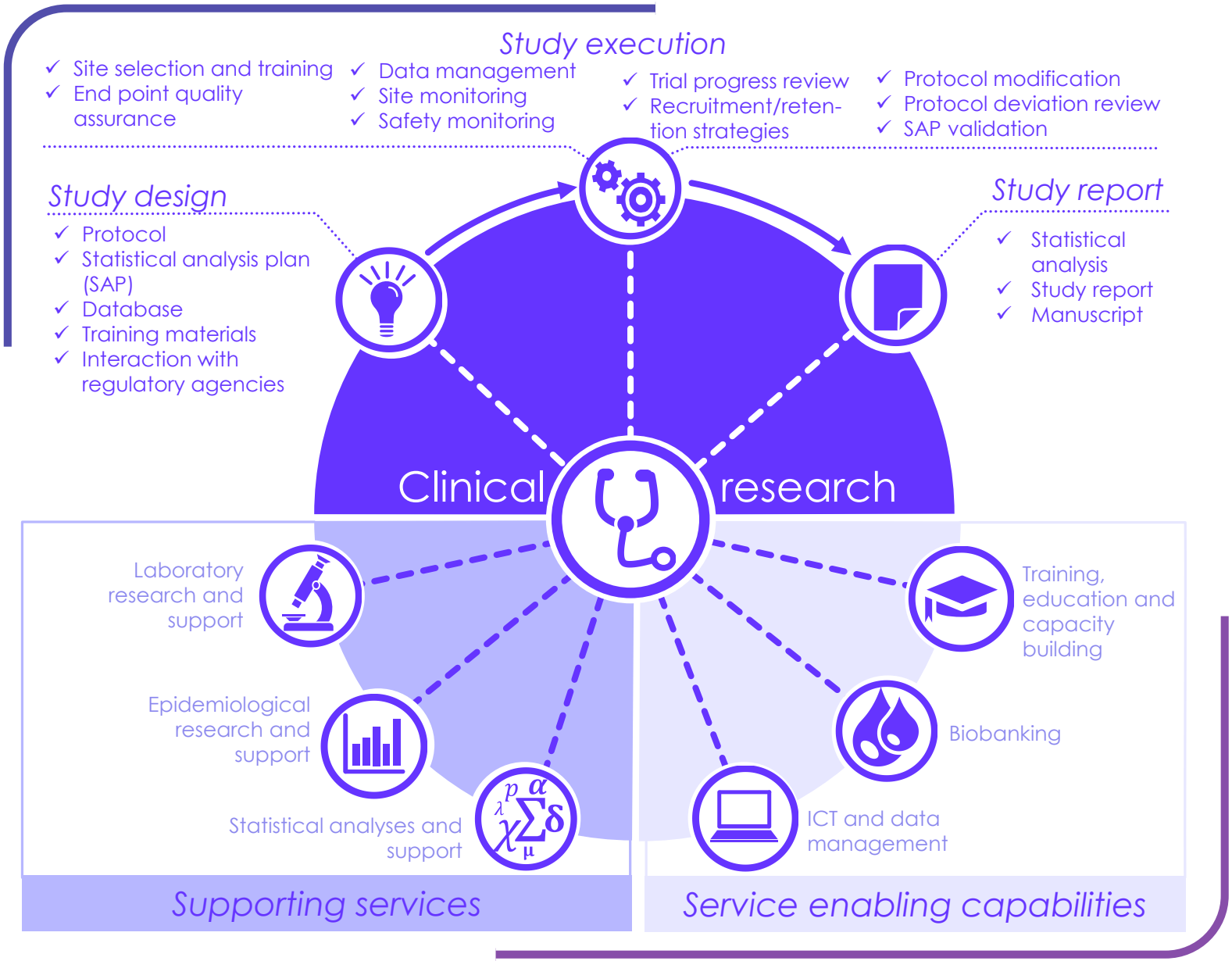
ND BB COMBACTE Epi-Net

European network of experts in epidemiological research on IDs

Our stakeholders

- Patients
- Private sector industry
- Universities and research organisations
- Primary, secondary, tertiary clinical care sites
- Government org's, health authorities and funding organisations
- Regulatory bodies
- NGOs
- Scientific societies
- International networks

Our services



Clinical research

Phases: Phase I - IV

Scope: Prospective and retrospective

Source: industry-driven and investigator driven

Pathogens: viruses, bacteria, protozoa

Interventions: vaccines, diagnostics, therapeutics, medical devices, routine care, etc.

Objectives: Prevention, treatment, diagnosis, screening, quality of life, health economic evaluation, epidemiological, etc.

Types: randomized controlled trials, observational (analytical and descriptive), database, perpetual, platform trials, etc.

What ECRAID could offer

- Clinical Trial Network for infectious diseases in hospital care and primary care
- European coverage and globally embedded
- Faster and easier clinical research
- As a single-point of access into a high quality, business oriented research network
- Rapid access to and knowledge of well trained clinical (hospital/primary care) and laboratory (specialized and routine) sites
- An active network, continuously including patients in platform trials
- Focus on services that alleviate the administrative, technical and organizational burden in clinical research and reduce timelines (lower costs, faster processes)
- Strong practice based scientific expertise and commitment

AMR Clinical Trial Network - Public Private Partnership

- Provides unique opportunities:
  - Incentive for pharma to invest in antibiotic discovery
  - Allows to broaden the spectrum to other antimicrobial drugs, vaccines, diagnostic tests
  - Allows investigator driven trials
  - Allows new models of clinical trials (e.g. Adaptive Platform Trials)
  - Creates innovation of the public and private (e.g. SMEs) sector
  - Results in improving quality of care delivery to our patients
  - Allows rapid clinical research response in the event of a pandemic threat
  - Reduces pressure on public sector budgets
  - Results in increased jobs for our European citizens
- Should develop rigorous performance criteria in terms of the interest of the European citizen and pharma (e.g. delivery on-time and on budget of clinical trials)
- Make transparent the economic, political, public health and tax payers returns on IMI-ND4BB investments
- Clinical trial research investments must reach EU citizens

WORLD VIEW *A personal take on events*

Shout about the European Union's success

As people in other nations watch the UK prepare to sever ties, **Herman Goossens** *urges more scientists to stress what the EU does for them.*

Herman Goossens *is professor of medical microbiology at the University of Antwerp and University Hospital Antwerp, Belgium.*
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MILLIONS OF EUROPEANS ARE QUESTIONING WHAT THE EUROPEAN UNION DOES FOR THEM.