The added value of Treatment Optimization: How does it apply to other fields of medicine?

A case study from the respiratory field

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ERS The added value of treatment optimisation in NCDs

1. *The problem*:
   a gap between pre-approval development of medicines and their post-approval (suboptimal) use in real-life in clinical practice

2. *The solution*:
   patient-centered applied clinical research - treatment optimisation studies - to inform and optimise clinical practice (guidelines)

ERS The added value of treatment optimisation in NCDs

3. *The opportunity*:

European Health Union; EU4Health; European Health Data Space;

Pharmaceutical Strategy; European Medicines Agency (EMA)

Innovative Health Initiative (IHI) / Innovative Medicines Initiative (IMI)

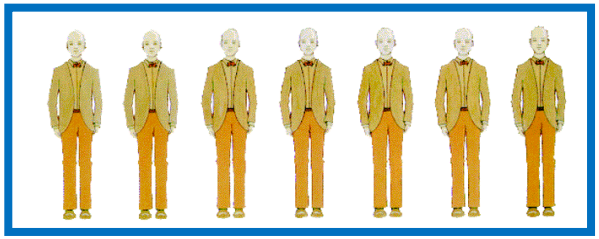
→ EU coordinating international, treatment optimisation studies to investigate the real life effectiveness and safety of drugs and other treatments in patients with NCDs in the EU

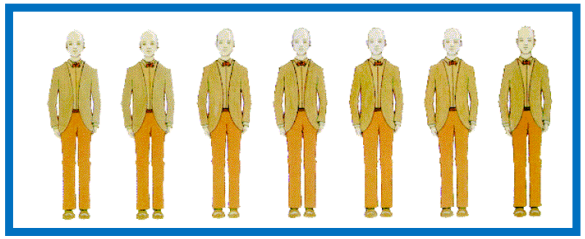
→ Optimal use of medicines and non-pharmacological treatments for patients and health systems.

NCDs: Non-Communicable Diseases

1. THE PROBLEM: A GAP BETWEEN DRUG DEVELOPMENT AND CLINICAL PRACTICE

Drug development:

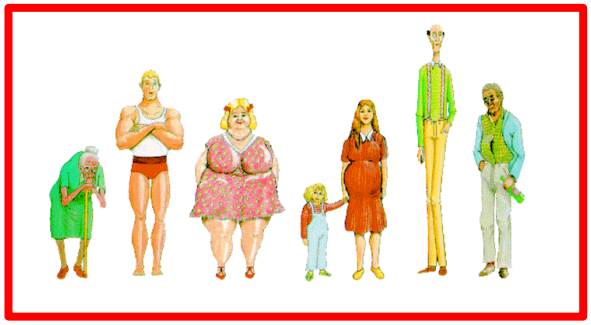


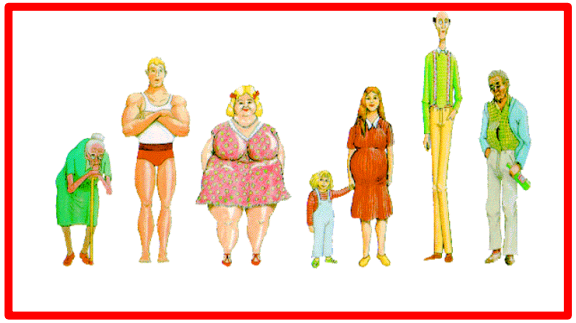


Drug development clinical studies (classical RCT)

→ Efficacy and short-term safety: *drug versus placebo drug development trials (drug-centered research)*

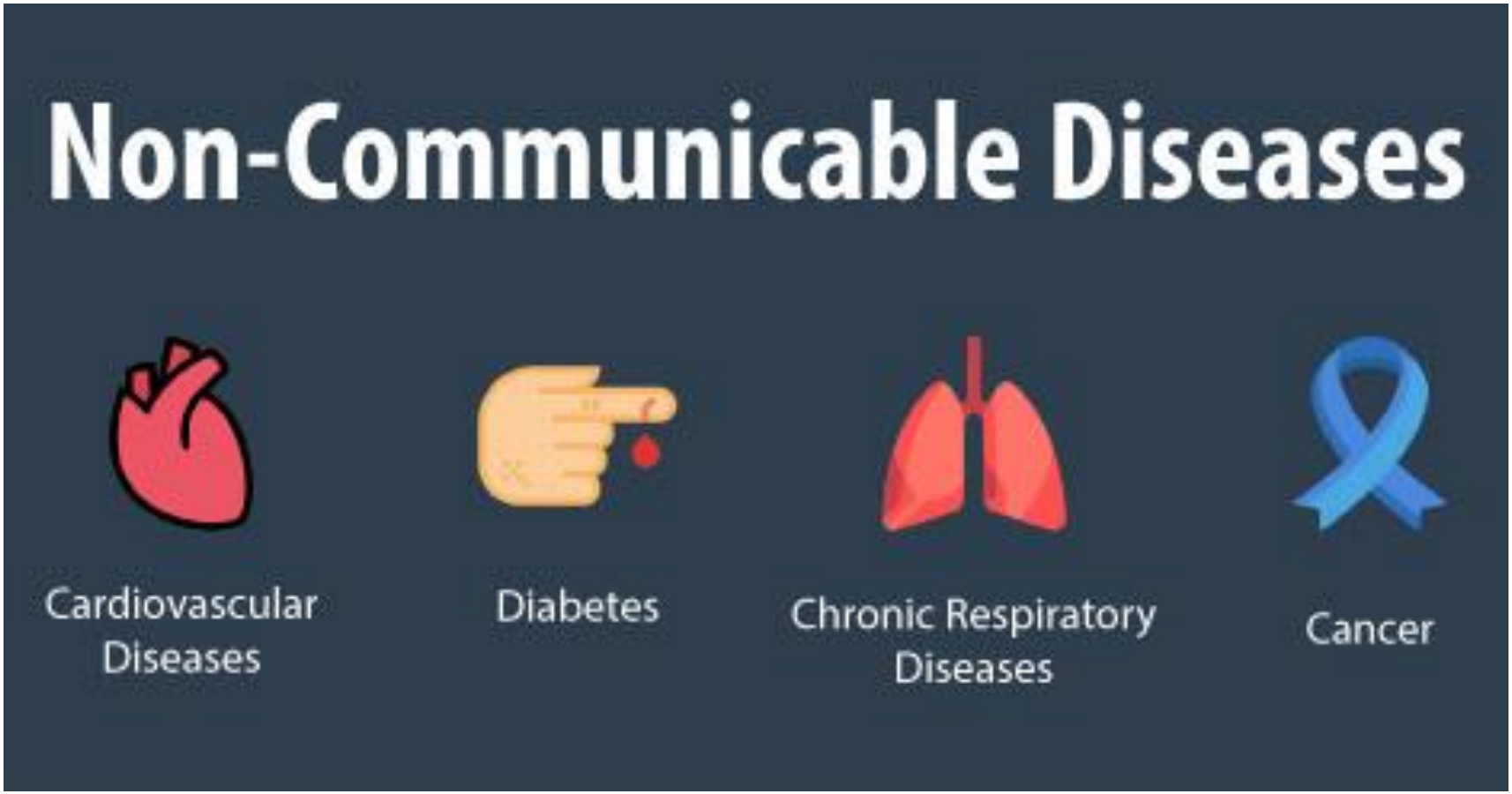
Clinical Practice:





Real life clinical studies (pragmatic RCT)

→ Effectiveness and long-term safety: *drug versus active treatment applied clinical research (patient-centered research)*



- **Heart failure**
- **Hypertension**
- **Myocardial infarction**
- **Obesity**
- **Stroke**

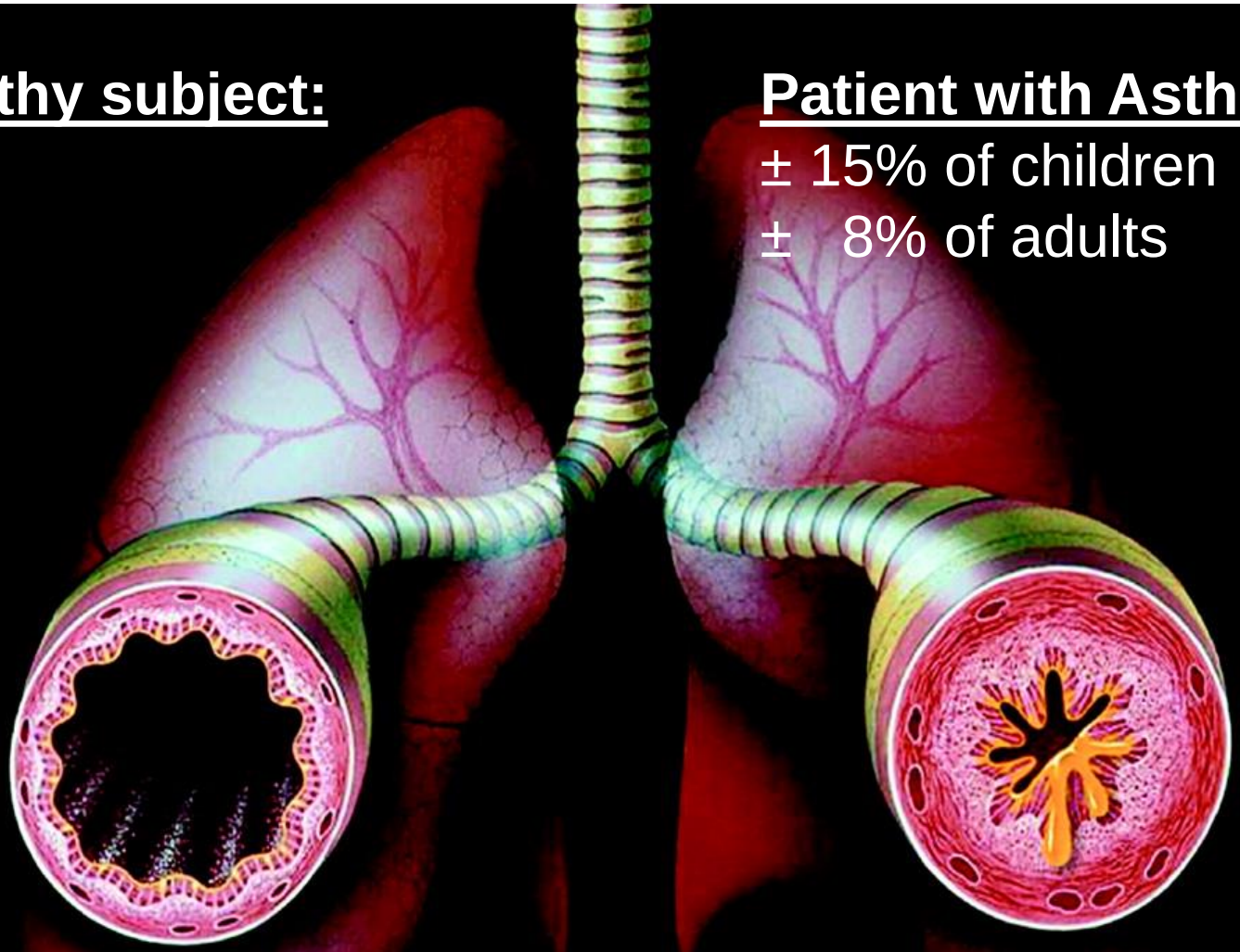
- **Allergy**
- **Asthma**
- **COPD**
- **Lung fibrosis**
- **Sleep apnea**

Healthy subject:

Patient with Asthma:

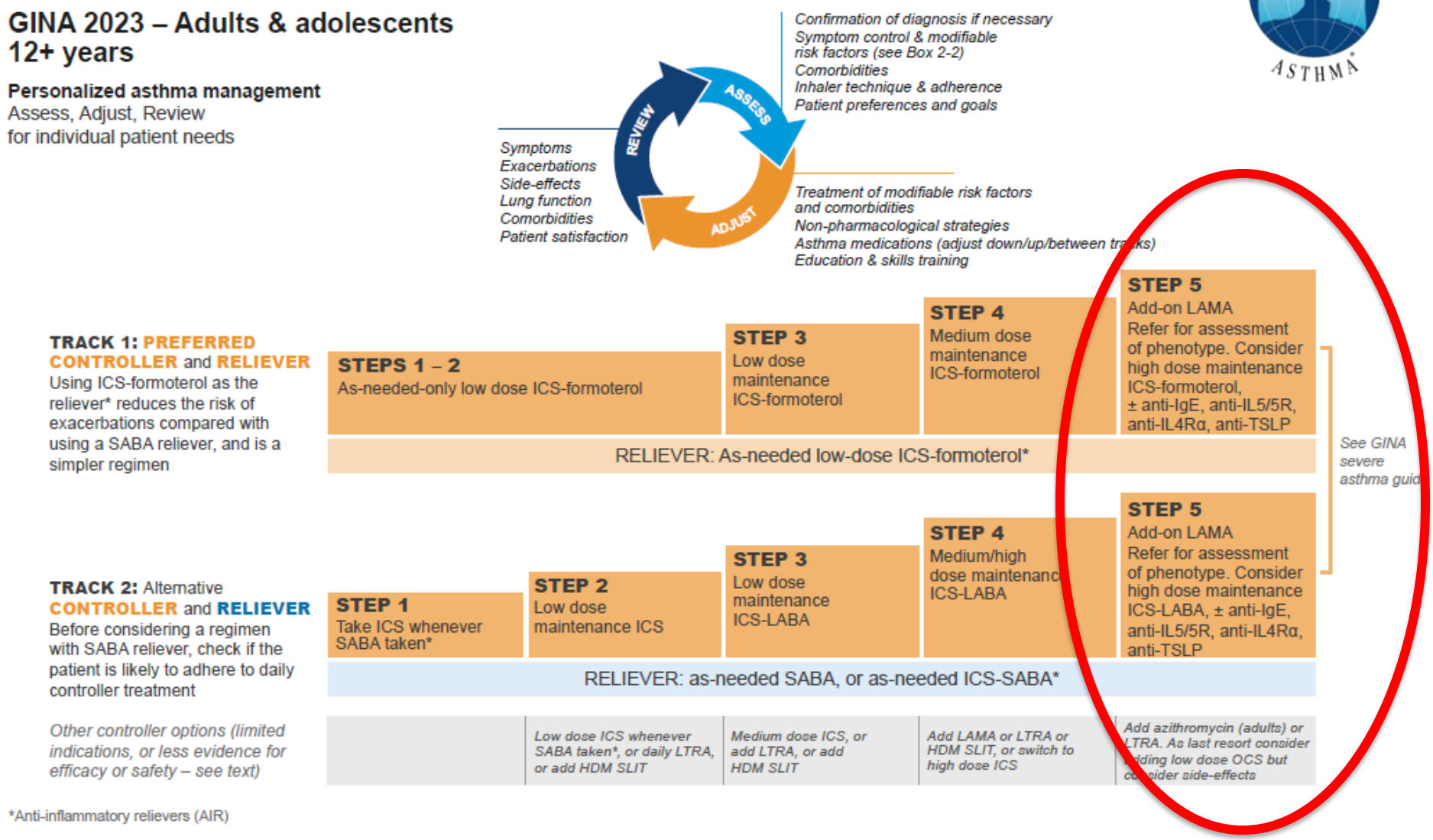
± 15% of children

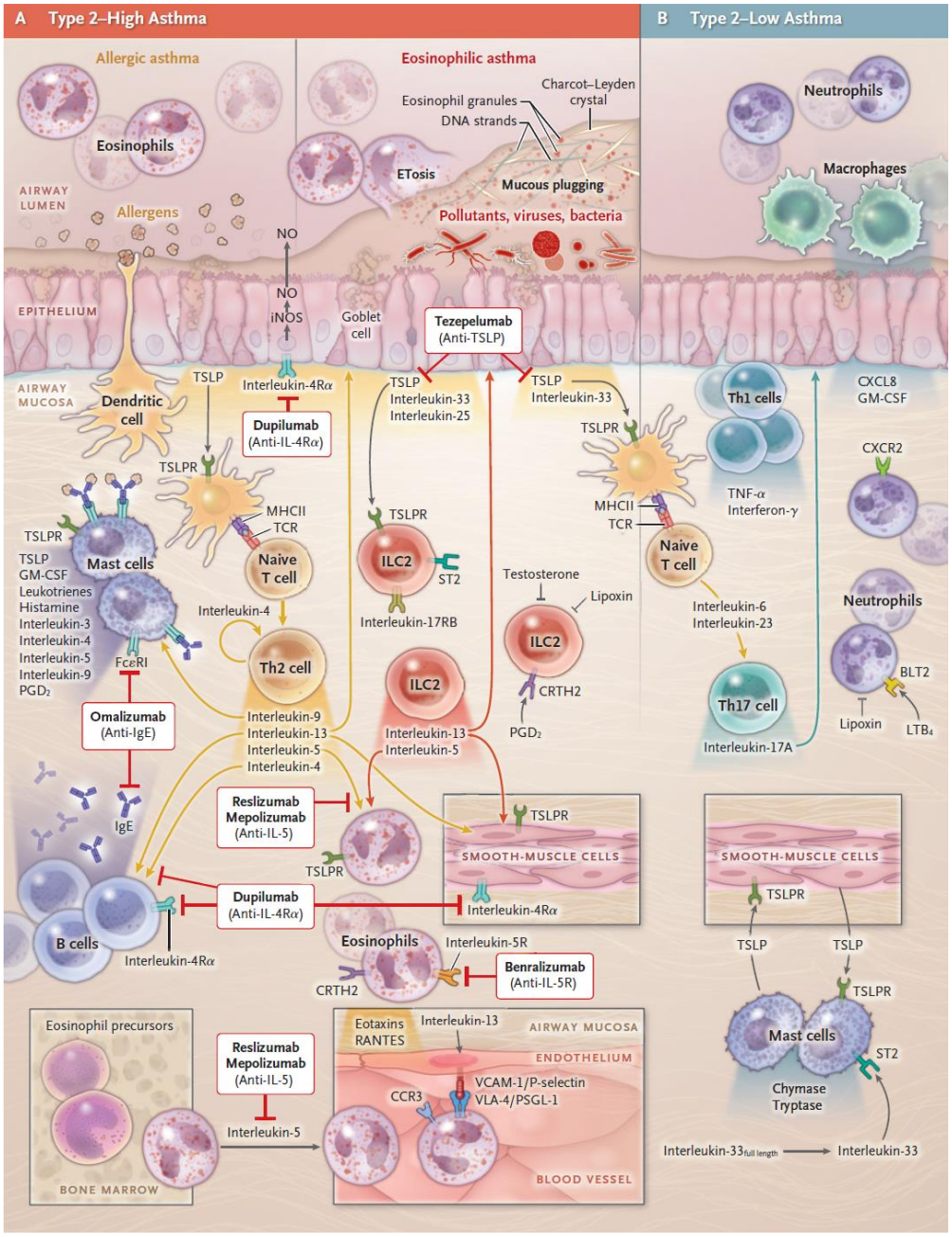
± 8% of adults



Asthma attacks can be life-threatening,
requiring emergency department visits and hospitalizations.

GINA 2023: Management of asthma





BIOLOGIC THERAPIES FOR SEVERE ASTHMA

Anti-IgE: omalizumab (Xolair);

Anti-IL5/anti-IL5R:

mepolizumab (Nucala)

reslizumab (Cinqaero) IV

benralizumab (Fasenra);

Anti-IL4R: dupilumab (Dupixent);

Anti-TSLP: tezepelumab (Tezspire)

SC injections (syringe or pen)

G. Brusselle and G. Koppelman,
New England Journal of Medicine 2022.

The gap between drug development and clinical practice

EMA-approved drugs for the treatment of severe asthma:

Biologic	Trade name	Therapeutic target	Route and Dosing	Indication
Benralizumab	Fasenra	IL-5 Receptor α (IL-5Rα)	SC 30 mg every 4 to 8 weeks	Severe eosinophilic asthma
Dupilumab	Dupixent	IL-4 Receptor α (IL-4Rα)	SC 200 mg every 2 weeks	Severe type 2 asthma
Mepolizumab	Nucala	Interleukin-5 (IL-5)	SC 100 mg every 4 weeks	Severe eosinophilic asthma
Omalizumab	Xolair	Immunoglobulin E (IgE)	SC every 2 or 4 weeks	Severe allergic asthma
Reslizumab	Cinqaero	Interleukin-5 (IL-5)	IV 3mg/kg every 4 weeks	Severe eosinophilic asthma
Tezepelumab	Tezspire	TSLP	SC 210 mg every 4 weeks	Severe asthma

For optimal use in clinical practice, crucial information is lacking:

Which drug is best for each unique individual patient?

No head-to-head comparisons!

Are there biomarkers which can predict the therapeutic response?

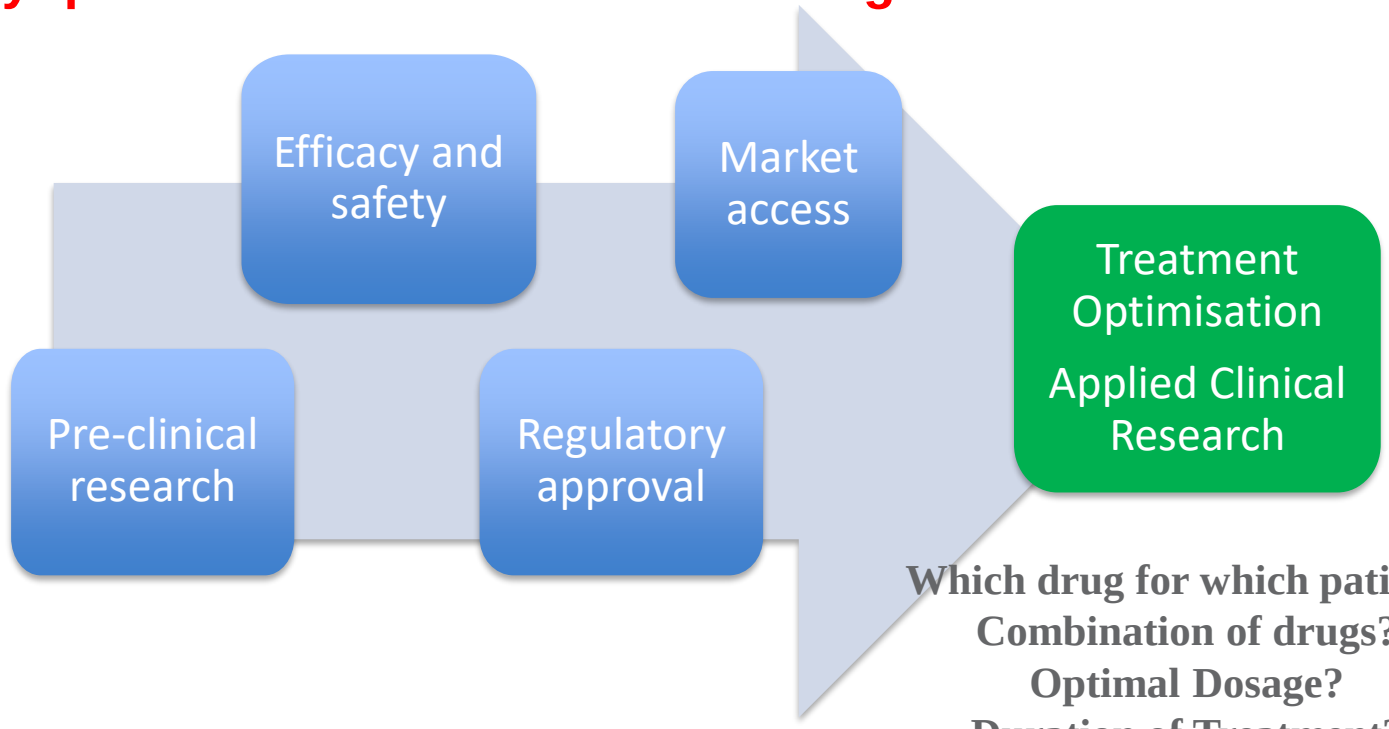
Real-life effectiveness and safety? e.g. in specific populations?

How long do we need to treat?

Asthma as an example for Non-Communicable Diseases (NCDs)

STEPS OF DRUG DEVELOPMENT AND OPTIMAL USE

Many questions do remain when a drug reaches the market



Which drug for which patient?
Combination of drugs?
Optimal Dosage?
Duration of Treatment?
Predictive biomarkers?
Specific populations?
Children, pregnant women, elderly …

ERS The added value of treatment optimisation in NCDs

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   patient-centered applied clinical research - treatment optimisation studies - to inform and optimise clinical practice (guidelines)

Moving forward from drug-centred to patient-centred research

A white paper initiated by EORTC and developed together with the BioMed Alliance members

Denis Lacombe[1], Colm O'Morain[2], Barbara Casadei[3], Kate Hill[4], Elsa Mateus[5], Rik Lories[6] and Guy Brusselle[7]

Affiliations: [1]Director General, European Organisation for Research and Treatment of Cancer. [2]Past President, Alliance for Biomedical Research in Europe and United European Gastroenterology. [3]President, European Society of Cardiology. [4]Chair of the ELF Patient Advisory Committee, European Lung Foundation. [5]EULAR/PARE representative, Patient Research Partner. [6]EULAR representative to BioMed Alliance, European League Against Rheumatism. [7]Chair of the ERS Science Council, European Respiratory Society.

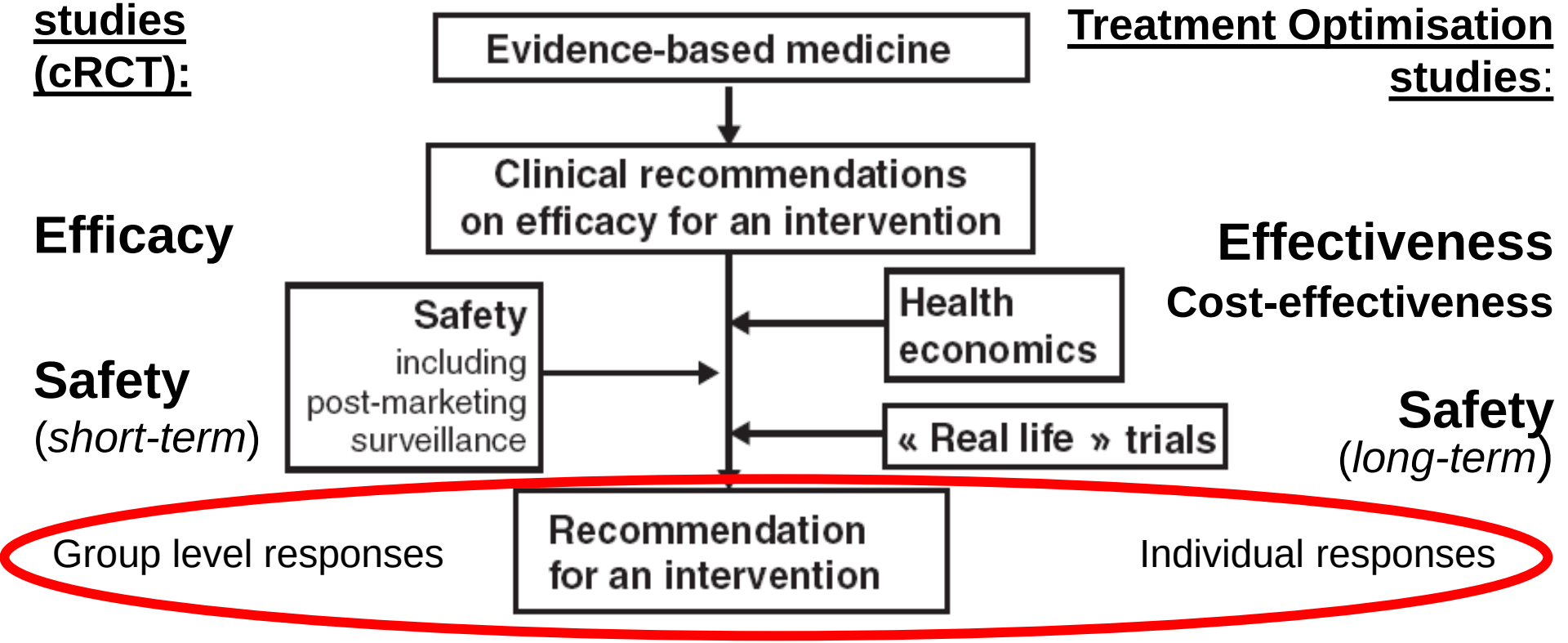
Correspondence: Denis Lacombe, Director General, European Organisation for Research and Treatment of Cancer, Avenue Mounier 83/11, Brussels, 1200, Belgium. E-mail: denis.lacombe@eortc.org

D. Lacombe et al, ERJ 2019.

DEVELOPING CLINICAL PRACTICE GUIDELINES

Drug-centered research: Phase 2 and 3 interventional studies (cRCT):

Patient-centered research: Phase 4 interventional (pRCT) and observational Treatment Optimisation studies:



Regulatory approval **Clinical Practice Guidance**

cRCT: classical Randomized Controlled Trials
pRCT: pragmatic Randomized Controlled Trials

UZ GENT

ERS The added value of treatment optimisation in NCDs

3. *The opportunity*:

European Health Union; EU4Health

European Health Data Space;

European Medicines Agency (EMA): extended mandate

EU Pharmaceutical Strategy: the full lifecycle of a medicine

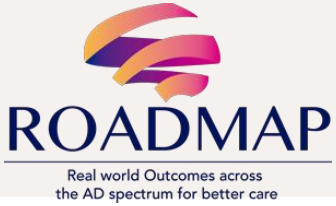
Innovative Health Initiative (IHI; IMI)

INNOVATIVE HEALTH INITIATIVE

Disease-oriented IHI / IMI projects and consortia:

Common needs:

- **Ethical, Legal, Regulatory issues**
- **IT, eCRF, Data(base) governance**
- ***Biobanking, Omics, Systems biology***
- ***Imaging, AI***



innovative health initiative

INNOVATIVE HEALTH INITIATIVE

Methods- and tools-oriented IHI / IMI projects and consortia:

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Common needs of IHI are permanent:

- **Ethical, Legal, Regulatory issues**
- **IT, eCRF, Data(base) governance**

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Big Data for Better Outcomes

EMIF

FAIRplus

conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

Methods- and tools-oriented global community:

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

european respiratory society every breath counts

as public by the Euro

THE **D**ATA **A**NALYSIS AND **R**EAL **W**ORLD **I**NTERROGATION **N**ETWORK OF THE **E**UROPEAN **U**NION **(DARWIN EU®)**

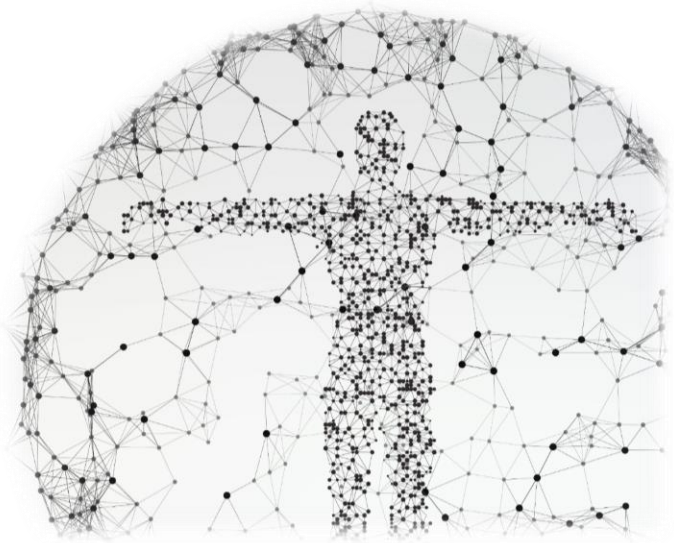
Generating Real-World Evidence (RWE) from Real-World Data (RWD):

Real-World Data (RWD): routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials

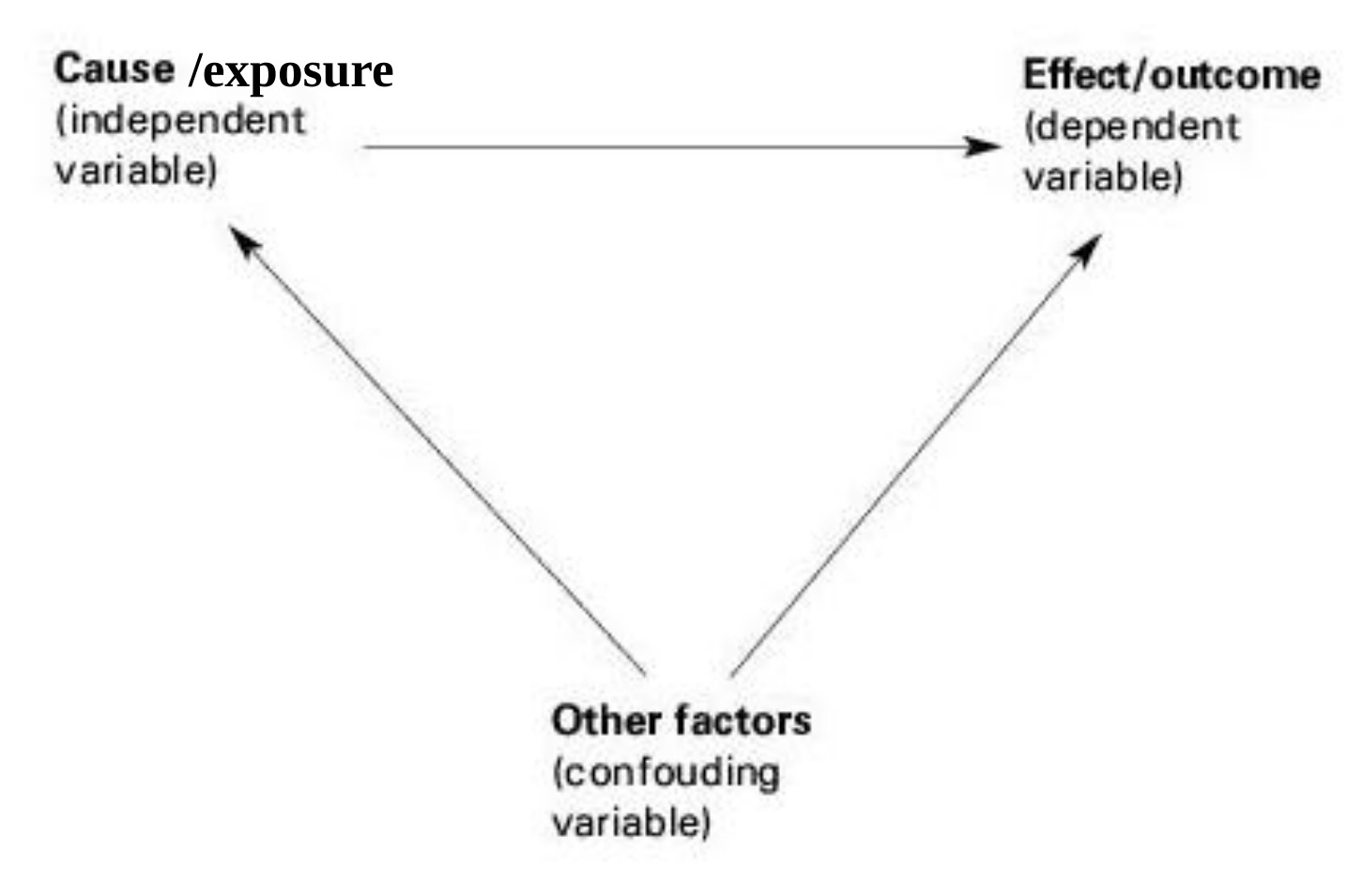
Real-World Evidence (RWE): information derived from analysis of real-world data

Regulatory Real-World Evidence (RWE) needs to be:

- Fast and transparent
- Representative (of EU regions)
- Reproducible, replicable, and robust



CONFOUNDING (BIAS)



CONFOUNDING VARIABLES

- ***Prerandomization* confounding variables**

  R/ Randomization:

  Randomization eliminates confounding by baseline variables.

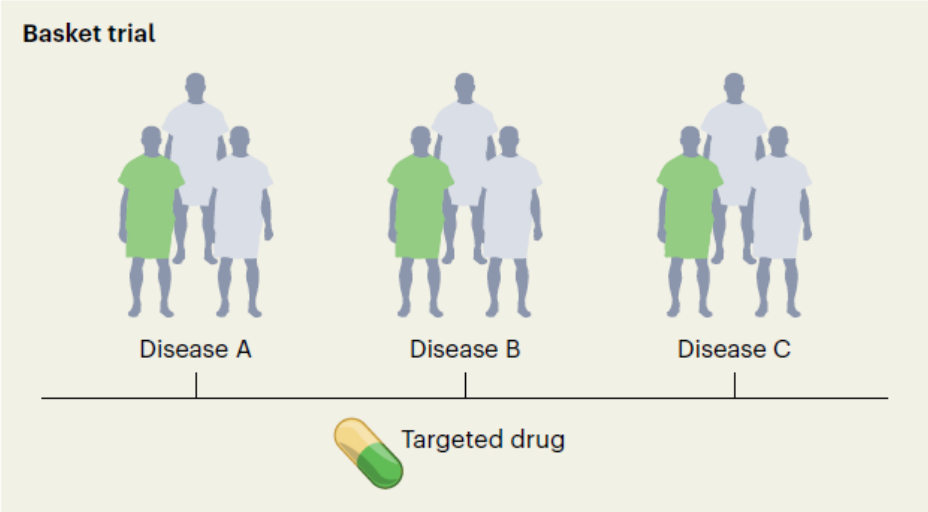
- *Postrandomization* confounding variables

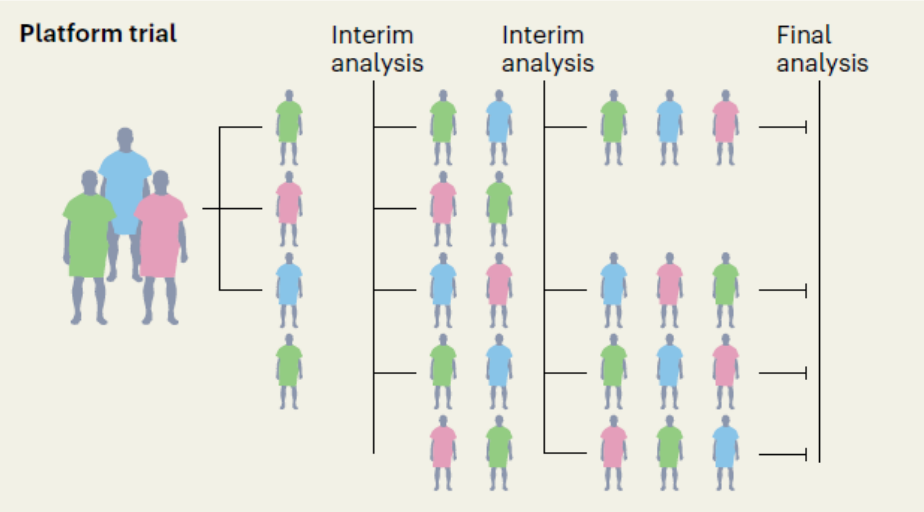
  (e.g. unintended interventions; biased assessment of outcomes)

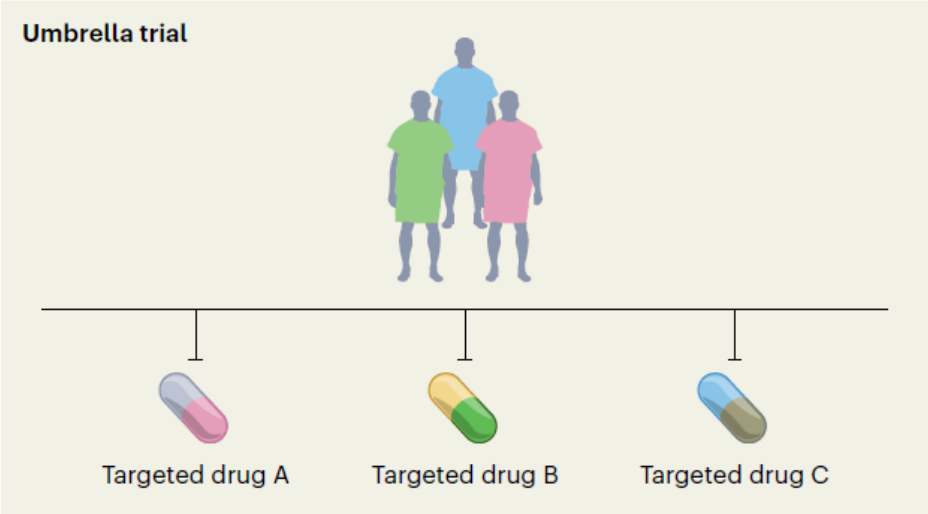
  R/ Blinding:

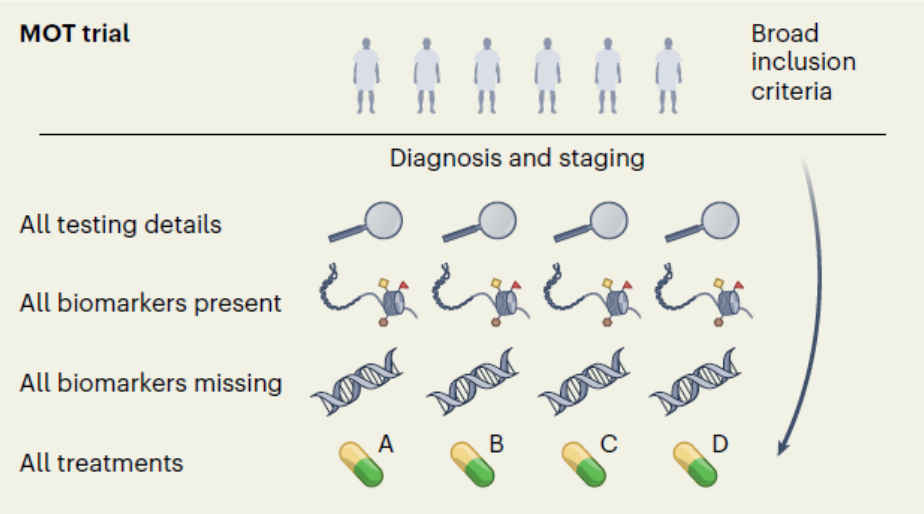
  Blinding eliminates confounding by co-interventions and minimizes the risk of a biased assessment of outcomes.

PLATFORM TRIALS AND MASTER PROTOCOLS



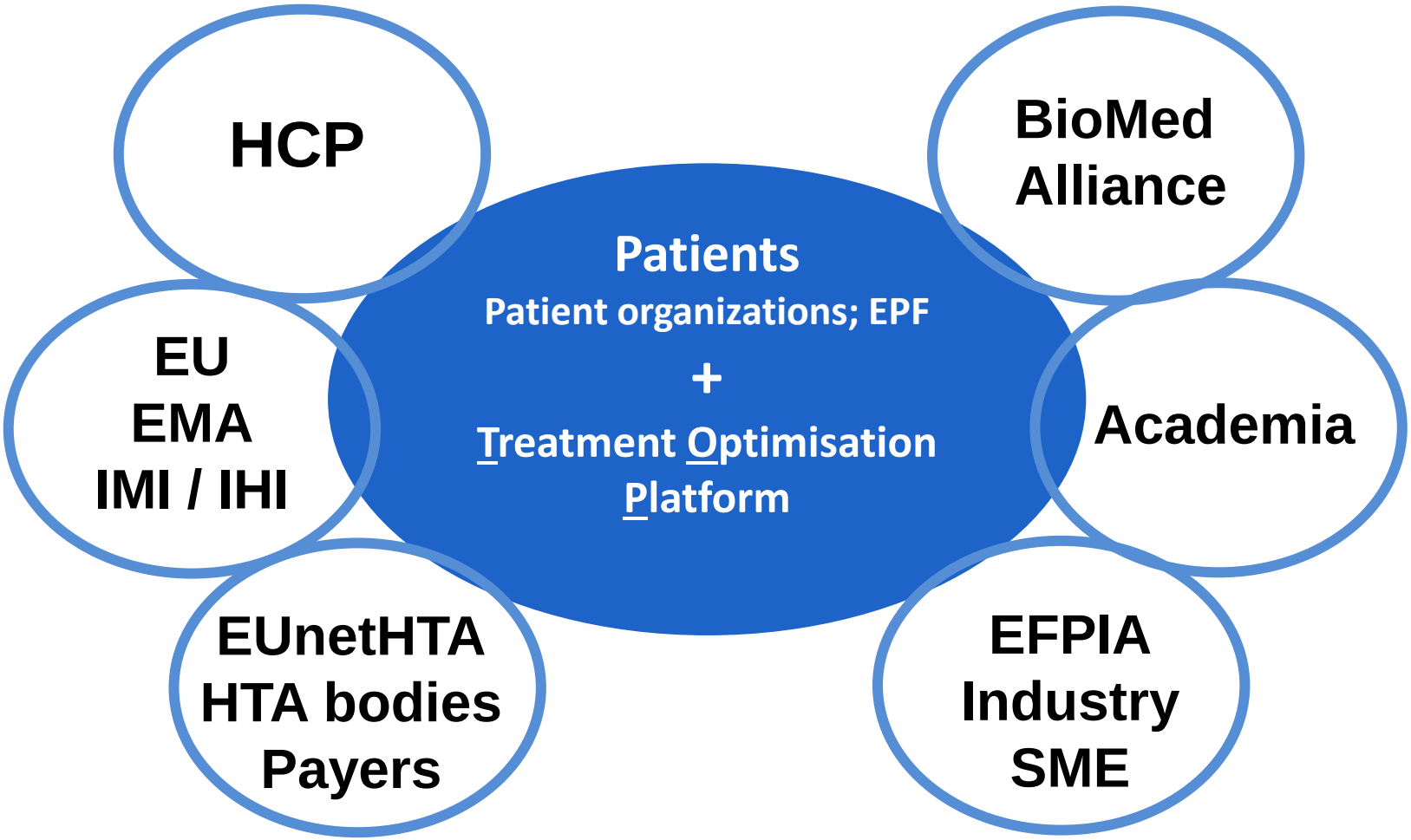






Vivek Subbiah. Nature Medicine 2023.

Treatment Optimisation Platform (TOP) coordinating patient-centered clinical trials in NCDs in EU



EFPIA: European Federation of Pharmaceutical Industries and Associations;
EMA: European Medicines Agency; EPF: European Patients Forum; EU: European Union;
HCP: Health Care Professionals; HTA: Health Technology Assessment; NCDs: Non-Communicable Diseases
SME: Small and Medium sized Enterprises

European Commission

A European Health Union: Tackling health crises together

13 NOVEMBER 2020

THE ROLE OF EU AGENCIES

European Medicines Agency (EMA)

Evaluating and monitoring the safety of medicines

CURRENT MANDATE	FUTURE MANDATE
Monitoring the safety of medicines	• **Monitoring and mitigating shortages** of medicines and medical devices caused by major events
Evaluating the safety of medicines	• Offering **advice on medicines** which may treat, prevent or diagnose a disease causing an outbreak
	• Coordinating studies to monitor the **effectiveness and safety** of vaccines and drugs
	• Coordinating and advising on **clinical trials** of medicines in communicable and NCD

NCD: non-communicable diseases

European Commission

A European Health Union: A Pharmaceutical Strategy for Europe

25 NOVEMBER 2020

The strategy covers the full lifecycle of a medicine

A EUROPEAN HEALTH UNION:
A PHARMACEUTICAL STRATEGY FOR EUROPE

WHAT WE INTEND TO ADDRESS:	HOW WE INTEND TO DO IT:
Unmet needs	• **Research and innovation** for new treatments, vaccines and antibiotics • Align **clinical trials** to patient and health system needs • Coordinate patient-centered applied clinical research within EU (**Treatment Optimisation Platform**)
Access to affordable medicines	• EU level cooperation on **pricing** and **reimbursement policies** • More **competition** from generic and biosimilar medicines • Promotion of **health technology assessment**

TOP: **T**reatment **O**ptimisation **P**latform

The added value of treatment optimisation in NCDs

1. *The problem*: a gap between pre-approval development of medicines and their post-approval (*suboptimal*) use in real-life in clinical practice.
2. *The solution*: patient-centered applied clinical research (i.e. **T**reatment **O**ptimisation studies) to inform and optimise clinical practice (guidelines).
3. *The opportunity*:

Establishing a permanent EU **T**reatment **O**ptimisation **P**latform (**TOP**)

→ Coordinating international, Treatment Optimisation studies (e.g. adaptive, pragmatic, platform RCTs) to evaluate the real-life effectiveness and safety of drugs and non-pharmacological treatments in patients with NCDs in the EU;

→ *Optimal, personalised and precise* use of medicines and other treatments for patients and health systems in the EU and globally.

NCD: Non-Communicable Diseases