WECAN SmartStart in Cancer Patient Advocacy

WECAN MASTERCLASS in Cancer Patient Advocacy

How drug development works, and key elements of a clinical trial protocol

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EUPATI / WECAN / Leukemia Patient Advocates Foundation / Patvocates

What I will cover

- How does medicines development work
  – from Phase I to Phase IV
- Why does patient involvement in clinical research make sense?
- What are the key elements of a clinical trial and trial protocol?
- Where to find additional info (on EUPATI)?

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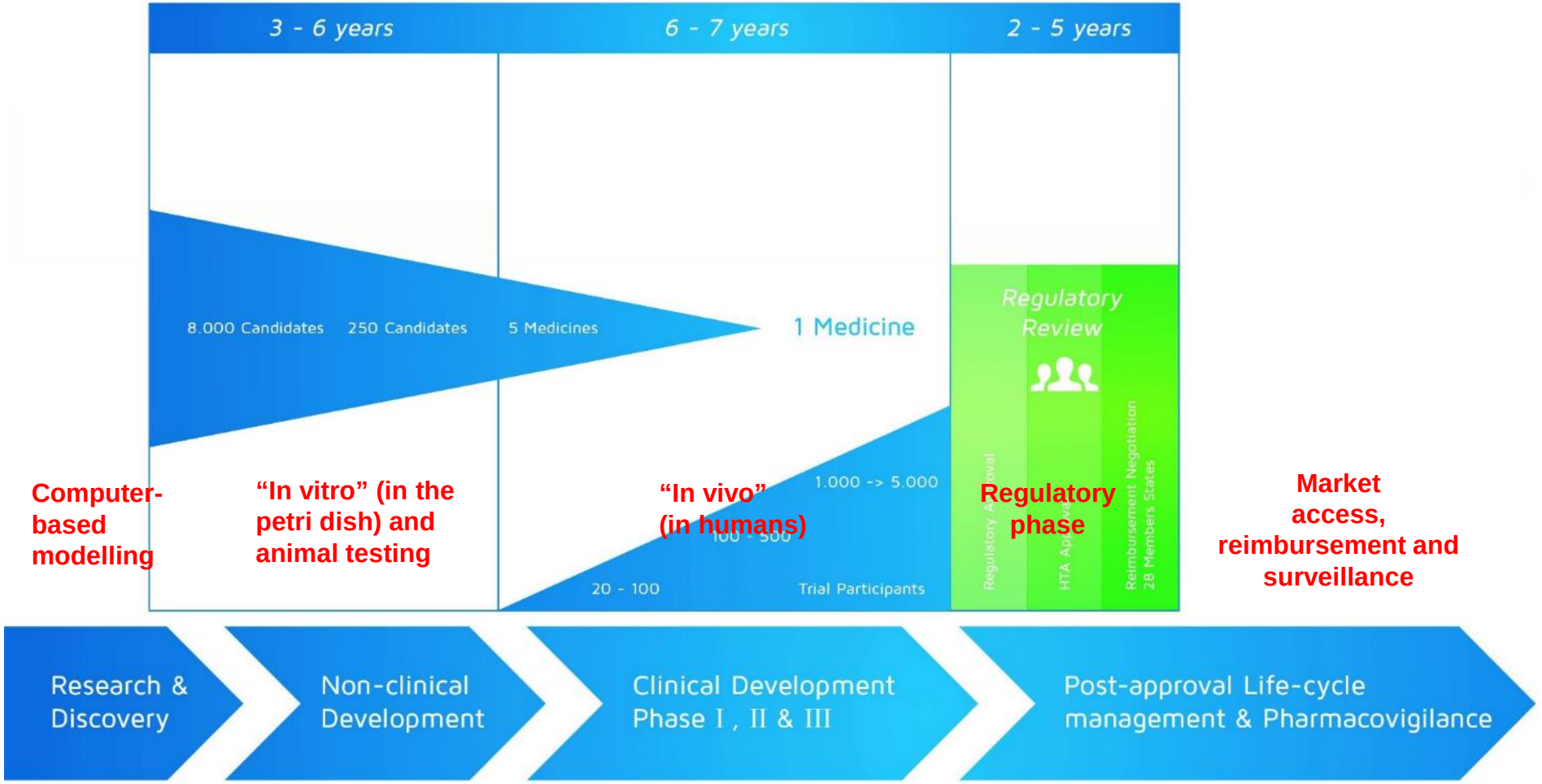
How does drug development work?

Phases of R&D

- It takes over 12 years and on average costs between €400 million and €1.5 billion before a new medicine can be made available to patients and reimbursement starts
- Only about 2% of substances evaluated in early research make it to the market as new medicines

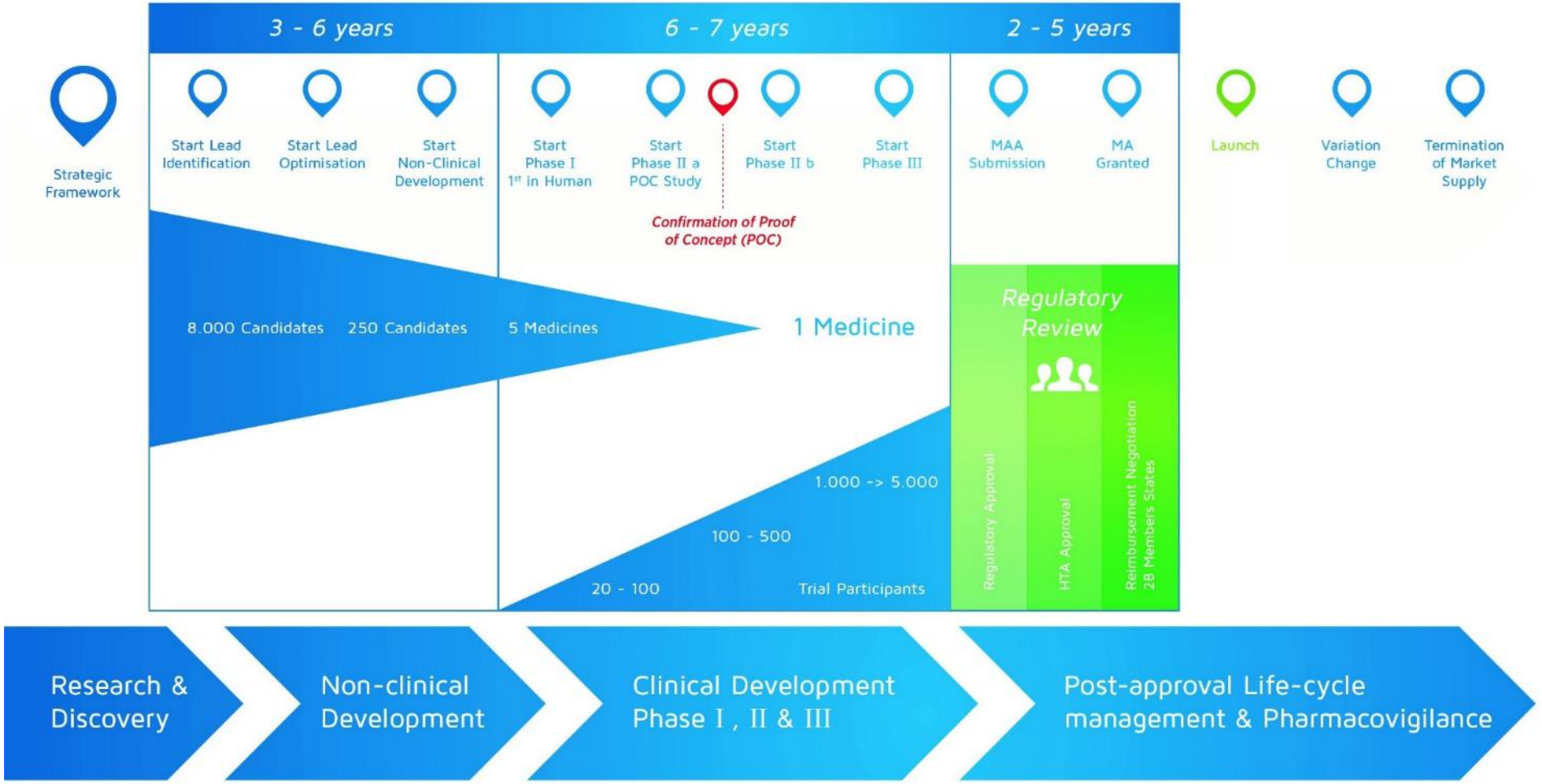
Source: EUPATI.eu

Of 8,000 molecules, only 5 ever get into human clinical trials, and only 1 makes it to market



Source: EUPATI.eu

Dosing, safety and efficacy are tested in phases in an increasing number of patients



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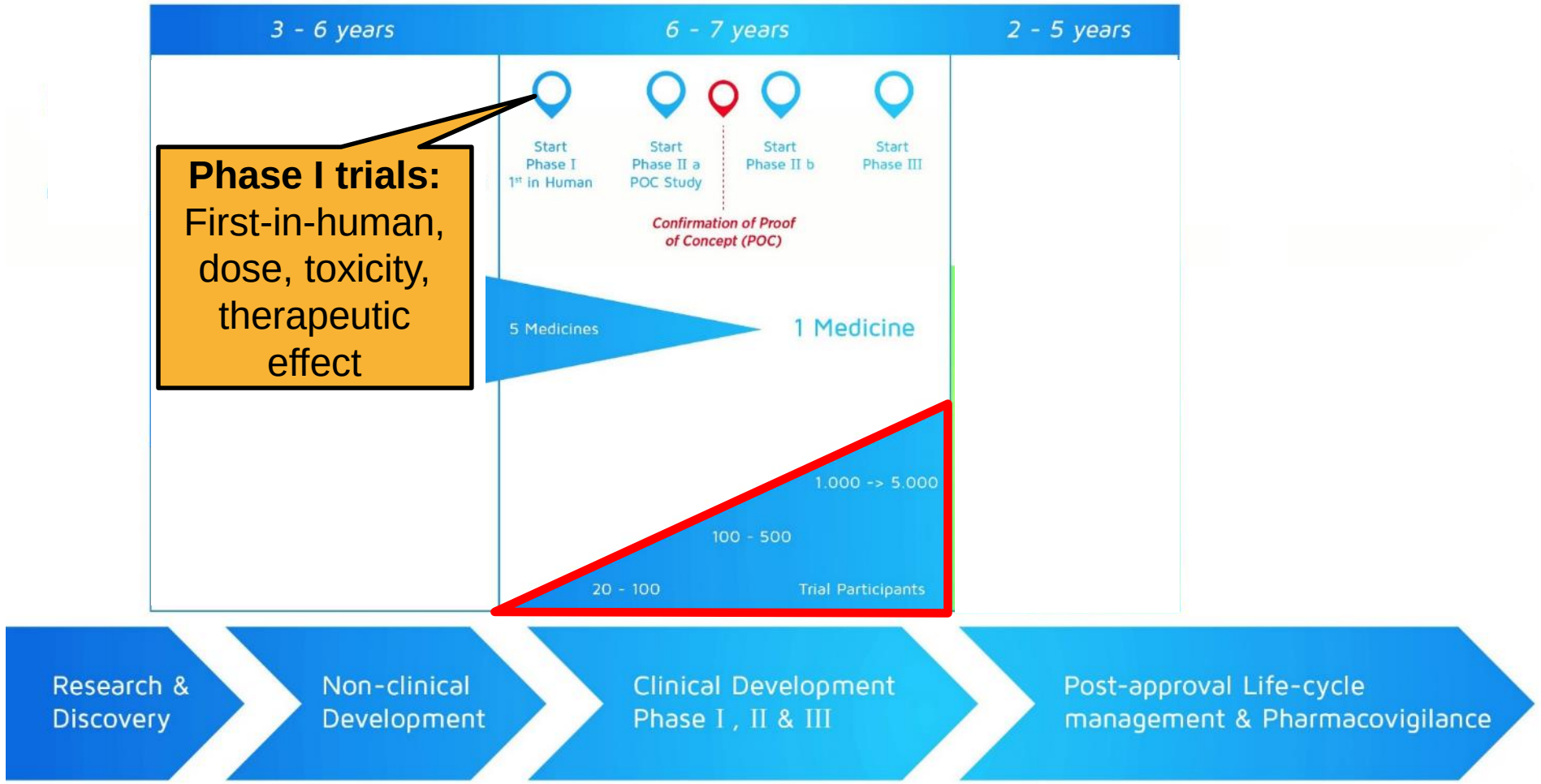

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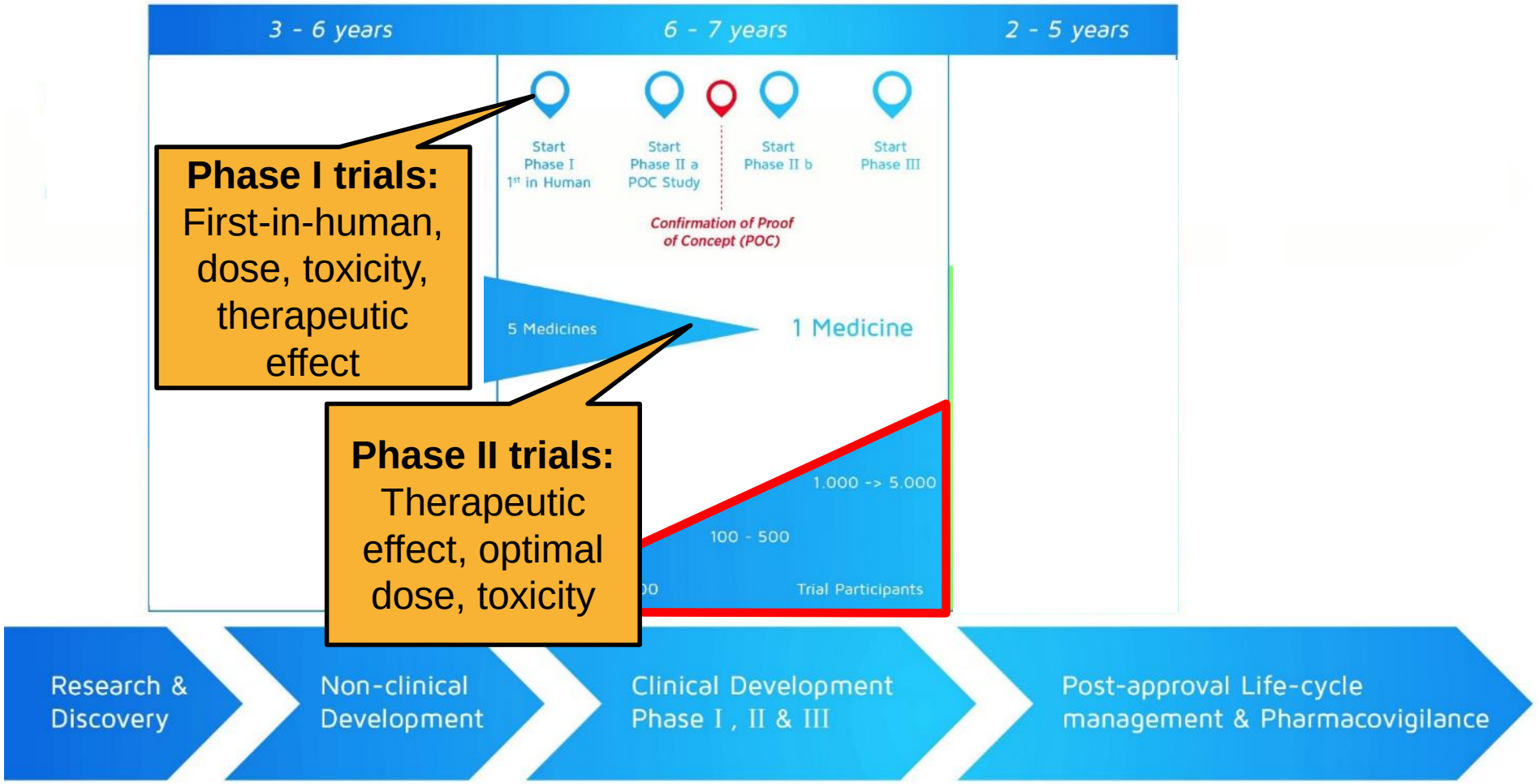

Source: EUPATI.eu

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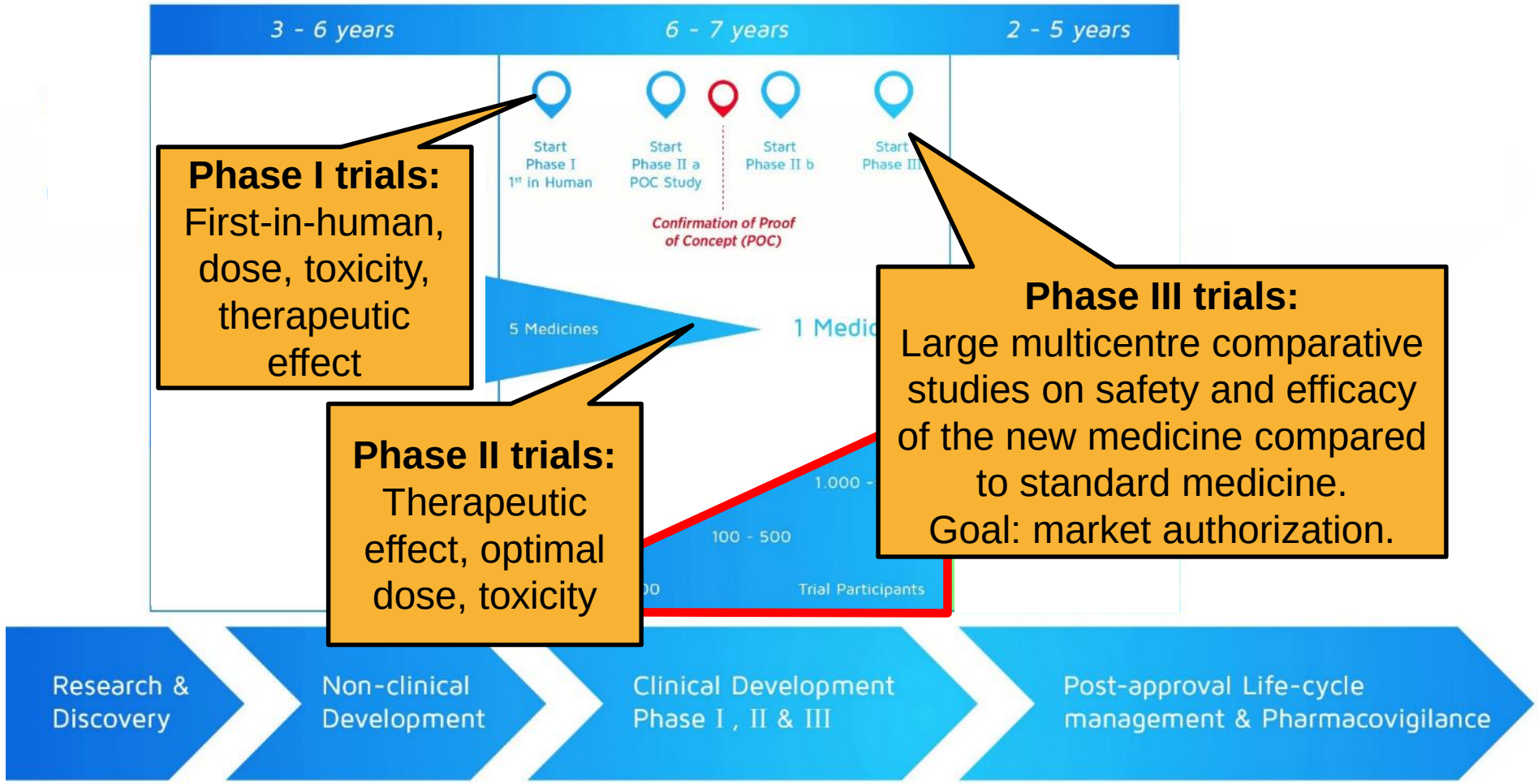


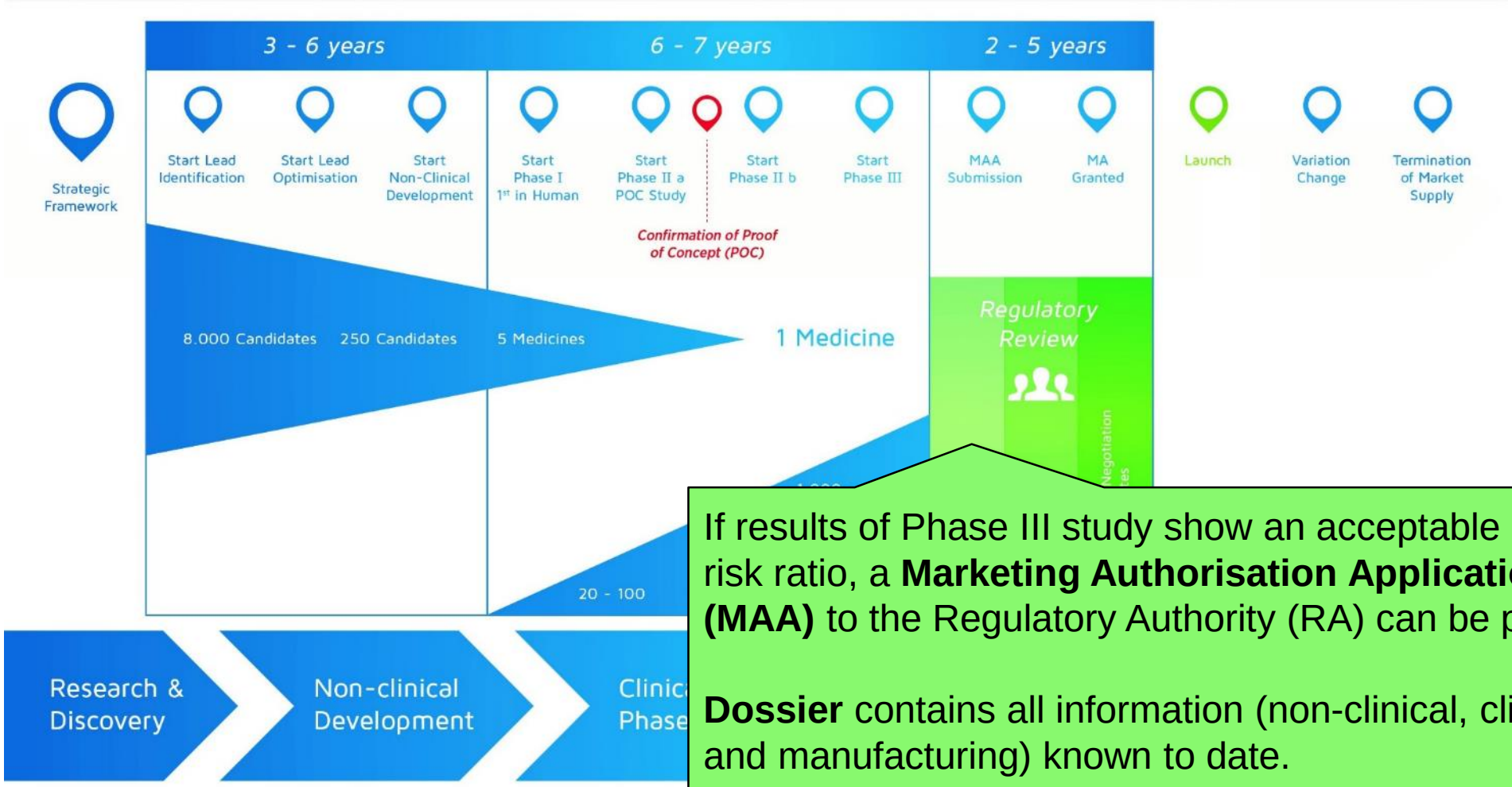
Phase I trials: First-in-human, dose, toxicity, therapeutic effect

Phase II trials: Therapeutic effect, optimal dose, toxicity

Phase III trials: Large multicentre comparative studies on safety and efficacy of the new medicine compared to standard medicine. Goal: market authorization.

Source: EUPATI.eu

Regulatory review towards marketing authorization



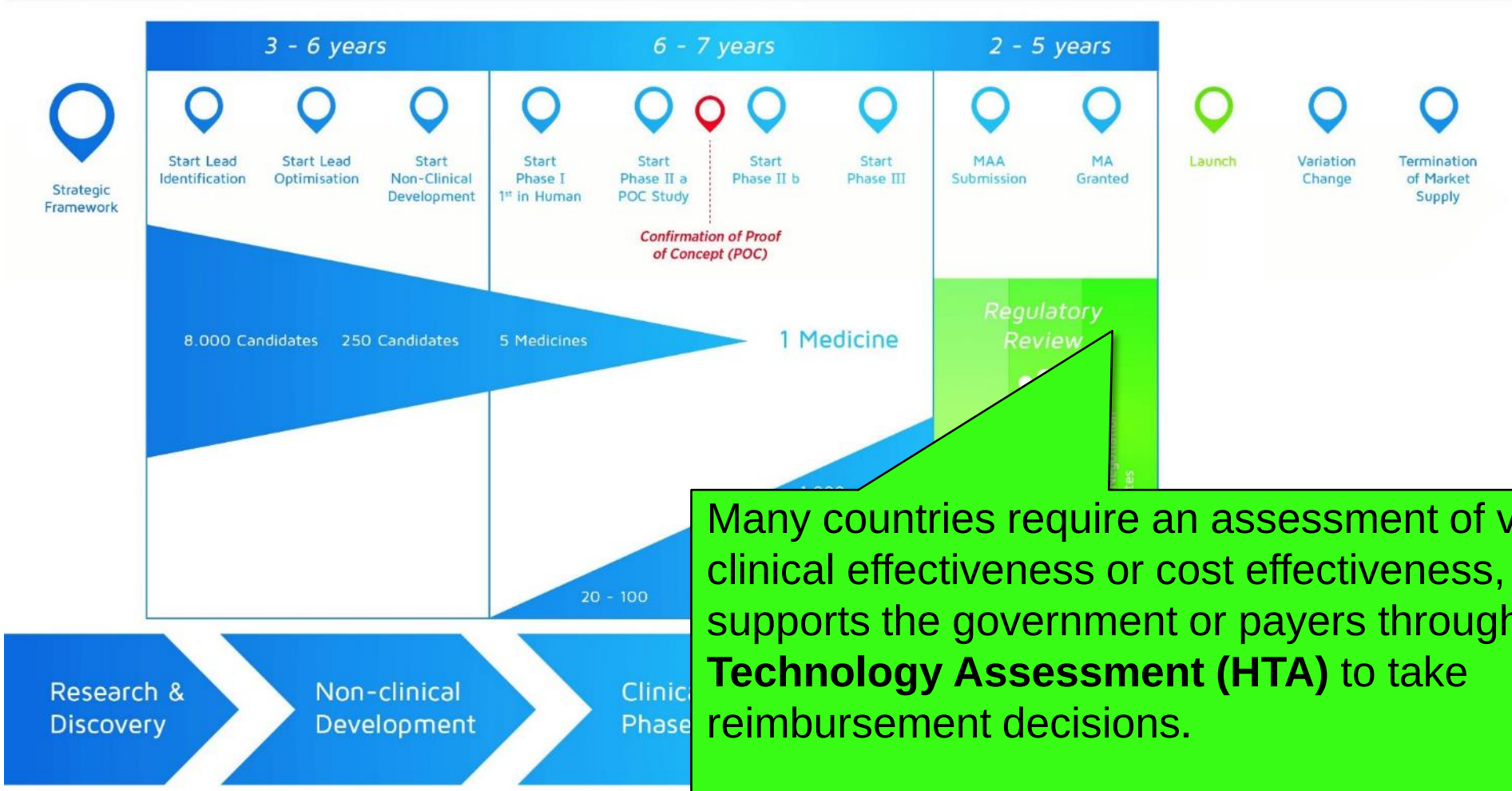
If results of Phase III study show an acceptable benefit-risk ratio, a **Marketing Authorisation Application (MAA)** to the Regulatory Authority (RA) can be prepared.

Dossier contains all information (non-clinical, clinical, and manufacturing) known to date.

The review process usually takes 12-18 months.

Source: EUPATI.eu

Decisions on reimbursement and patient access

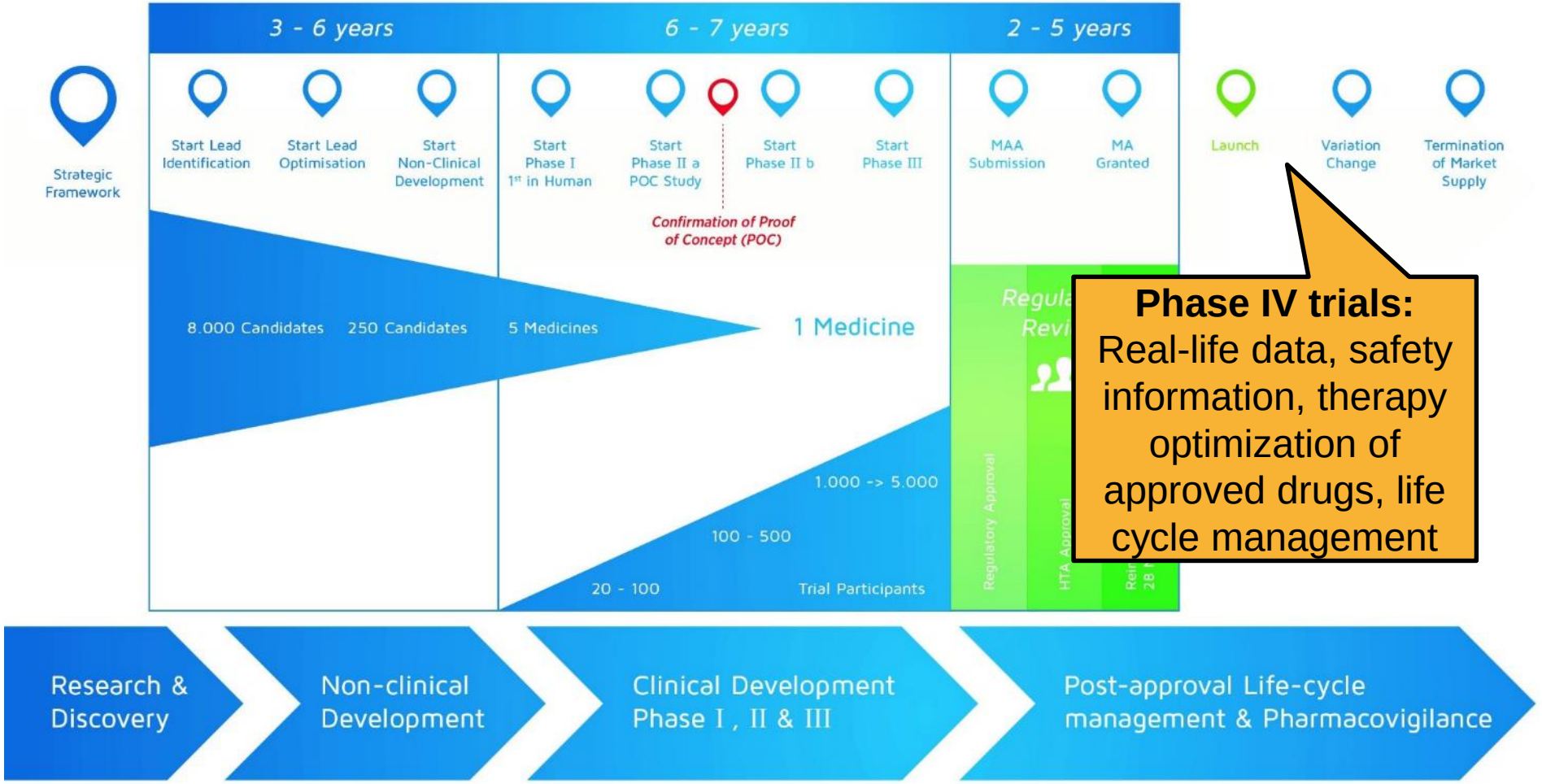


Many countries require an assessment of value, clinical effectiveness or cost effectiveness, which supports the government or payers through **Health Technology Assessment (HTA)** to take reimbursement decisions.

Reimbursement decisions / HTA are the remit of Member States. The EU has no influence.

Source: EUPATI.eu

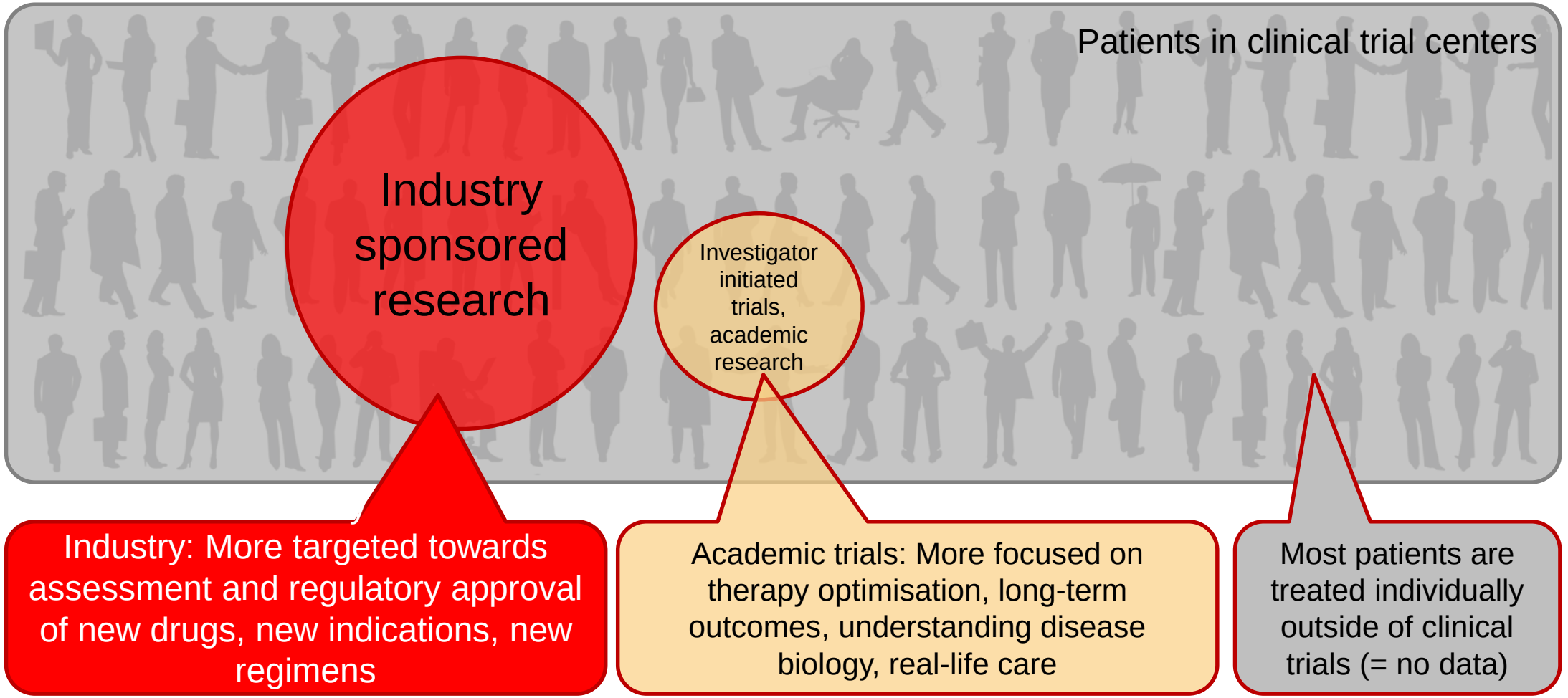
After regulatory approval decision, late-phase trials optimize therapy and collect more (safety) data



Phase IV trials:
Real-life data, safety information, therapy optimization of approved drugs, life cycle management

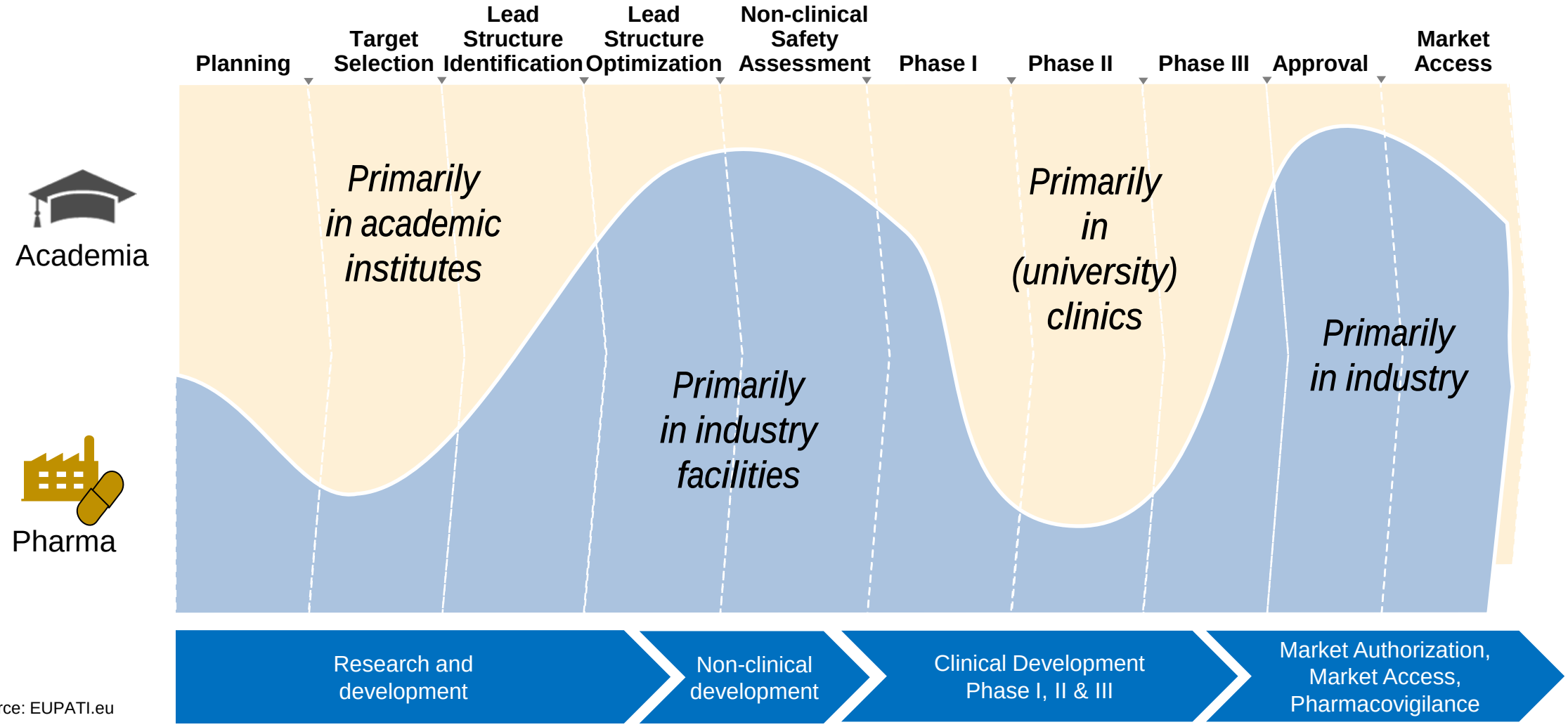
Source: EUPATI.eu

Most trials are initiated/sponsored by industry and then run at academic and community trial centres. Not so many trials are purely academic



Most trials are sponsored by industry and then conducted at academic and trial centers

(industry/academia is not either/or)



Source: EUPATI.eu

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Why patient involvement in R&D?

Patients have a key role to play in all aspects of health-related research and policies

Public

BfArM MHRA EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Competent authorities

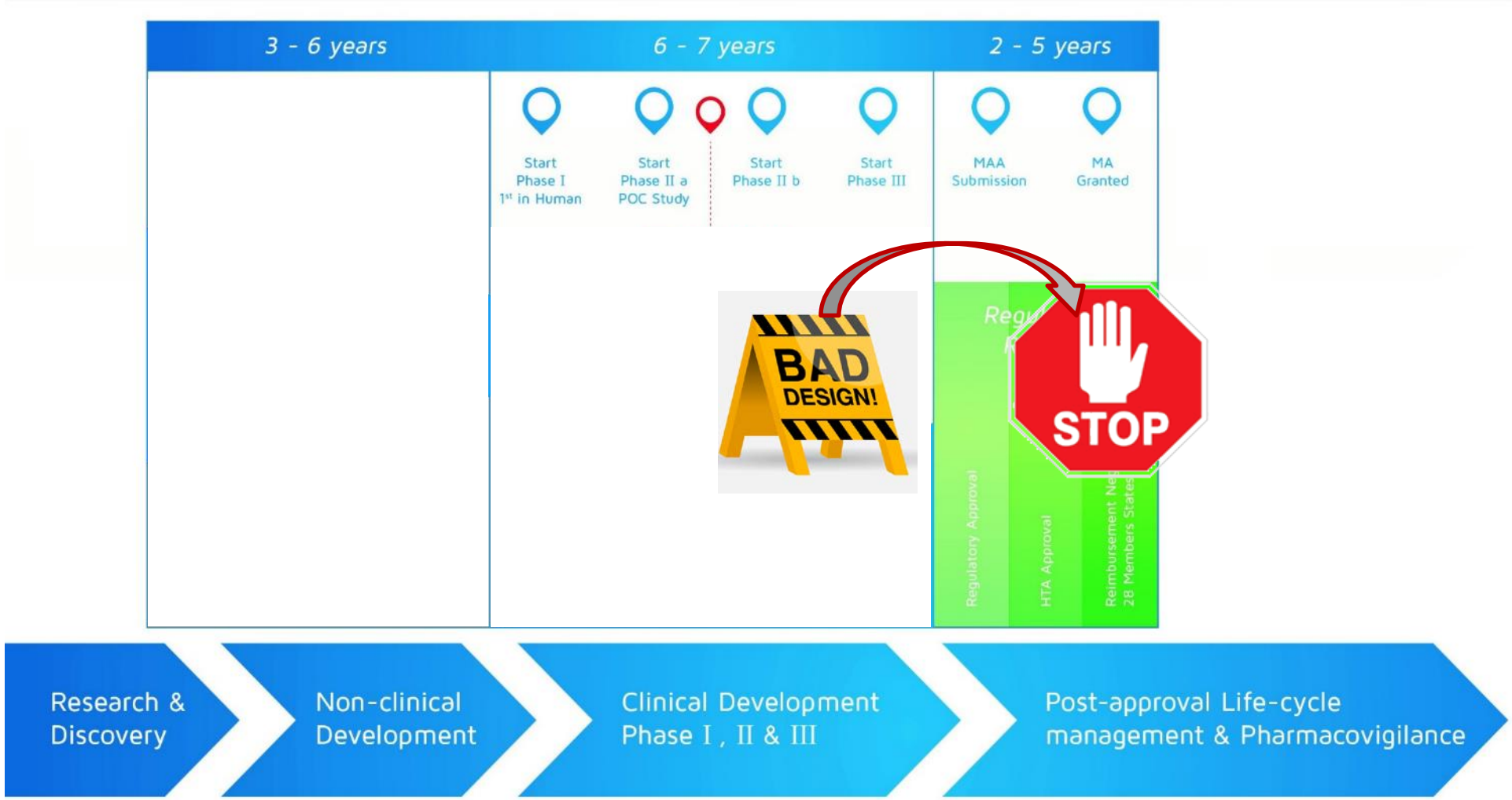
Policy makers /Research Policy

Research Ethics Committees

HTA agencies & committees

Clinical Research

You can‘t fix bad data, if you only address them by the time when market authorization/reimbursement decisions are being made



Source: EUPATI.eu

Avoidable waste in the production and reporting of research evidence

WECAN Academy 2019

1	2	3	4
Questions relevant to clinicians & patients?	**Appropriate design and methods?**	**Accessible full publication?**	**Unbiased and usable report?**
Low priority questions addressed **Important outcomes not assessed** **Clinicians and patients not involved in setting research agendas**	Over 50% studies designed without reference to systematic reviews of existing evidence Over 50% of studies fail to take adequate steps to reduce biases, e.g. unconcealed treatment allocation	Over 50% of studies never published in full Biased under-reporting of studies with disappointing results	Over 30% of trial interventions not sufficiently described Over 50% of planned study outcomes not reported Most new research not interpreted in the context of systematic assessment of other relevant evidence

85% research waste = over $85 billion / year

Chalmers I, Glasziou P. *Lancet* 2009;374:86–9

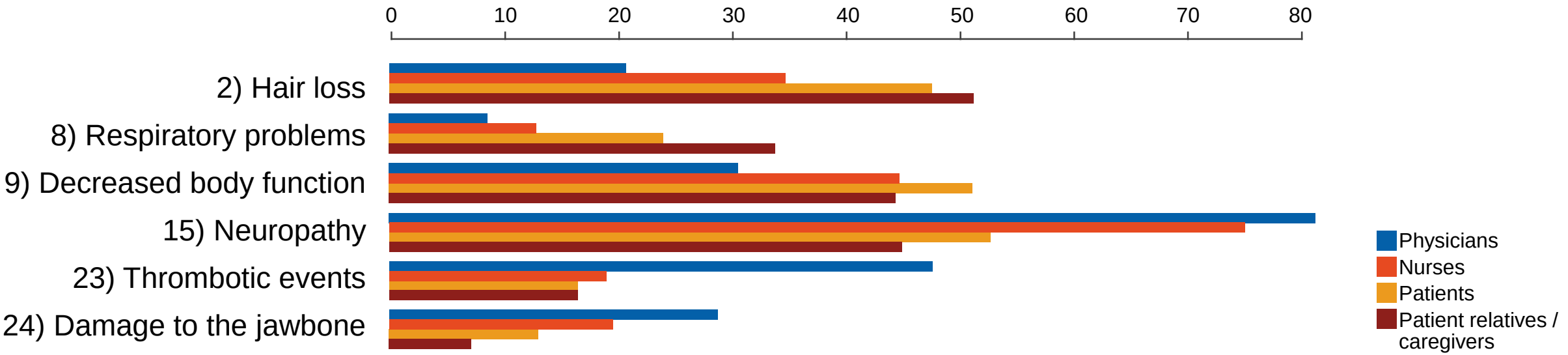
What do patients expect from clinical trials?

Move away from glossy statements on „patient centricity“ towards real involvement of patients in plans, actions and outcomes:

- Gather insights into the day-to-day reality of patients
- Understand the „unmet need“ and „real value“ to patients
- Co-create clinical trials, services and info resources, leading to wiser investment of limited resources through better trial design, more effective research, better data
- Let patients drive research

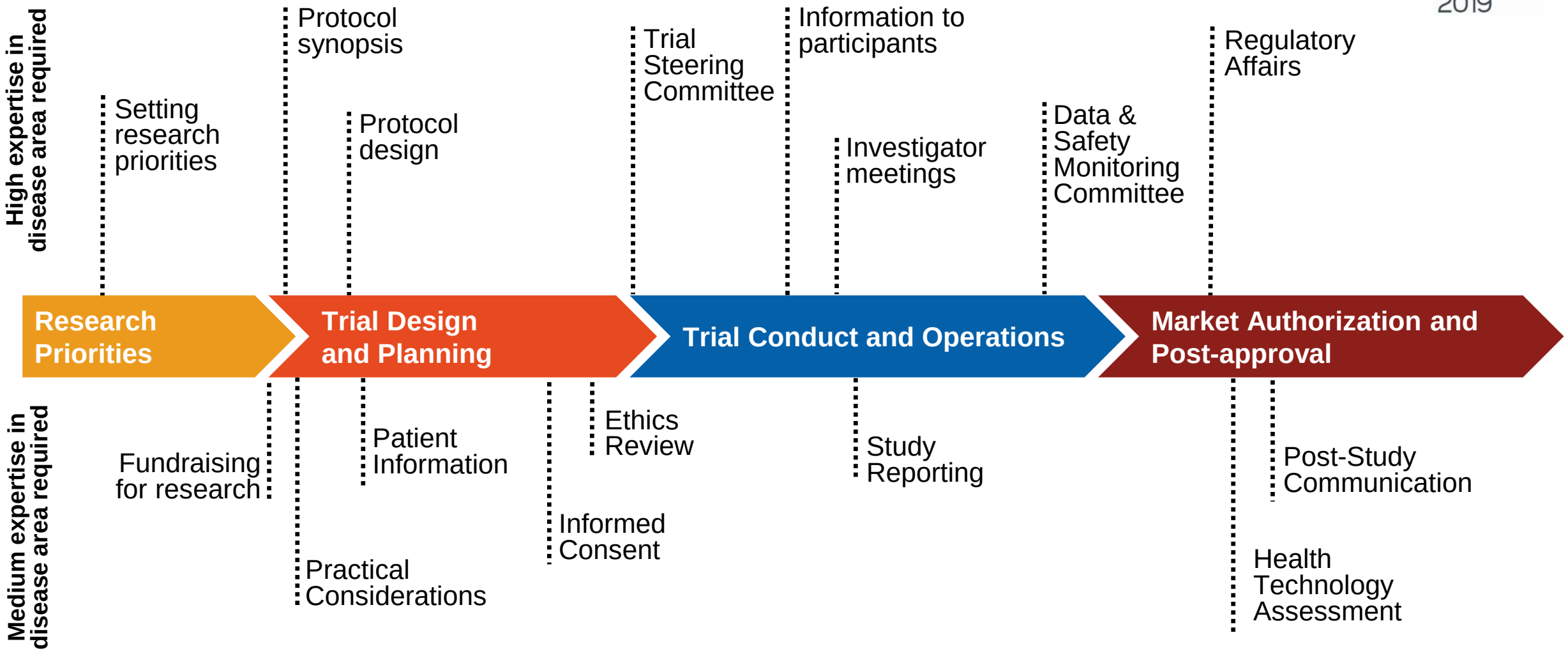
Why do patients have a unique perspective? Example side effects

Treatment side-effects with the most negative impact on overall well-being (%)



Detecting Myeloma, ways to shortening an often painful and tedious patient odyssey: Results from an international survey. Myeloma Euronet (2009). 314 physicians & nurses, 260 patients & carers, 43 countries

Patient involvement in clinical development in practice



Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Geissler, Ryll, Leto, Uhlenhopp, Therapeutic Innovation & Regulatory Science (2017), doi: 10.1177/2168479017706405, and at www.eupati.eu

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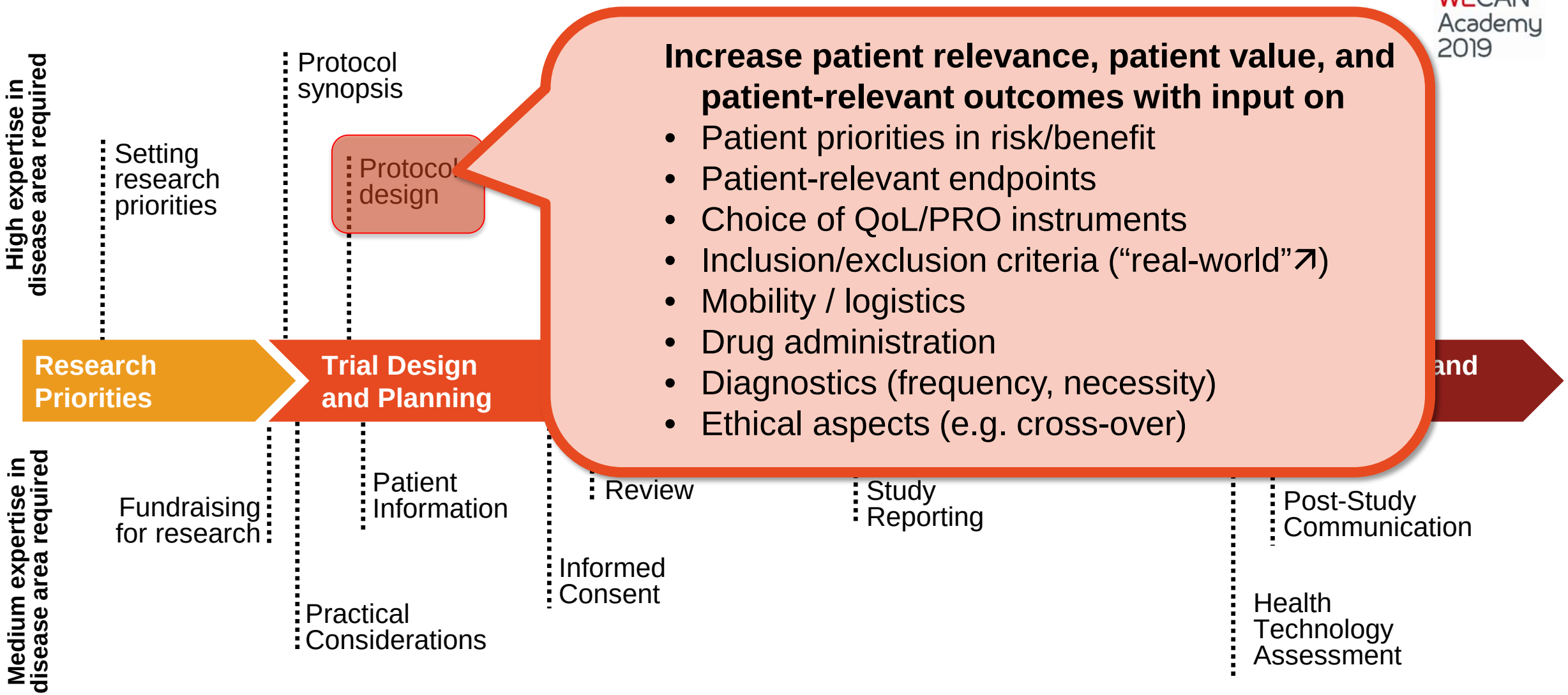

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What are the key elements of a trial protocol?

Clinical Development

[redacted]

Protocol Synopsis [redacted]

A multicenter, randomized, open-label Phase 2 study evaluating the safety and efficacy of three different doses of oral *Investigational Drug* in combination with subcutaneous [redacted] in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents

Authors	[redacted]
Document type	Oncology Synopsis
EUDRACT number	Enter number
Version number	00 (Original Protocol)
Development phase	II
Document status	Draft
Release date	*DD-Mmm-YYYY (To be completed by the ODA)*

Template version 17-Nov-2014

Please note that this Protocol has been redacted for confidentiality reasons

Table of contents

List of tables

Source: MPE (2019)

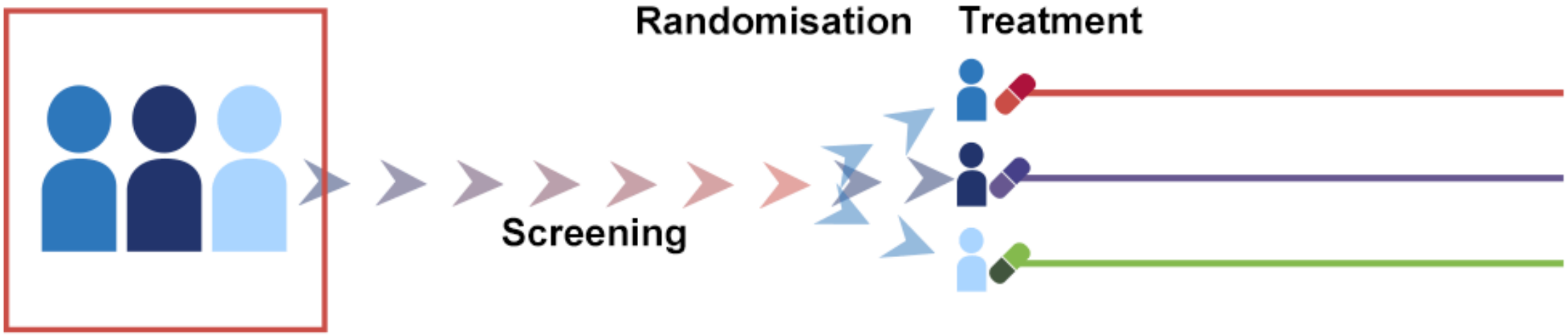
Type of comparisons

In a clinical trial design, there are a number of different types of comparisons that can be included:

- **Superiority comparison trials**
  = demonstrate that the investigational medicine **is better** than the control.
- **Equivalence comparison trials**
  = demonstrate that the endpoint is similar (no worse, no better) to the control.
- **Non-inferiority comparison trials**
  = demonstrate that the investigational medicine is **not worse** than the control.
- **Dose-response relationship trials**
  = demonstrate various dose parameters including starting dose and maximum dose.

Source: EUPATI.eu

Randomisation



- Randomisation is the process of assigning a trial participant randomly (by chance) to treatment or control groups.
- Randomisation removes potential for bias at the time of recruitment

Source: EUPATI.eu

Blinding

Type	Description
Unblinded or **open label**	**All are aware** of the treatment the participant receives
Single blind or single-masked	**Only the participant** is unaware of the treatment they receive
Double blind or double-masked	**The participant and the clinicians** / data collectors are unaware of the treatment the participant receives
Triple blind	**Participant, clinicians / data collectors and outcome adjudicators / data analysts** are all unaware of the treatment the participant receives.

Endpoints

- **Endpoint = primary outcome** measured by a clinical trial.
  A cancer drug may compare the 5-year survival rate of patients using an experimental therapy against the 5-year survival rate of patients using another treatment or a placebo.

- A clinical trial might use a
  - **clinical endpoint** or a
  - **surrogate endpoint**.

- A clinical endpoint is an outcome that represents direct **clinical benefit**, such as survival, decreased pain, or the absence of disease.
- A surrogate endpoint is **a substitute for a clinical endpoint** used in trials where the use of a clinical endpoint might not be possible or practical (if, for example, a drug's direct benefits would take many years to measure).
  Surrogate endpoints do not represent direct clinical benefit, but instead ***predict*** **clinical benefit**.

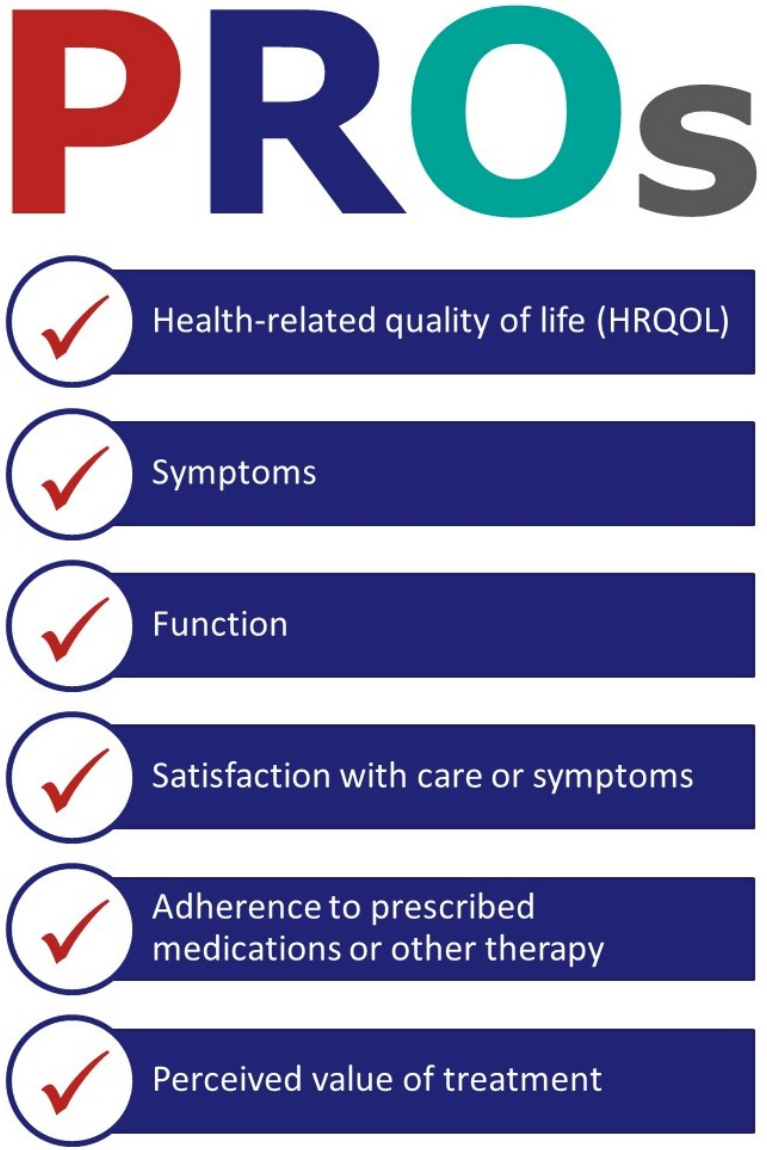
Adapted from: https://www.focr.org/clinical-trial-endpoints

Patient Reported Outcomes (PRO)

- PROs give an unique insights into how a therapy can affect a patient, e.g.
  - **Health-related Quality of Life (HRQoL)**, e.g. physical, social, emotional, psychological role function and well-being
  - **Patient Satisfaction** (e.g. patient preferences, healthcare delivery systems, evaluation of treatments and medical devices)
  - **Activity of Daily Living** (ADL)

- Individuals with the exact same health status, diagnosis, or disease may have different perceptions about how they feel and function.

- Measuring well-being as an outcome becomes especially important where the primary goal of treatment is patient well-being, rather than prolonging life or reducing disease events.



Inclusion and exclusion criteria

- **Inclusion criteria** = the key features of the target population to be included to answer research question.
  - Typical inclusion criteria include demographic, clinical, and geographic characteristics.
- **Exclusion criteria** = features of potential study participants who meet the inclusion criteria but present characteristics that could interfere with the success of the study, or increase their risk for an unfavourable outcome.
  - Common: characteristics that make them highly likely to be lost to follow-up, miss scheduled appointments to collect data, provide inaccurate data, have comorbidities that could bias the results of the study, or increase their risk for adverse events (most relevant in studies testing interventions).

Patients may have a different perception or understanding about who is and who is not eligible or fit for the trial – your opinion matters!

Adapted from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6044655/

Schedule of Events / Activities / Visits, Study Matrix

= The plan of care that the typical participant will receive during his or her participation in the study.

It describes the **timing of procedures** that will be accomplished during all clinic visits and assessments of the study.

Procedures	Screening	Enrollment/Baseline (Visit 1)	Follow-Up (Visit 2)	Follow-Up (Visit 3)	Follow-Up (Visit 4)	Follow-Up (Visit 5)	Follow-Up (Visit 6)	Follow-Up (Visit 7)	Follow-Up (Visit 8)	Follow-Up (Visit 9)	Follow-Up (Visit 10)	Follow-Up (Visit 11)	Follow-Up (Visit 12)	Final Study Visit (Visit 13)
Informed consent	X													
Demographics	X													
Medical history	X													
Randomization	X													
Administer Investigational Product		X			X			X			X			
Concurrent meds	X	X----------											X	
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test [b]	X													
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	X
Radiologic evaluation/Imaging	X				X				X					X
Other tests, as appropriate														

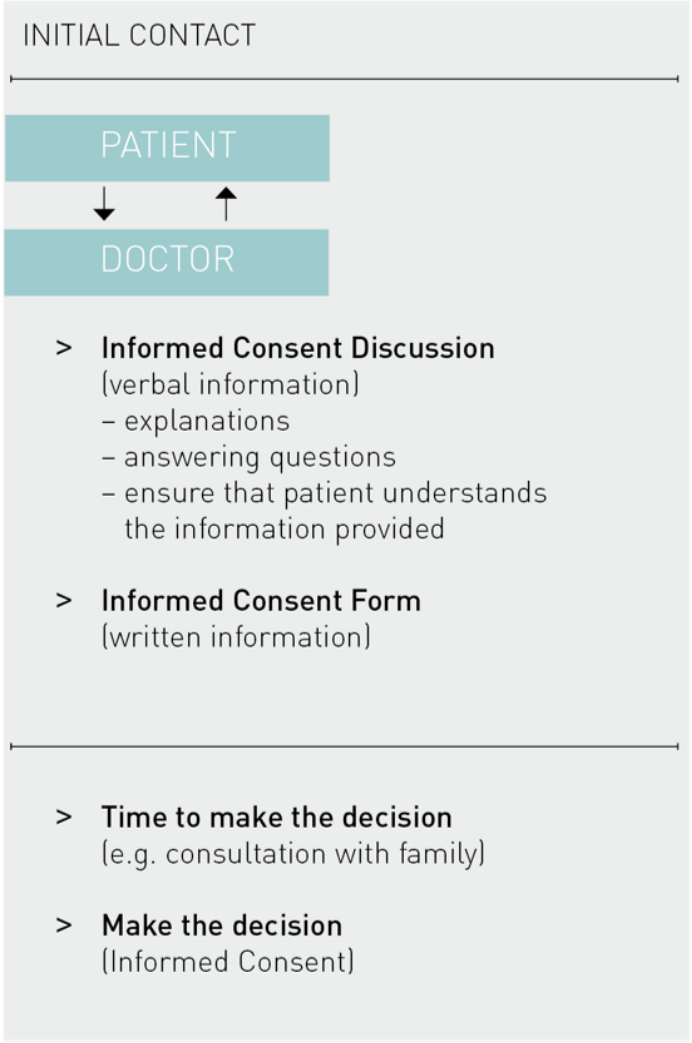
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).

Example schedule of events. Source: NIH-FDA Clinical Trial Protocol Template – v0.1 20160205

Informed consent

- Informed Consent has its roots in the 1947 Nuremberg Code and the 1964 Declaration of Helsinki and is a key component of medical research today (Human Right).
- A person's **voluntary agreement**, based on an understanding of the relevant information, to participate in a clinical trial.
- Before any research may be carried out, participants must be **informed**
  - **about all aspects of the study and/or intervention**, including the aims, methods, anticipated benefits, and potential risks.
  - that they can **withdraw** from the research at any stage without any negative consequences to their ongoing care or treatment.
  - In an **accessible and understandable way**, having the opportunity to ask questions about the research.

- Informed consent is usually **documented in writing with a signed and dated consent form.** However, informed consent should be an ongoing process throughout a study,



Source: EUPATI.eu

Informed Consent: Difficult balance between lack of information, information overload, legal requirements

- Informed Consent comprises: **verbal** information through the doctor and **written** information and consent (comprehensive patient information)
- Written patient information is **highly legally and ethically regulated**
  - Defined in several laws, regulations, guidance (ICH GCP, International and National Laws, Regulations)
- The state of “being informed” is very individual and leaves lots of space for interpretation
- It is a sensible path between **lack of information and information overload**
- **Patient involvement** in making informed consent documents more readable, understandable and relevant (verbal and visual improvement) is strongly recommended, but not formally required

Source: EUPATI.eu

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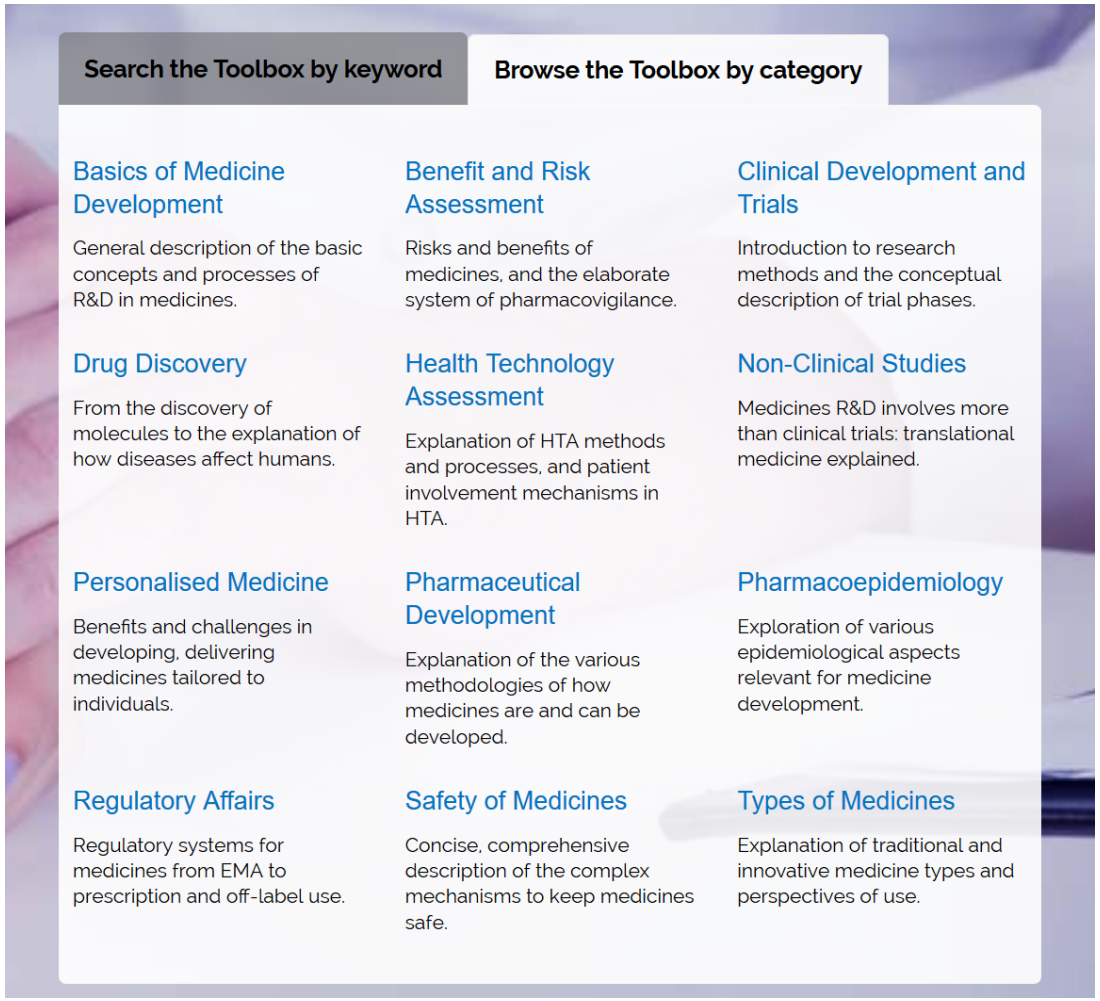
Where to find additional information about medicines research & development?

European Patients‘ Academy (www.EUPATI.eu) Toolbox



1. Discovery of Medicines
2. Pre-clinical Development
3. Clinical Development
4. Clinical Trials
5. Regulatory Affairs, Drug Safety, Pharmacovigilance
6. Health Technology Assessment

Source: EUPATI.eu

Search the Toolbox by keyword | Browse the Toolbox by category

Basics of Medicine Development
General description of the basic concepts and processes of R&D in medicines.

Benefit and Risk Assessment
Risks and benefits of medicines, and the elaborate system of pharmacovigilance.

Clinical Development and Trials
Introduction to research methods and the conceptual description of trial phases.

Drug Discovery
From the discovery of molecules to the explanation of how diseases affect humans.

Health Technology Assessment
Explanation of HTA methods a processes, and patient involve mechanisms in HTA.

Non-Clinical Studies

Glossary

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'Me too' medicine
'Me too' medicines are products which have more or less identi compounds structurally very similar to already known medicine only minor pharmacological differences. They can present som and in a few cases lead to price reductions, but also involve dis treatments.

AB
An antibody (AB), also known as an immunoglobin, is a protein p detects harmful substances (called antigens). Antigens can be r parasites, and viruses), or chemicals (insect venom). Antibodies neutralise them.

Absorption
In pharmacology and pharmacokinetics, absorption is the proce from the site of administration (by mouth, inhalation, intravenous capillary, osmotic, solvent, or chemical action in the cells. This c membranes. In specific situations, such as intravenous (IV) thera variability, because the medicine goes directly in to the bloodst the compound is 100%. Absorption is a primary focus in medicin absorbed before any medicinal effects can take place. Moreove significantly changed by factors that affect absorption.

Patients Involved – Informed consent Writer's guide

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Introduction

Partners from Ethic Committees (National Commission of Ethic Committees patient associations, and investigating centres worked in a writer's guide of recommendations and six rules for Informed Consent Forms.

Fig. 1 - Where in the process? – Phase II-III

When does it happen? – Phase II-III

Patient advocates involved in clinical development

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Patient advocates can be involved in early clinical development through partnerships and working relationships with regulatory authorities, ethics committees, investigators, and industry.

Patient advocates can provide input into:

- Study design:
  - Studies should take into accou research priorities and researc important to and provide value
- Study literature and informed cons
  - Study literature and informed c process) should be clearly und
- Study logistics (such as travel, time
  - The study should be planned s takes their needs into account, indication/disease.
- Recruitment and retention:
  - Raising awareness of studies w Patient organisations should al able to provide information to p
- Dissemination:
  - The results of research should

Patient advocates can have roles as:

- Driving force:
  - Lobbying for the development

EUPATI
European Patients' Academy on Therapeutic Innovation

Patient-reported outcomes (PROs) assessment

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Introduction

cal effectiveness typically reflect outcomes that are important to symptoms, morbidity, or mortality.

omes – such as a heart attack, a malignant growth (cancer), or death – and measured using a clinical definition by someone other than the there is increasing awareness that treatments should not just be and economically efficient, but should also be acceptable and to patients. Clinical effectiveness measures cannot tell us how a nctions, or what they want to achieve from a treatment. Measuring ceptability requires patient-based evidence that includes measures

Participants' rights, responsibilities, organisations

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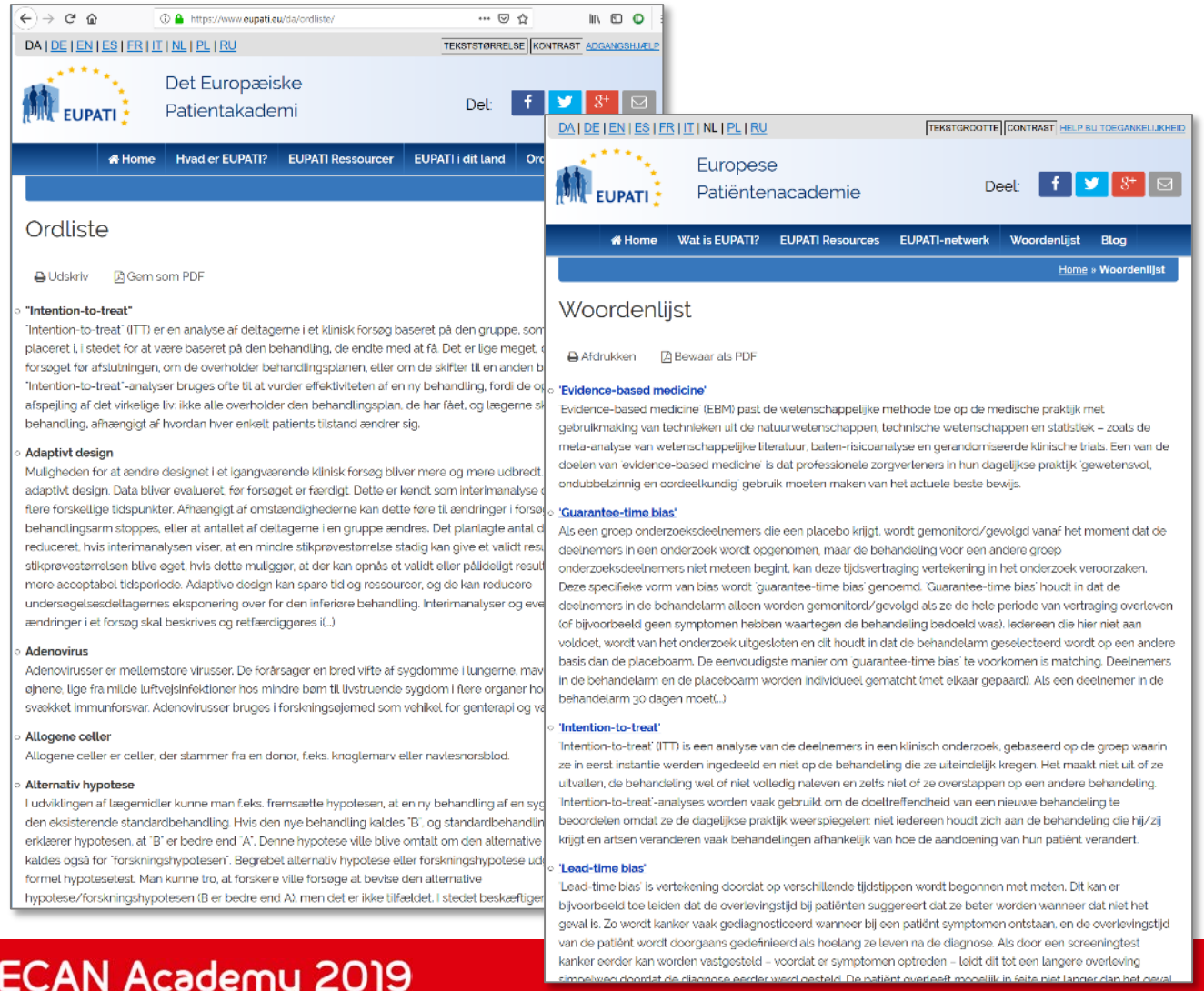
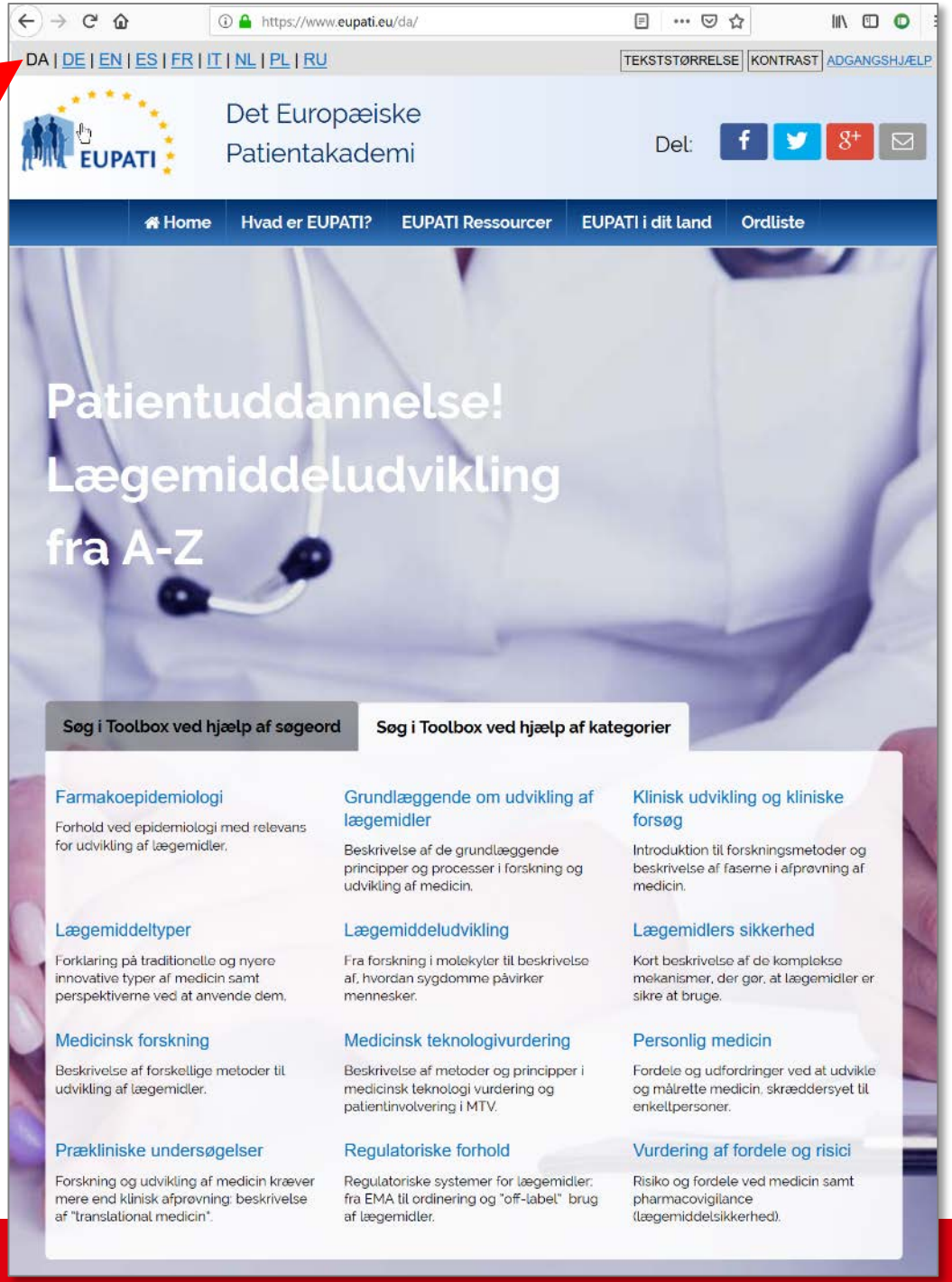
The EUPATI Toolbox is also available in other languages





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No research about us without us

- your input is important!

Jan Geissler
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