KCE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Single arm trials

A Health Technology Assessment perspective

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Senior Researcher, KCE

RSNN Annual workshop, Utrecht, November 18, 2025

.be

KCE, Belgian Health Care Knowledge Centre

www.kce.fgov.be

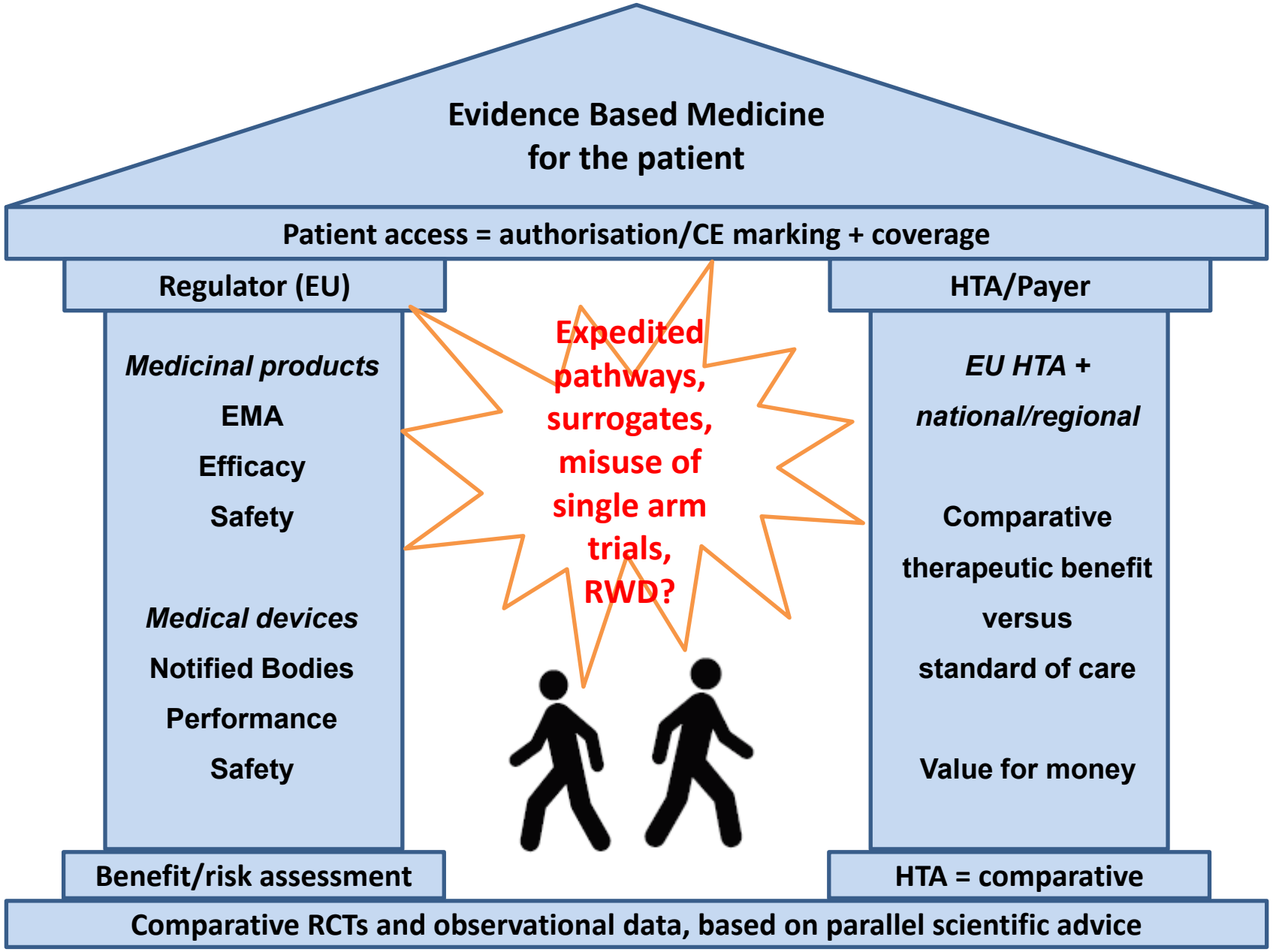
- Semi-governmental institution
- Operational 2004

- >50 researchers
  - medicine, economics
  - statistics, sociology, law

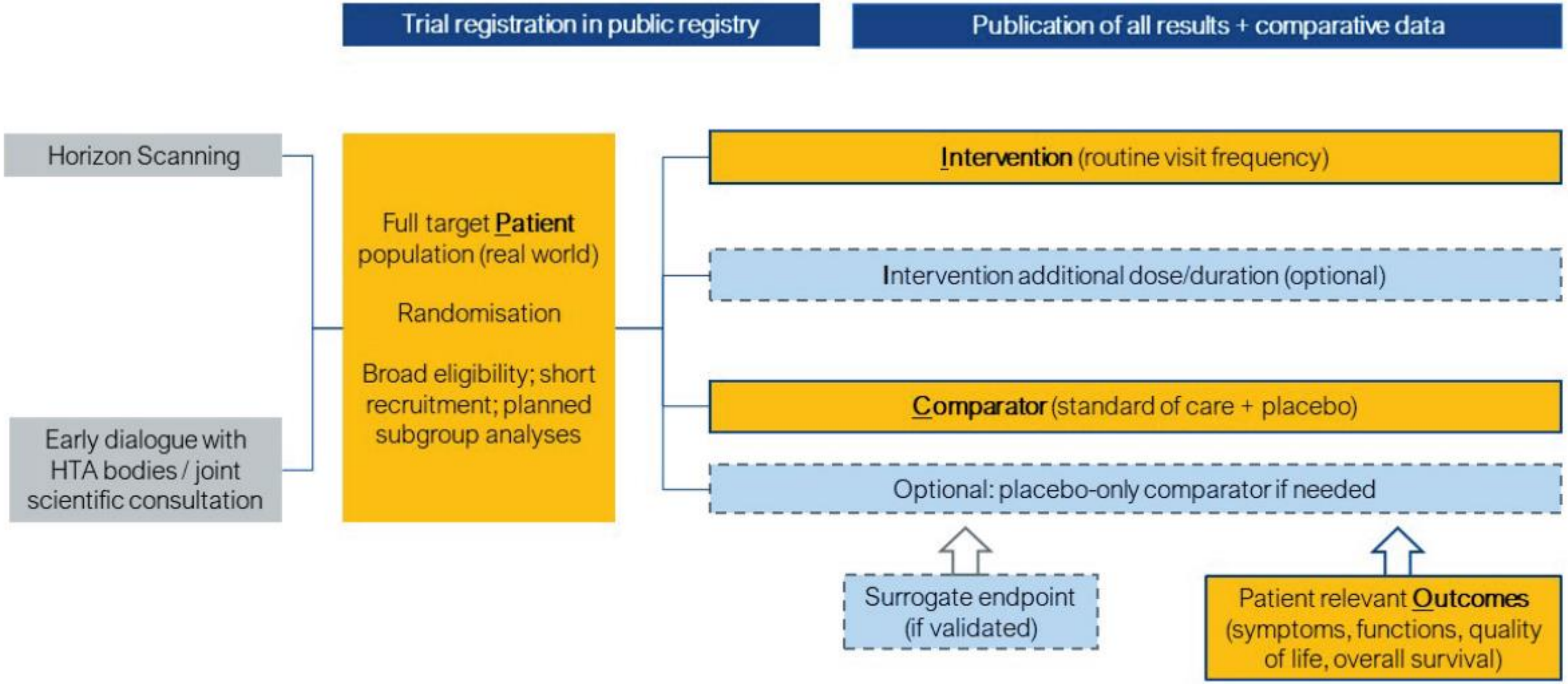
- Studies (>400)
  - Clinical practice guidelines
  - Health services research (HSR)
  - Health technology assessment (HTA)

  + KCE Trials (started in 2016)

- Policy recommendations, no decisions

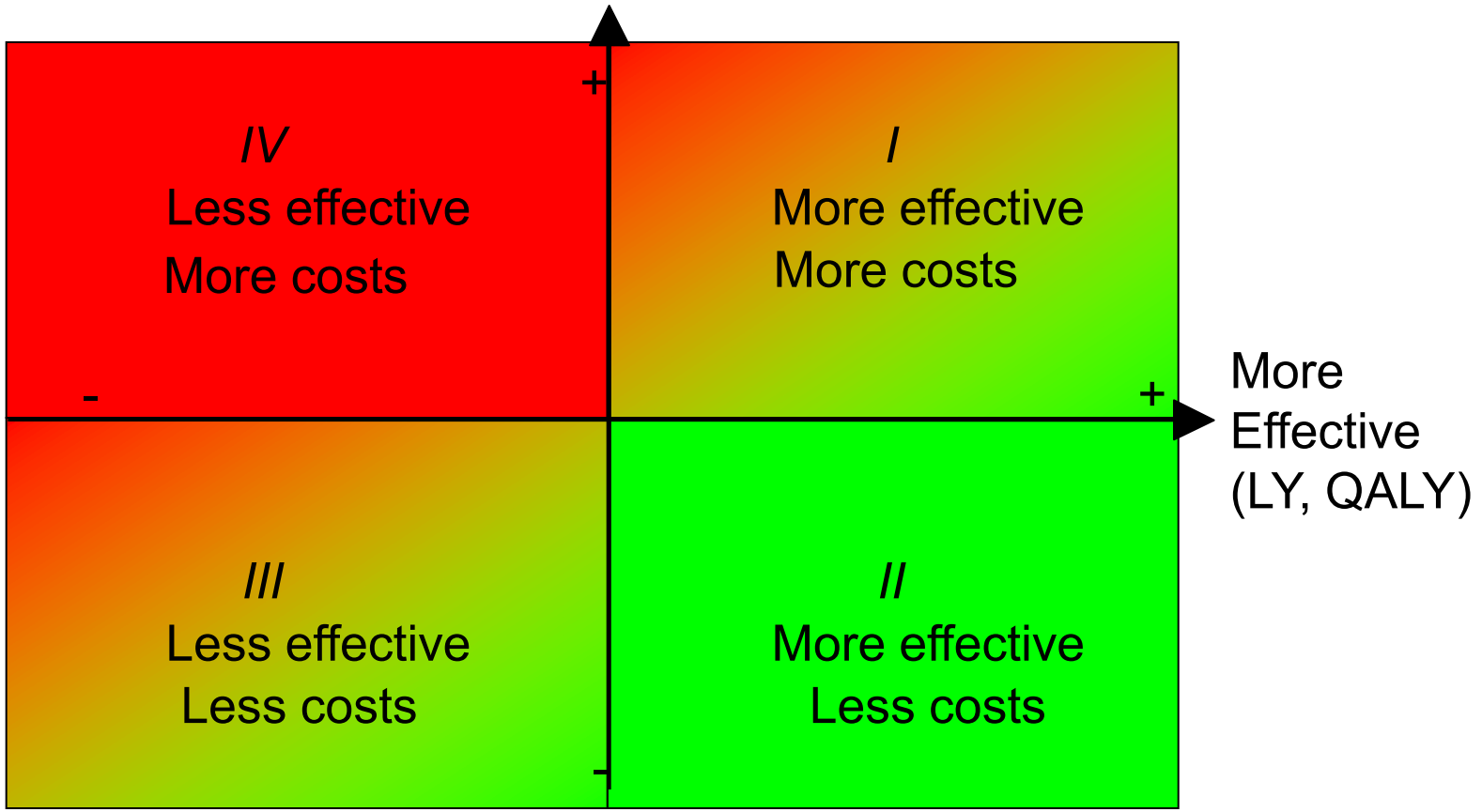

Evidence Based Medicine
for the patient
Patient access = authorisation/CE marking + coverage
Regulator (EU)
HTA/Payer
Medicinal products
EMA
Efficacy
Safety
Medical devices
Notified Bodies
Performance
Safety
Expedited pathways, surrogates, misuse of single arm trials, RWD?
EU HTA + national/regional
Comparative therapeutic benefit versus standard of care
Value for money
Benefit/risk assessment
HTA = comparative
Comparative RCTs and observational data, based on parallel scientific advice

Informative confirmatory trial from a HTA/payer perspective



Incremental Cost-Effectiveness Ratio (ICER)

$$\frac{\textit{Incremental Cost}}{\textit{Incremental Effect}}$$



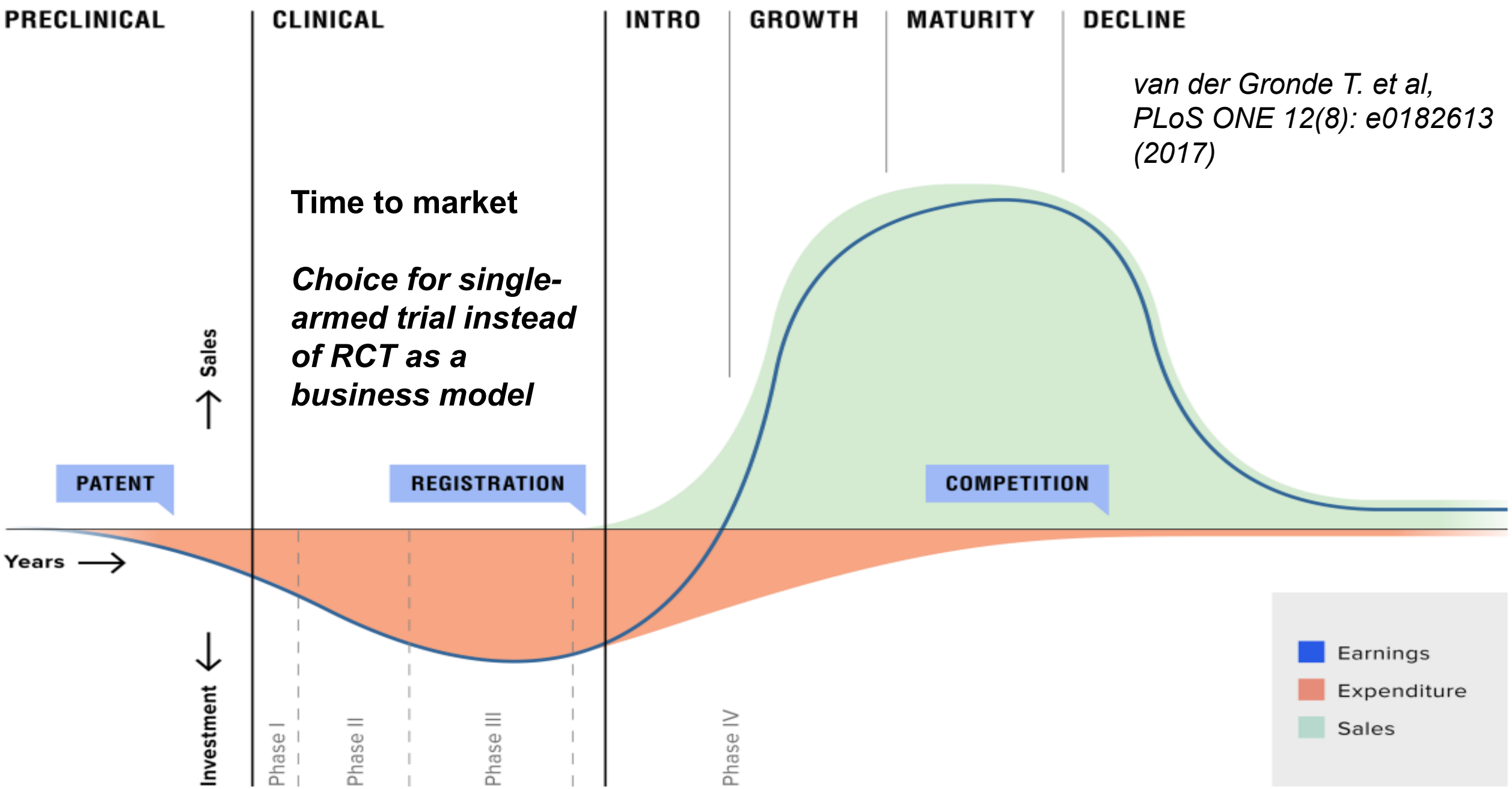
The perspective and the narrative

“The patient is central”

- **Additional therapeutic benefit**
  - **Overall survival + quality of life**
- **Rapid access - - - - - - - - - - -**
- **Cost-effectiveness**
- **Budget impact**

"It's the economy, stupid"

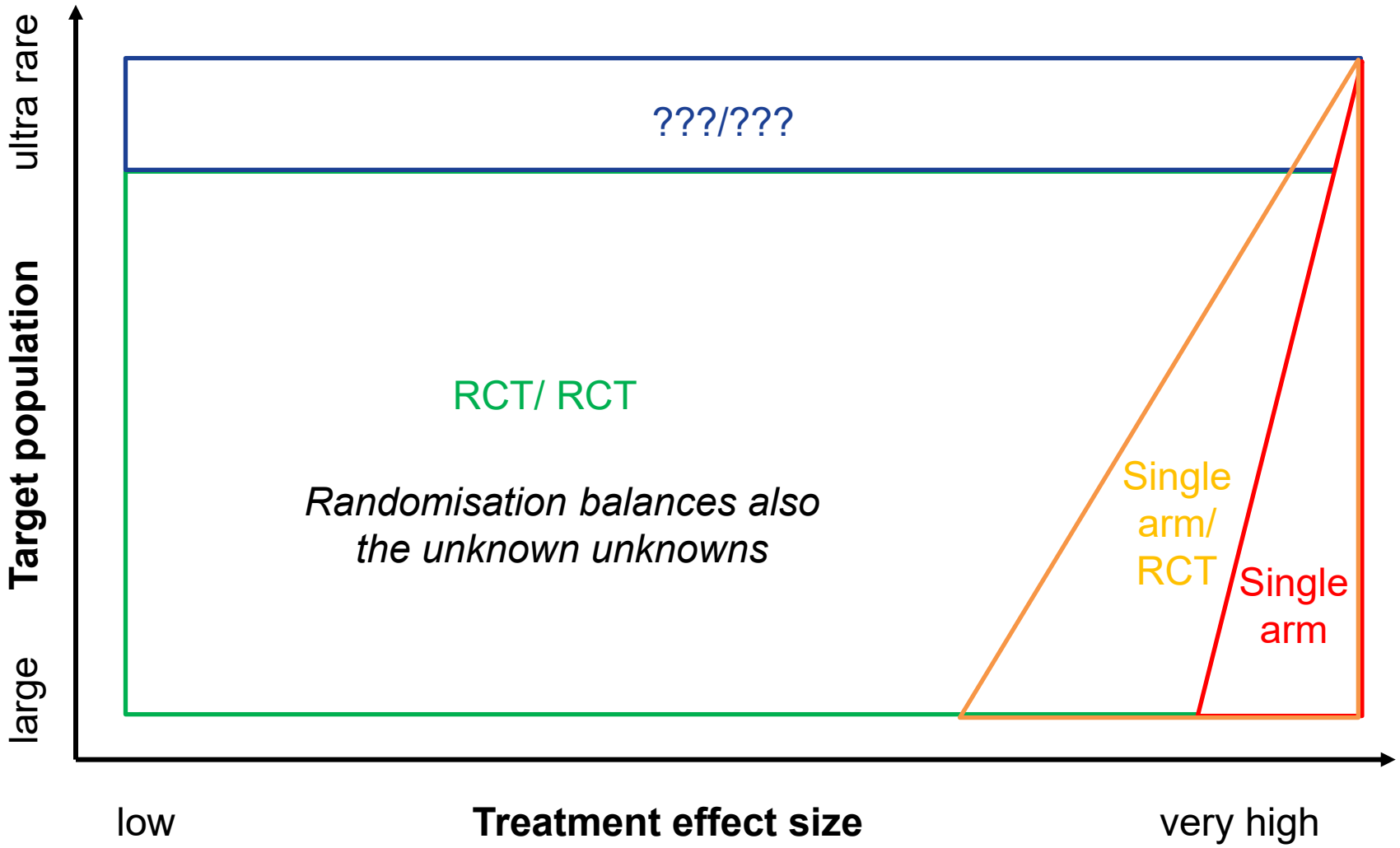
- **Profitability**
  - **Pension plan**
- **Time to market**
- **Return on investment**
- **Employment**



van der Gronde T. et al, PLoS ONE 12(8): e0182613 (2017)

Fig 2. Drug life cycle curve. General curve describing an innovator drug's investments and earnings during R&D and market performance. The life cycle phases are indicated above the graph, and the phases of the R&D trajectory are below the graph. Own work.

What data can indicate/measure a treatment effect?



Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy?

BMJ 2023;380:e073100

Real world data are advocated as an alternative approach to RCTs for closing knowledge gaps on drugs, but **Beate Wieseler and colleagues** argue that this approach is the wrong remedy for current challenges in drug development

Beate Wieseler, [1] Mattias Neyt, [2] Thomas Kaiser, [1] Frank Hulstaert, [2] Jürgen Windeler[1]

Key messages

- Enthusiasm is growing for the use of observational real world data as a basis for regulatory, clinical, and health policy decision making
- But such study designs are ill suited to measure the treatment effects of new drugs
- Promoting the use of observational studies from routine practice data sources might hinder efforts needed to improve the feasibility of randomised controlled trials
- To ensure high quality and efficient healthcare, the conduct of RCTs, including those in routine care, should be made easier, faster, and cheaper

Replacing RCTs: a choice rather than a necessity

The hypothesised infeasibility of RCTs is largely based on the assumption that they cannot be implemented in small populations. This might be true for specific "ultra-rare" diseases, but the generalisability of this argument is contradicted by findings from orphan drug development programmes. Analyses have shown that, in most cases, RCTs were actually available.[24 25] The German Institute for Quality and Efficiency in Health Care found that RCTs were available for about 60% of the new orphan drugs entering the German market between 2014 and 2018, with a wide overlap in the size of the target populations of the interventions between RCTs and observational studies.[25 26] In addition, a systematic analysis in ClinicalTrials.gov identified RCTs for diseases with a prevalence of less than one in a million.[27]

Difficulties with single-arm trials in drug development

- No evidence for comparative effectiveness
- Suggested ways to overcome the problem:
  - external control arms (including data from routine practice) *…from other trials?*
    - suggested methods uncertain (e.g. underlying assumptions often cannot be tested)
    - data required for effect estimation (confounders, endpoints) often not available in the required quantity and quality (especially not from routine practice data sources)
  - post-licensing evidence generation
    - randomised comparative studies with licensed drugs often difficult (due to perceived loss of equipoise)
    - shortcomings of observational studies as with external control arms
    - delays evidence-based health care

Randomisation balances also the unknown unknowns

Traffic lights and drug approval

Making the orange light visible for patients, to improve trial feasibility

Dose/duration tested
Comparative RCT vs standard care

Routine care EBM

Single arm trial

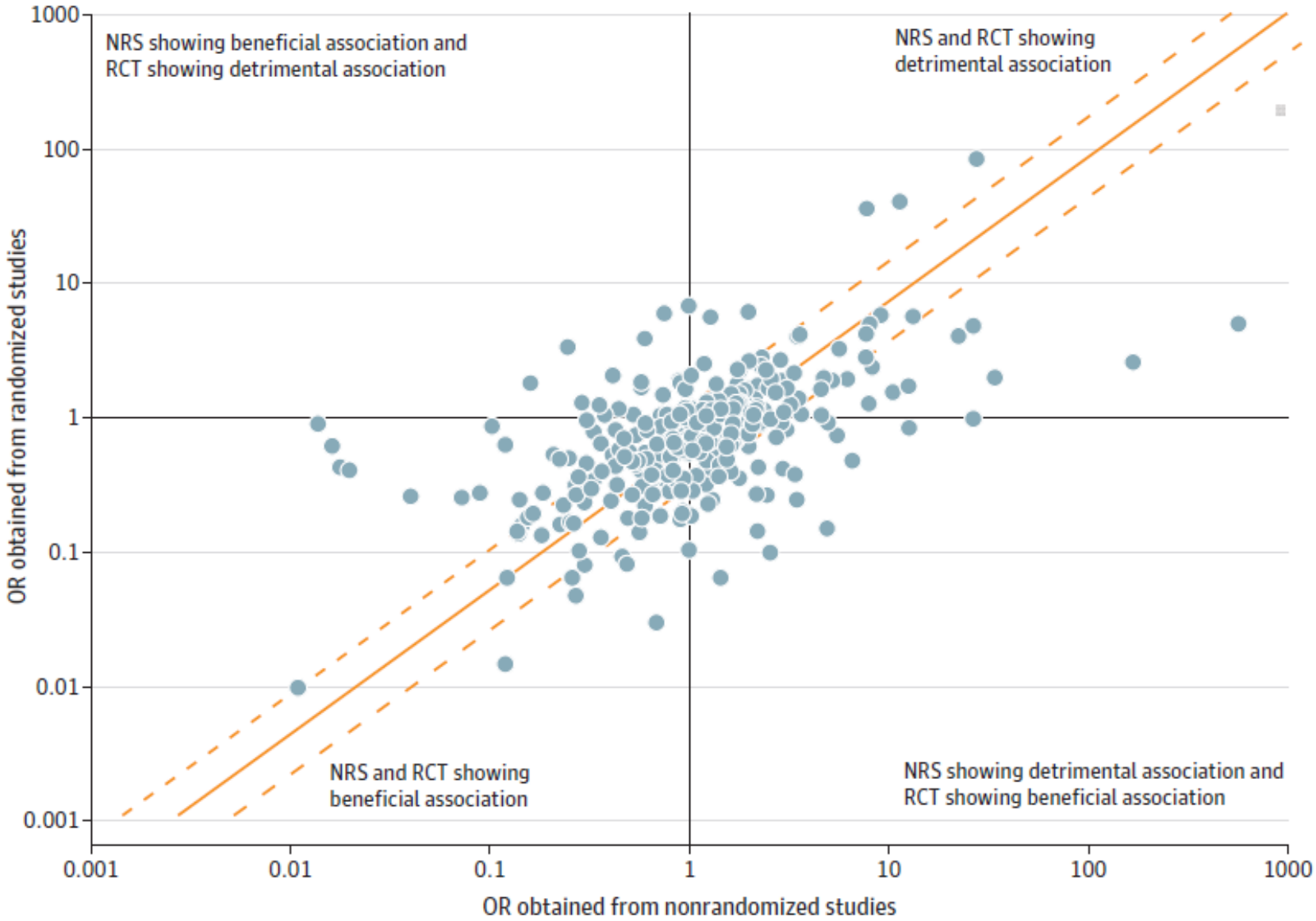
RCTs under conditional marketing authorisation
-
Coverage with evidence development
-
Treatment optimisation trials

Routine care EBM

Treatment Effects in Randomized and Nonrandomized Studies of Pharmacological Interventions, A Meta-Analysis
Salcher-Konrad M, et al.
JAMA Network Open.
2024;7(9):e2436230

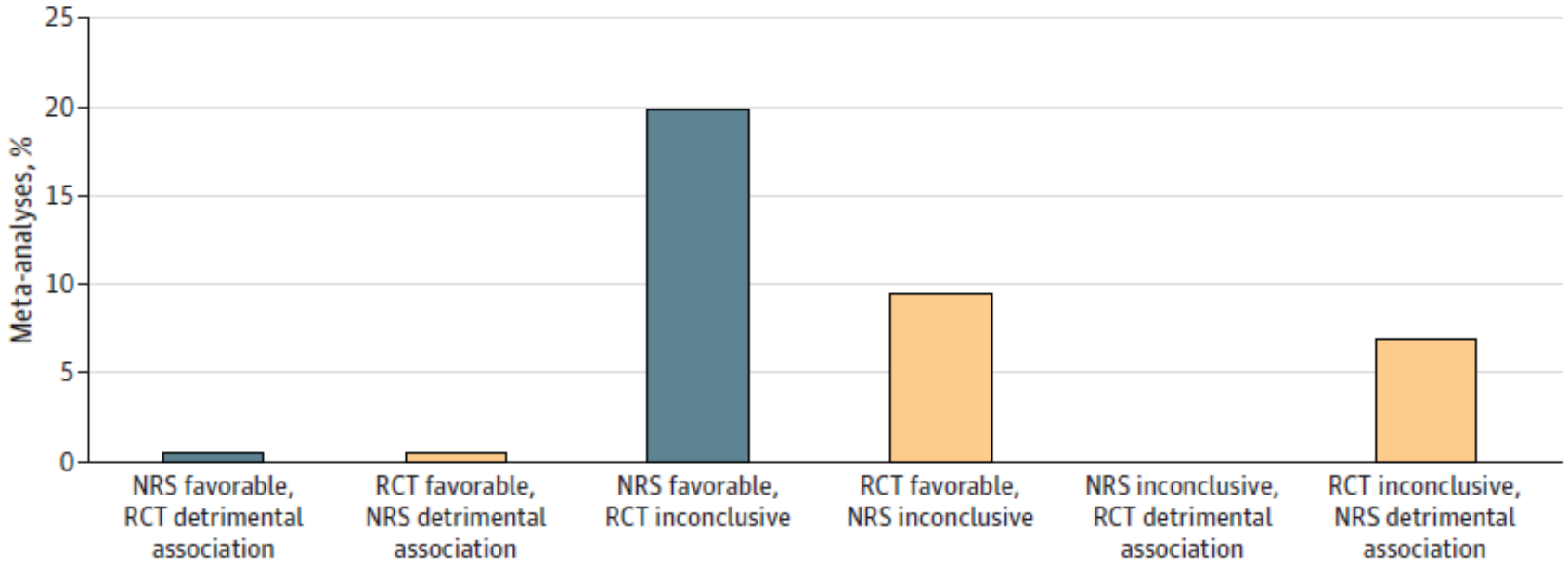
Discordant results in about a third of the comparisons, similar to previous reports, e.g.
Evaluation of the Use of Cancer Registry Data for Comparative Effectiveness Research
Kumar A, et al.
JAMA Network Open.
2020;3(7):e2011985

Figure 2. Agreement of Summary Effect Size Estimates Obtained From Randomized and Nonrandomized Studies for 346 Clinical Questions



RCTs and NRSs led to **different statistical conclusions** about the therapeutic benefit of pharmacological interventions in 130 meta-analyses (**37.6%**) and 216 (**62.4%**) reached the same statistical conclusion, based on comparing 95%CIs around the OR from either study type with a null effect (Figure 3).

Figure 3. Discrepancies in Statistical Conclusions About Therapeutic Benefit of Pharmacological Interventions Based on Evidence Obtained From Nonrandomized Studies (NRSs) or Randomized Clinical Trials (RCTs)



The figure shows proportions of meta-analyses based on the statistical conclusions about the existence of a therapeutic benefit drawn from NRS or RCT evidence. A favorable or detrimental effect was deemed to exist if the 95% CI of the summary odds ratio did not include 1. Evidence was considered inconclusive if the 95% CI of the summary odds ratio included 1.

JAMA Network Open. 2024;7(9):e2436230. doi:10.1001/jamanetworkopen.2024.36230 September 27, 2024 7/30

Divergent outcomes in non-randomised and randomised cardiovascular studies

Type of device	Observational study	Smaller RCT	Larger RCT
First-generation DES *vs.* bare metal stents ↓ / = / =	**PMID** 17296822 / 2007 • Propensity-score adjusted analysis (n=19,771) • **Increased mortality** with DES vs. BMS	12050336 / 2002 • 1:1 randomization (n=238) • No in-stent restenosis with DES • No stent thrombosis • **No difference in mortality**	14724301 / 2004 • 1:1 randomization (n=1,314) • Less restenosis and repeat revascularization with DES • **No difference in mortality**
Absorb bioresorbable vascular scaffold *vs.* everolimus-eluting metallic stent = / ↓ / ↓	26875648 / 2016 • Propensity-score matching (n=905 pairs) • **No difference** in clinical outcomes	27806897 / 2016 • **ABSORB II** • 2:1 randomization (n=501) • No difference in vasoreactivity • **Higher late luminal loss** with Absorb • **Higher TV-MI** with Absorb	26457558, 30266412, 31553222, 37207924 / 2015–2023 • **ABSORB III** • 2:1 randomization (n=2,008) • Noninferiority of BVS for TLF at 1 yr • **More TLF, TV-MI, thrombosis** to 5 yrs • **ABSORB IV** • 1:1 randomization (n=2,604) • Noninferiority of BVS for TLF, 30 d & 1 y • **More TLF** through 5 yrs
Manual thrombus aspiration *vs.* standard PCI ↓ / ↑ / = ,↓	20550973 / 2010 • Multivariable adjustment (n=22,632) • **More deaths** with thrombus aspiration (RR 1.16, 95% CI 1.05–1.28)	18256391, 18539223 / 2008 • **TAPAS, TAPAS-FU** • 1:1 randomization (n=1,071) • Better reperfusion and clinical outcomes with thrombus aspiration • **Reduced risk of cardiac death** with thrombus aspiration	23991656, 25176395 / 25853743, 26474811 / 2013–2016 • **TASTE, TASTE-FU** • 1:1 randomization (n=7,244) • **No difference in mortality** at 30 d & 1 y • **TOTAL, TOTAL-FU** • 1:1 randomization (n=10,732) • **Composite CV outcomes ns** 30 d & 1 y • **Increased risk of stroke**

PCI: Percutaneous Coronary Intervention

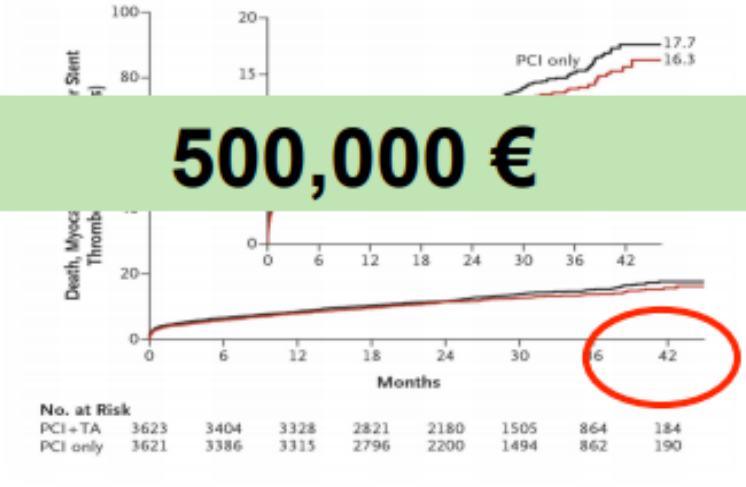
Presentation Alan Fraser, CORE-MD project, Brussels, 15 March 2024

Registry-based RCT or Trials within Cohorts (TwiCs)

R-RCT vs. RCT

STEMI Thrombectomy Story

TASTE (R-RCT)

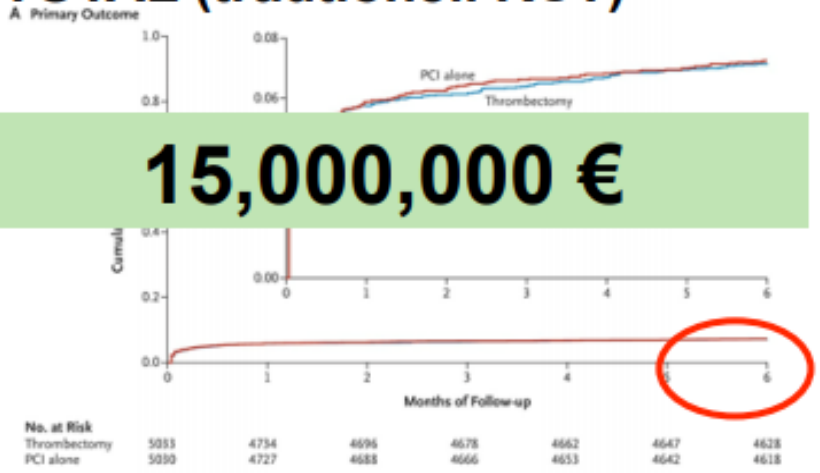


500,000 €

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

TOTAL (tradtionell RCT)



15,000,000 €

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients

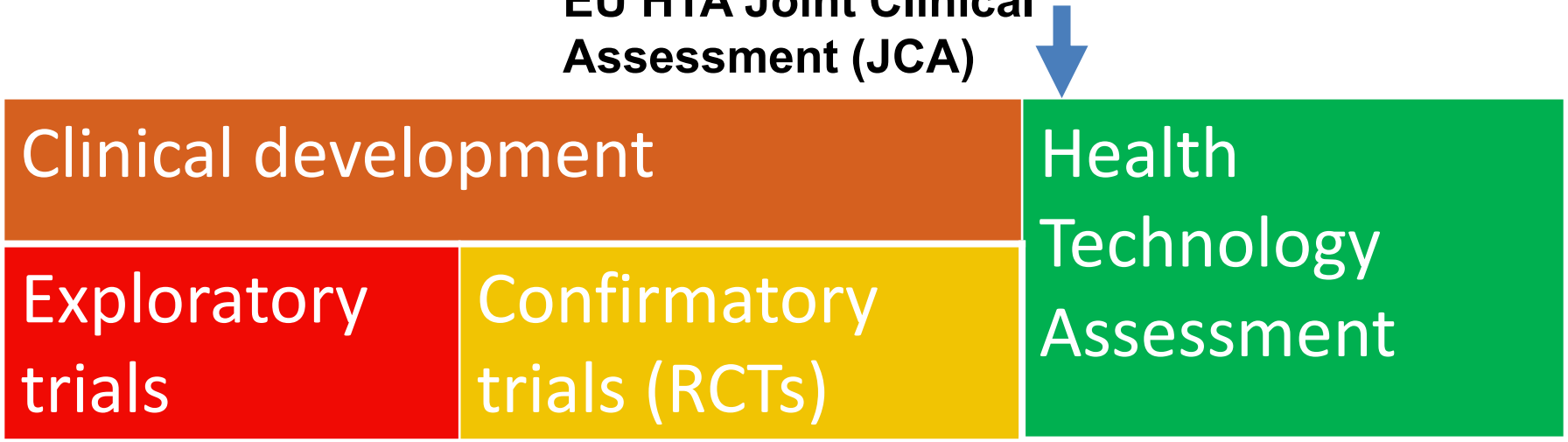
UCR

Jolly SS et al. N Engl J Med 2015;371:1389-1398

"70% of the patients in the registry accepted to be randomised"

The EU HTA regulation

Set of relevant PICOs
EU HTA Joint Clinical Assessment (JCA)



EU HTA Joint Scientific Consultation (JSC)

- internal validity
- safety
- efficacy

- external validity
- comparative effectiveness
- added therapeutic benefit
- (cost-effectiveness)
- (budget impact)

Joint scientific consultation

- Article 17:

JSC

1. For health technologies referred to in Article 16(2), health technology developers may request a joint scientific consultation.

- Relevant PICO?
  - Remark: article 18 → preference RCTs
    Avoidable uncertainty?

4. The assessor, with the assistance of the co-assessor, shall prepare the draft joint scientific consultation outcome document in accordance with the requirements set out in this Article and in accordance with the guidance documents and procedural rules established pursuant to Article 3(7), points (d) and (f), and Article 20. For medicinal products, in accordance with international standards of evidence-based medicine, directly comparative clinical studies which are randomised, blinded and include a control group shall be advised whenever appropriate.

  - Advice, however…

ANNEX I

Dossier specifications for medicinal products

(e) if a health technology has been subject to a joint scientific consultation, the explanation from the health technology developer on any deviation from the recommended evidence;

HTA - Guidance

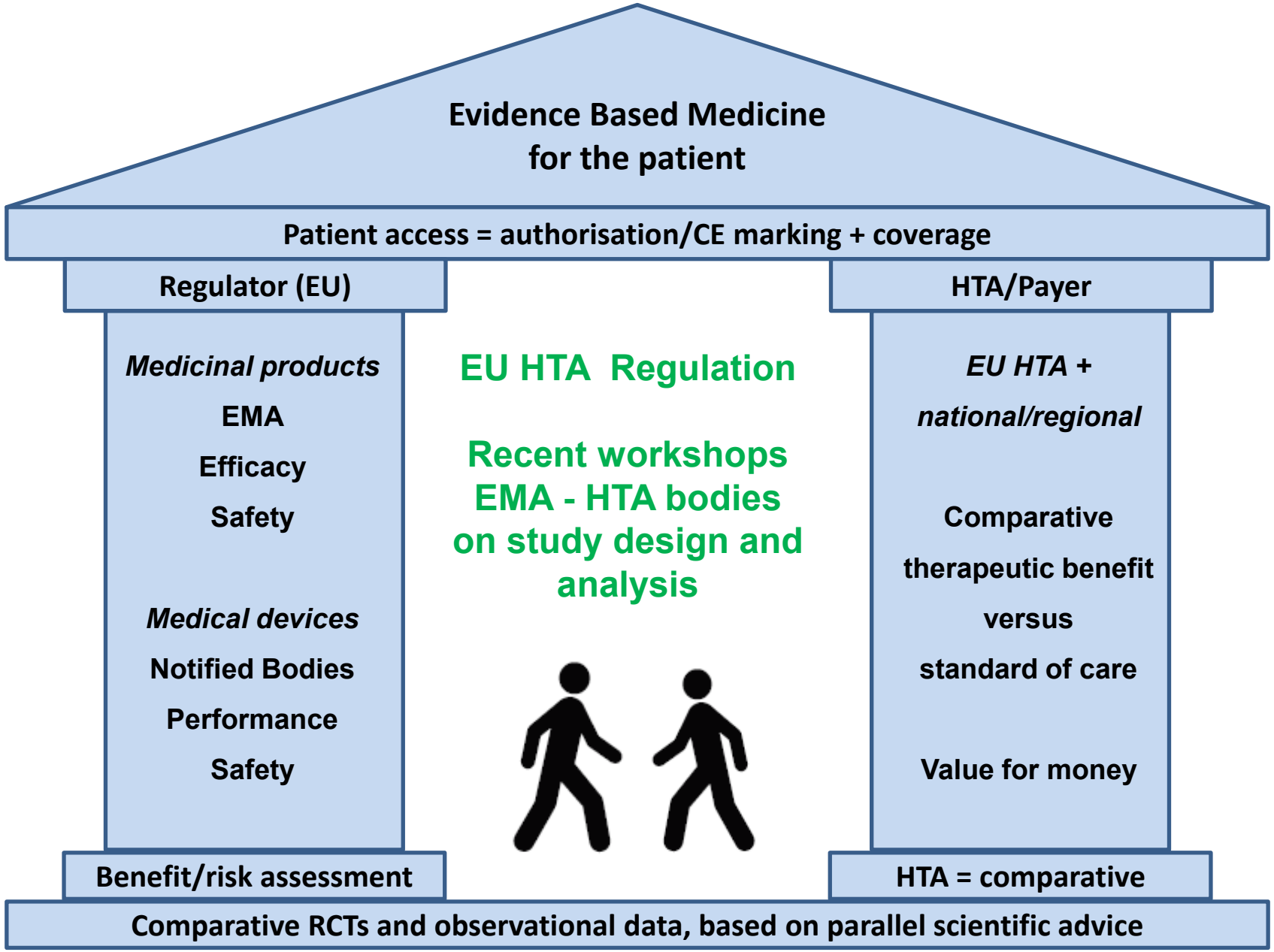
HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

- Source: https://health.ec.europa.eu/health-technology-assessment/key-documents

JCA

- Guidance on the validity of clinical studies for joint clinical assessments
- Scientific specifications of medicinal products subject to joint clinical assessments
- Guidance on outcomes for joint clinical assessments
- Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments
- Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons
- Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

A number of statistical approaches has been proposed for dealing with cases in which non-randomised evidence (e.g., single-arm trials, comparative observational studies and registry data) is used to inform an estimate of relative effectiveness. Although it is possible to provide summaries of evidence syntheses generated in this way, the certainty of the results provided by these techniques remains controversial. Results from such analyses are more likely to suffer from bias and are more likely to underestimate the true uncertainty and to depend on untested assumptions in comparison to syntheses with RCT evidence alone. Therefore, any analyses extending the network using single-arm or non-randomised evidence should include sensitivity analyses and an examination of the assumptions and should provide appropriate caveats for users. The use of single-arm or non-randomised evidence usually threatens the internal validity of results. Therefore, it is incumbent on the assessor to judge whether this evidence is sufficient for adequate estimation of the relative treatment effectiveness. For some interventions, single-arm or non- randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA.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Patient access = authorisation/CE marking + coverage
Regulator (EU)
HTA/Payer
Medicinal products
EMA
Efficacy
Safety
Medical devices
Notified Bodies
Performance
Safety
EU HTA Regulation
Recent workshops
EMA - HTA bodies
on study design and
analysis
EU HTA +
national/regional
Comparative
therapeutic benefit
versus
standard of care
Value for money
Benefit/risk assessment
HTA = comparative
Comparative RCTs and observational data, based on parallel scientific advice

Working Group of assessors, statisticians, methodologists from EU HTA and regulatory agencies

Organisers:

HTA: Dr David McConnell

Senior Statistician, National Centre for Pharmacoeconomics

Regulatory: Dr Dominik Karres

Senior Scientific Officer, Evidence Generation Department, European Medicines Agency

IQWiG

KCE
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

NCPE
National Centre for Pharmacoeconomics, Ireland

Federal Institute for Drugs and Medical Devices

CBG MEB
MEDICINES EVALUATION BOARD

Norwegian Medical Products Agency

Infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

RIZIV-INAMI

Austrian Federal Office for Safety in Health Care
BASG

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

ansm
Agence nationale de sécurité du médicament et des produits de santé

famhp
federal agency for medicines and health products

NCPE
National Centre for Pharmacoeconomics, Ireland

HEADS OF HTA AGENCIES GROUP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2025

EMA/115125/2025

Joint HTAb-regulatory perspectives on understanding evidence challenges, managing uncertainties and exploring potential solutions

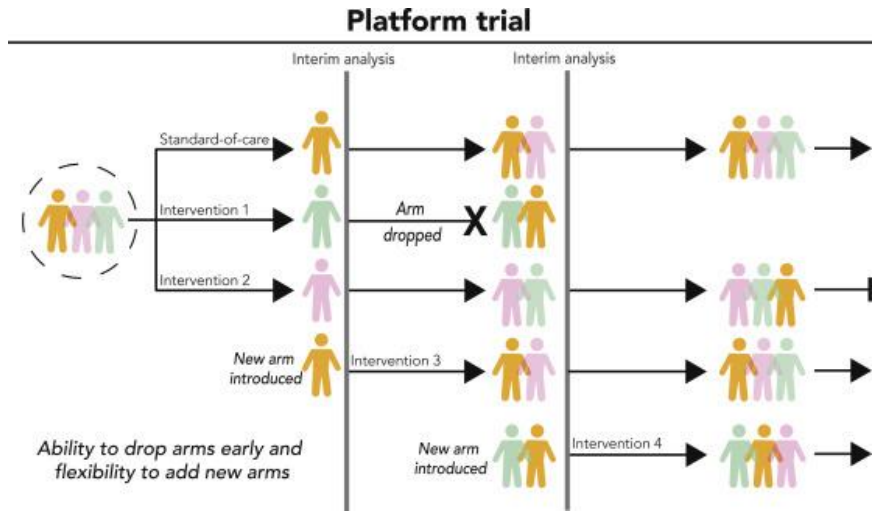
Outcome of a workshop series between HTA bodies and regulators

https://www.ema.europa.eu/en/documents/other/joint-htab-regulatory-perspectives-understanding-evidence-challenges-managing-uncertainties-exploring-potential-solutions_en.pdf

NCPE
National Centre for Pharmacoeconomics, Ireland

There is a strong preference for randomised evidence from both HTAbs and regulators.

- Despite recognised limitations, **single-armed trials** often used where RCTs possible
- **Novel randomised designs** present a promising approach in many situations
- **RCTs** may be feasible before marketing authorisation but infeasible afterwards – **randomise early in development process**
- **Pragmatic RCTs** to close the evidence gap in the post-launch phase



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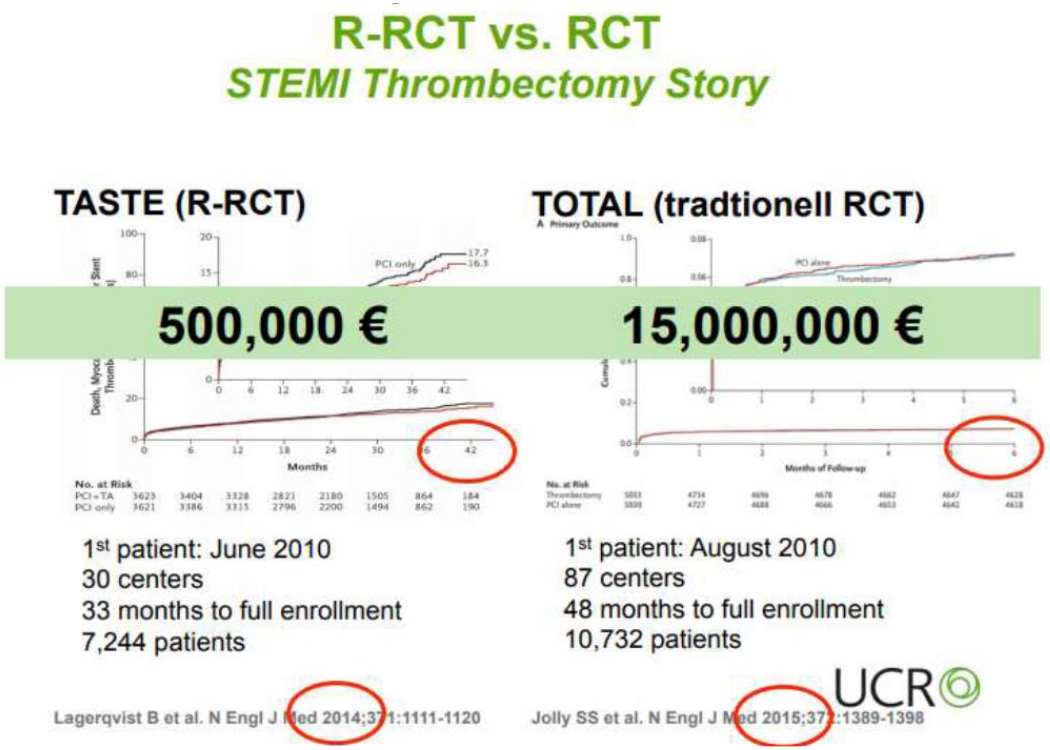
National Centre for Pharmacoeconomics, Ireland

Opportunities to advance the use of real world data for high-quality evidence generation

- Registry-based RCTs - enrolment and outcome measurement via registry
- Investigate potential surrogate outcomes
- Inform future trial design

Investment in **high-quality disease registries** required to advance evidence generation



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Next steps for collaboration on methodology

- Establish a **methodology network** in the EU HTA community
- Publish **guidance documents** on key methodological issues
  - Adaptive randomised designs (e.g. platform trials)
  - Pragmatic trials
  - The estimand framework
  - External controls
- Joint regulatory-HTA **assessors' discussion forum**

HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

HAG HEADS OF HTA AGENCIES GROUP

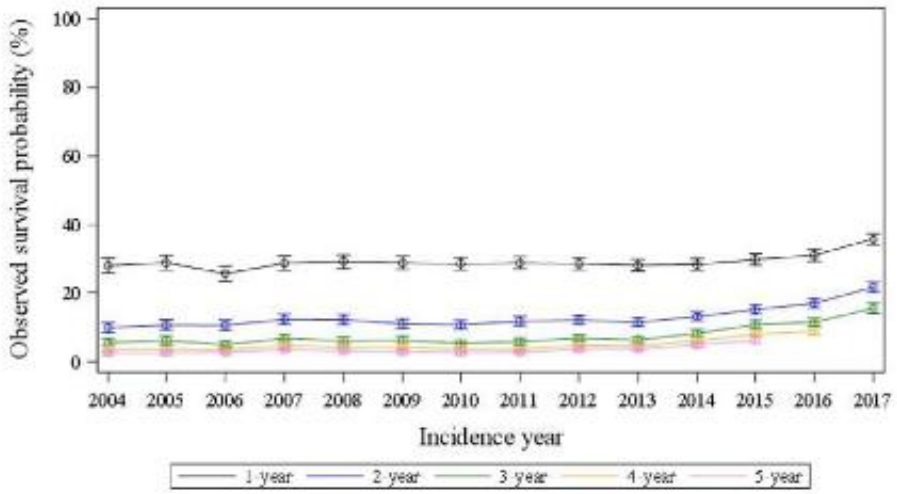
NCPE National Centre for Pharmacoeconomics, Ireland

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

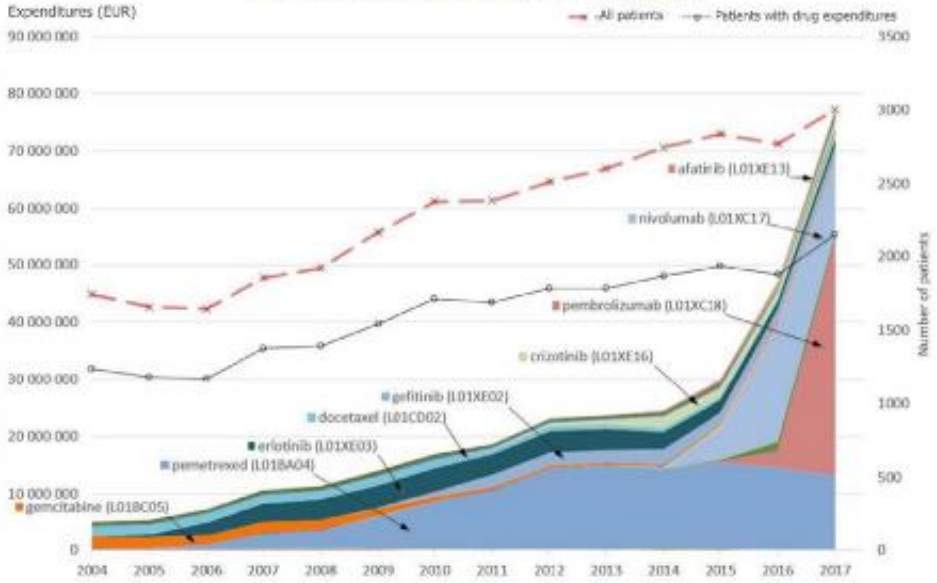
Belgian observational survival data (incidence years 2004-2017) and expenditure for innovative oncology drugs in twelve cancer indications KCE Report 343 (2021) and Eur J Cancer:182; 23-37, 2023

NON-SMALL-CELL LUNG CANCER (STAGE IV)

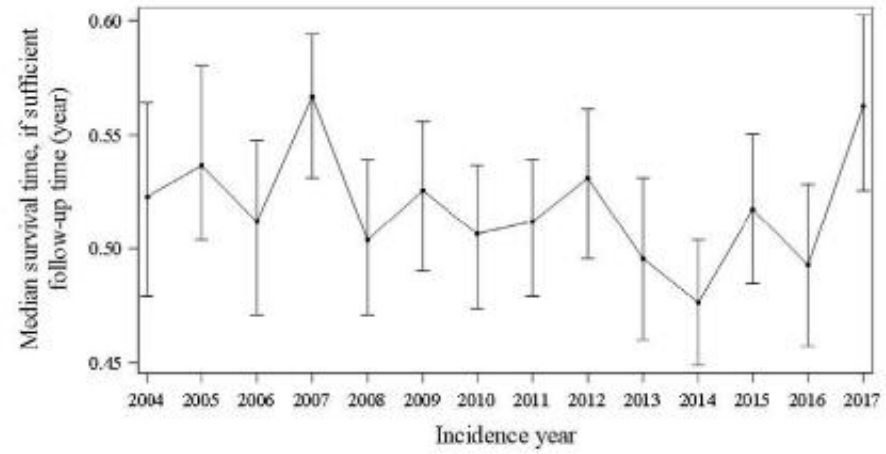
1 to 5-year survival probability



Gross cancer drug expenditures (within the first 2 years after diagnosis)



Median survival time



Average gross cancer drug expenditures (within the first 2 years after diagnosis)