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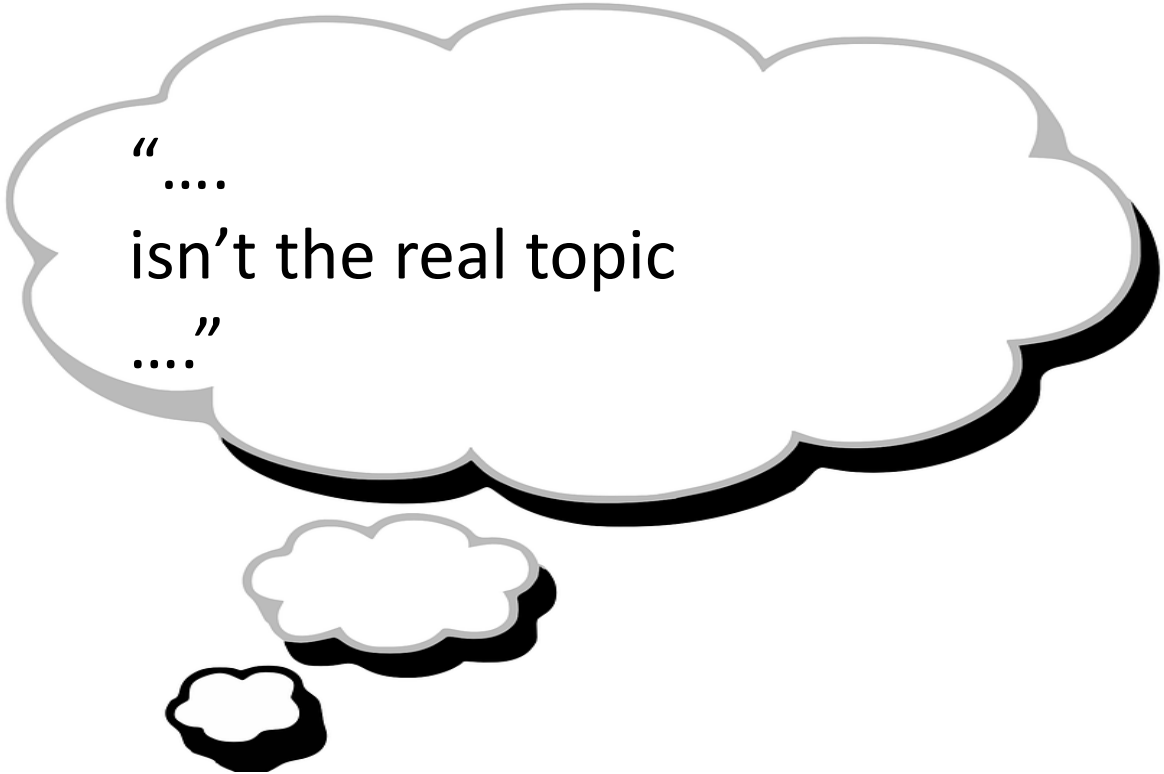
Evidence generation for innovative products in oncology

Paula van Hennik, PhD
Alternate CHMP-NL; CBG-MEB

Initial thoughts



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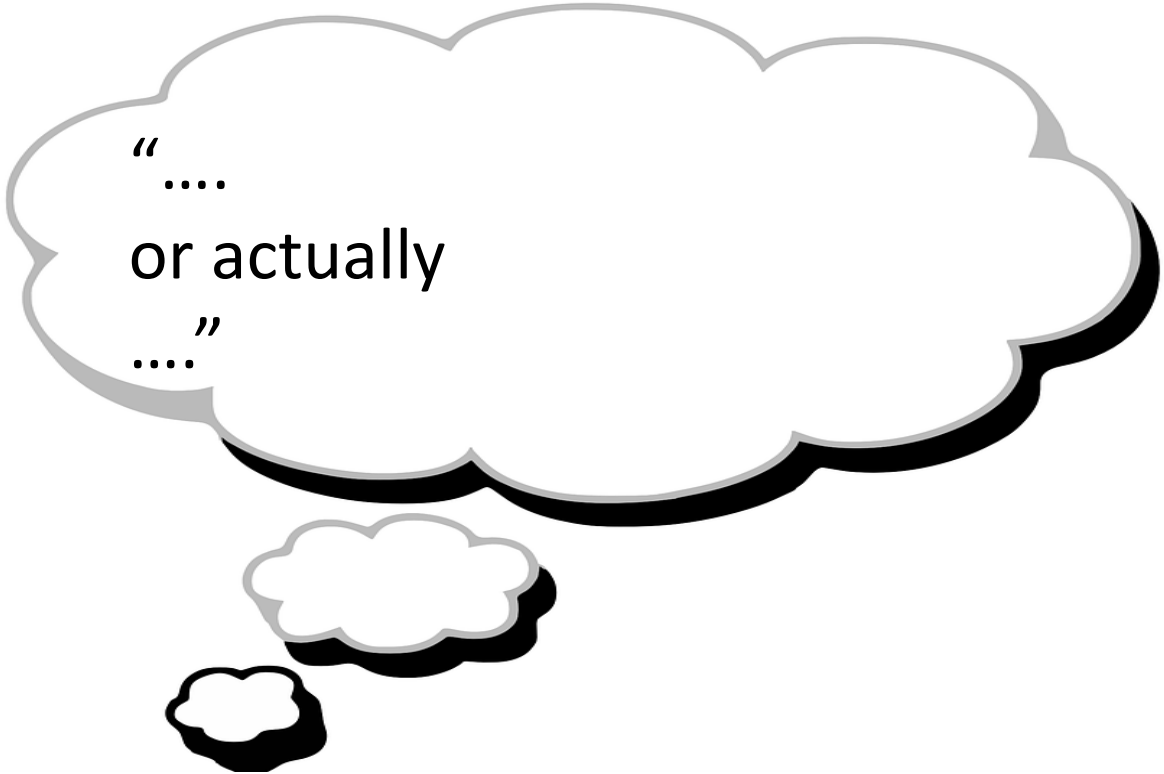
Innovative evidence generation in oncology drug development?

Further thoughts



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Innovative evidence generation in oncology drug development to speed up patient access?

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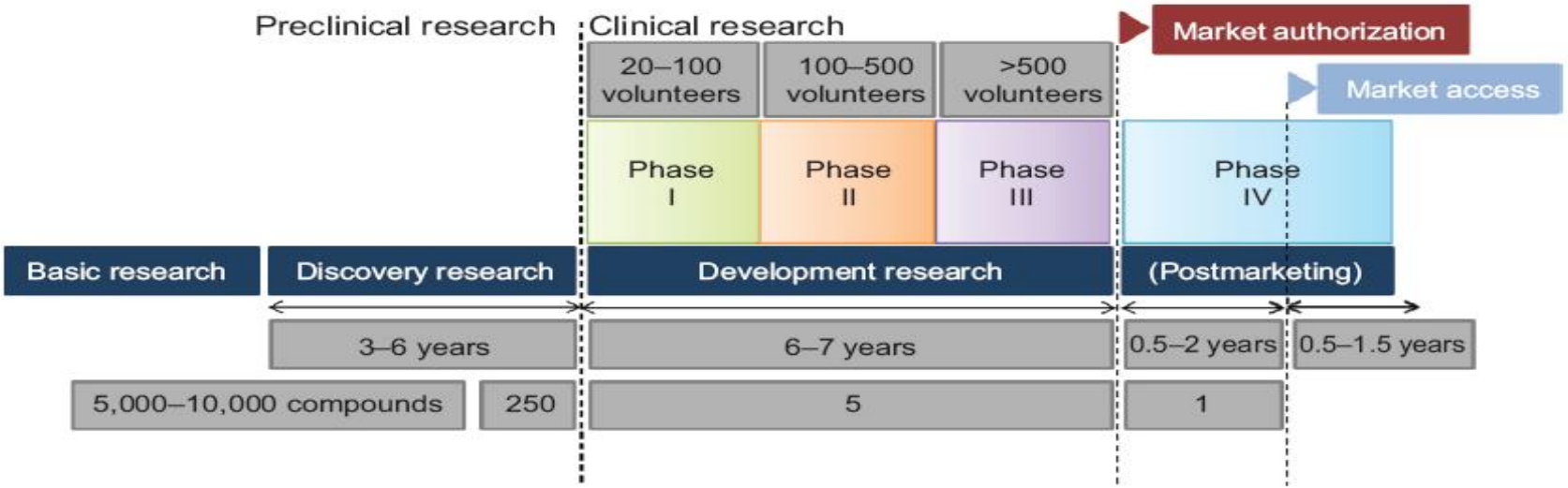
Innovative evidence generation in oncology drug development to speed up patient access - a system's approach

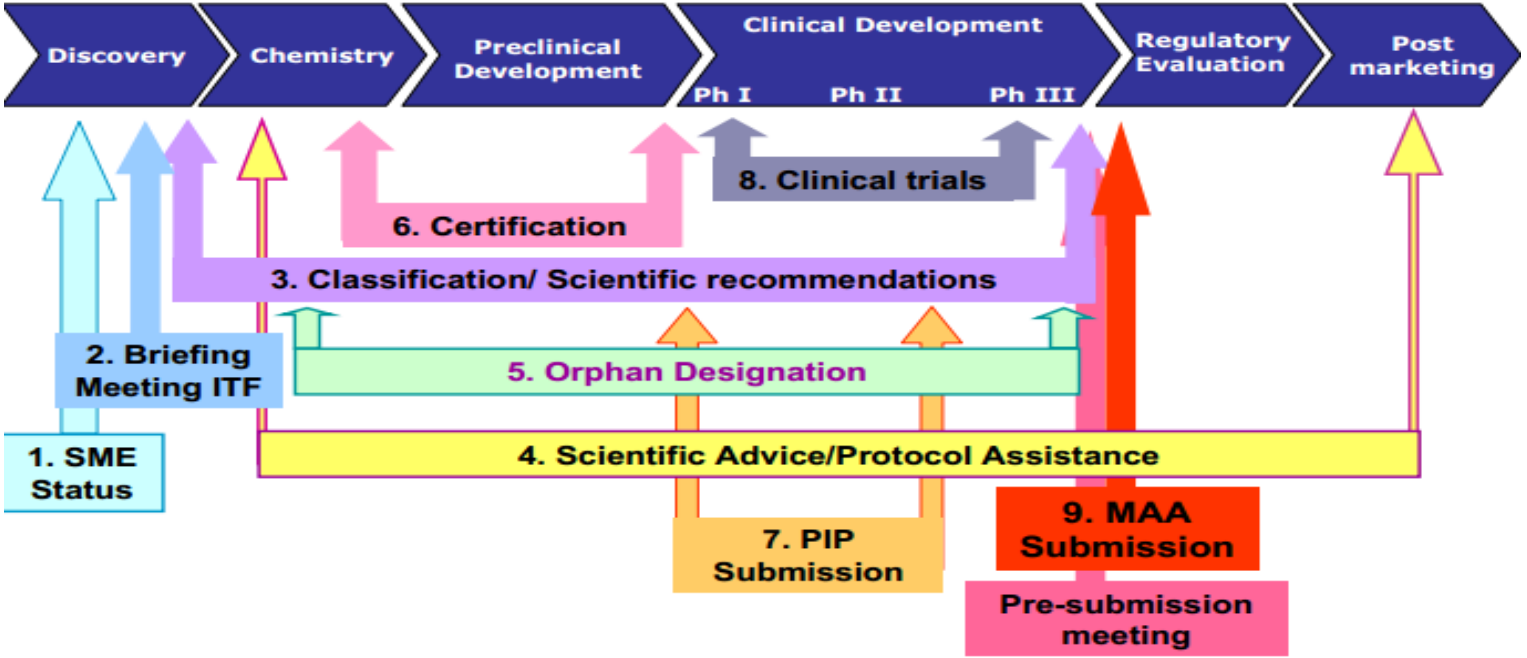
Conventional drug development



Van Nooten et al., Drug Discovery Today 2012

Regulatory processes througout the EMA

To be followed by …



Regulatory decision making

Favourable vs unfavourable effects

with

uncertainties

→

assessment of the **benefit/risk**

for that **product**

in that **target population**

But then …
the work is not done yet ….

↓

Re-imbursement - yes/no

↓

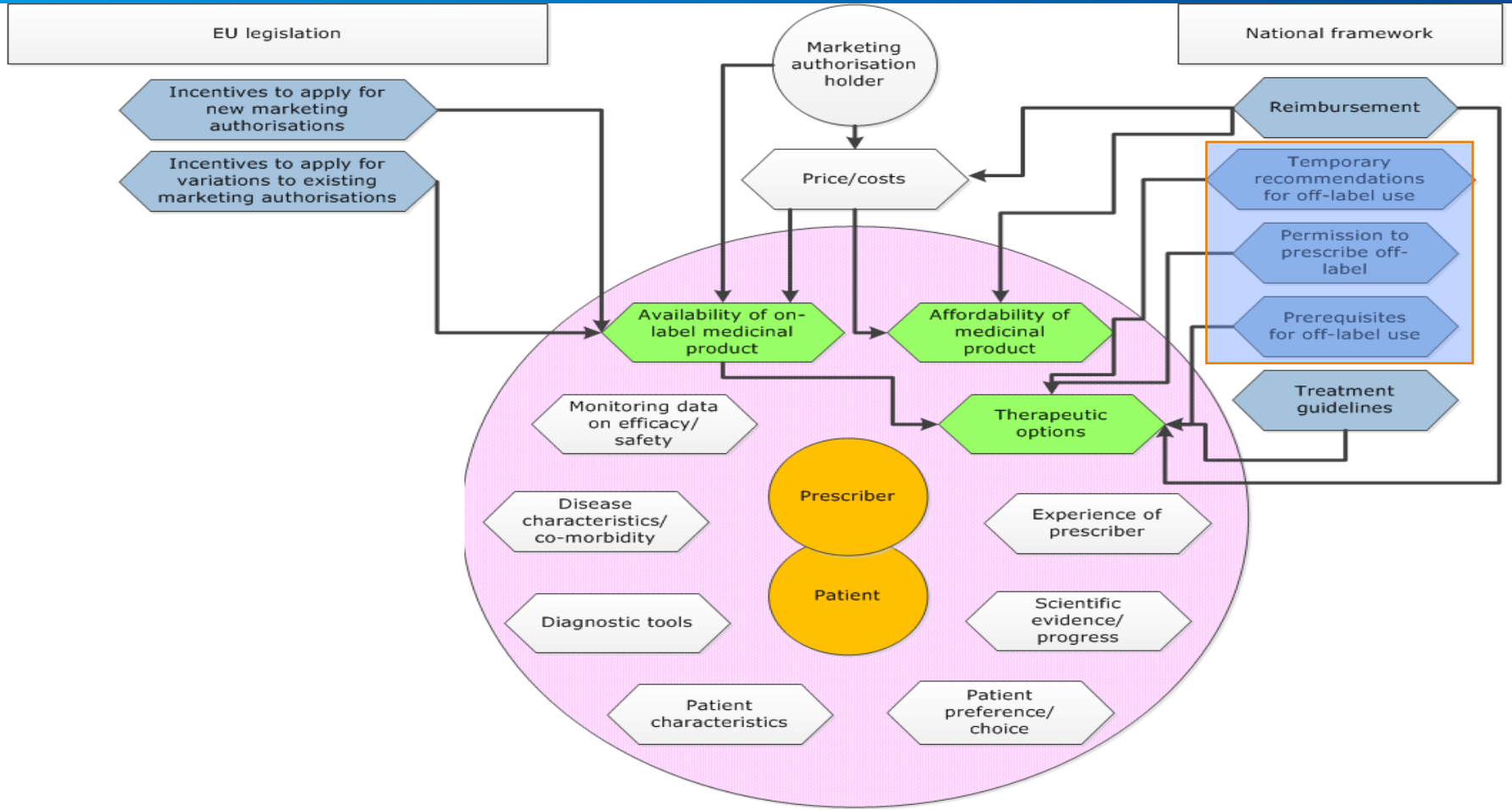
“Embraced” by professional community - yes/no

↓

Discussions by individual physician and patient

↓

Patient is treated – yes/no



Bron: Weda M, Hoebert J, Vervloet M, Moltó-Puigmarti C, Damen N, Marchange S, Langedijk J, Lisman J, van Dijk L. EU-report '**Study on off-label use of medicinal products in the European Union**'; European Union, 2017.

The gold standard for confirmatory trial design

Double-blinded randomised controlled trials (RCTs) represent the gold standard for performing confirmatory clinical trials to demonstrate efficacy and safety of new drugs

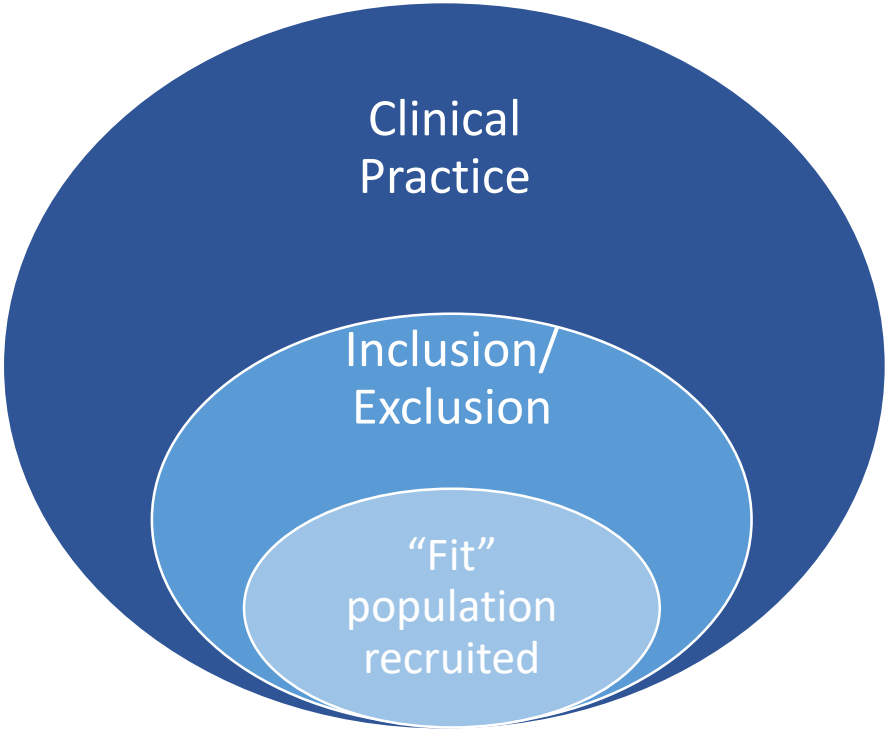
Minimize bias by design -> strengthening the evidence that differences in outcomes are due to the treatment

RCTs are not perfect: external validity

Balance homogeneity to interpret an overall treatment effect vs heterogeneity for generalisability

Questions to ask:

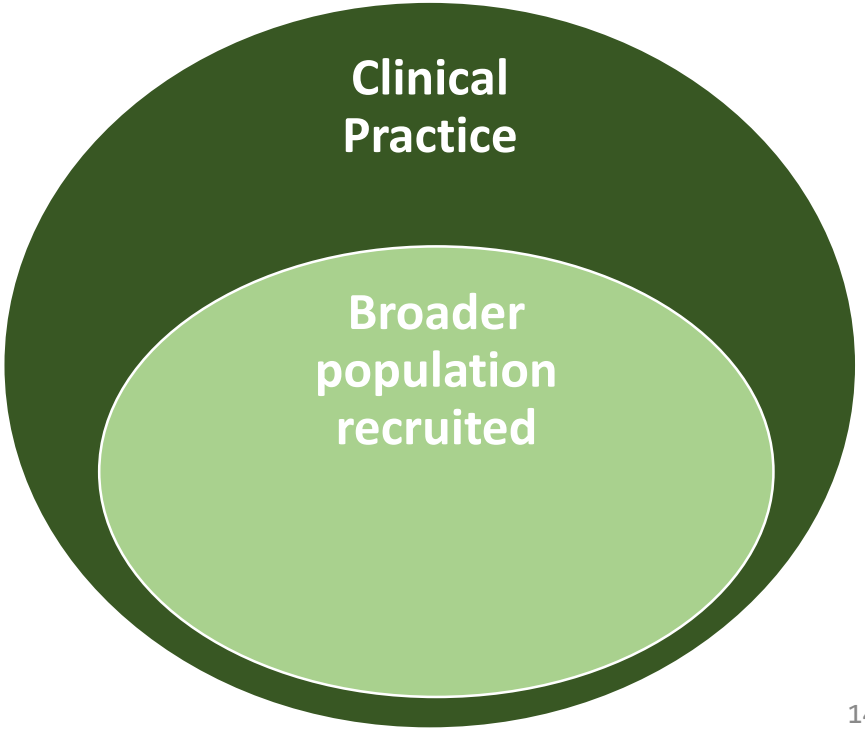
- do regulators impose excessive homogeneity?
- should the balance lie more towards generalisability?



RCTs are not perfect: generalisibility – inclusion/exclusion

homogenous study population

heterogenous study population



RCTs - interpretation of data

Also - how should we interpret the treatment effect in clinical trials?

- The average effect across a population of patients regardless of whether they continue with treatment or not, take other treatments or not etc.?
- The effect in patients who complete the treatment and follow-up?
- The effect if all patients had completed treatment and follow-up?

RCTs - interpretation of data

Or …?

- What chance I can tolerate and continue taking the medicine?
- What toxicity might I experience?
- If I can continue, what beneficial effect can I expect?

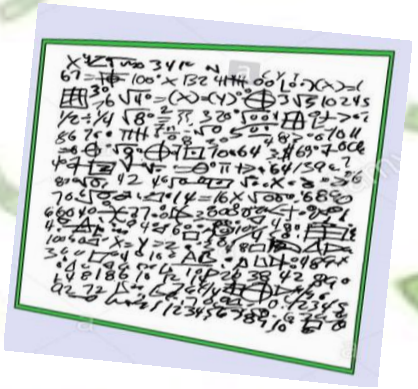
→ **Research question or “estimand” determines design**

Comments …

Slow

Complex

Expensive



If not RCTs, then what?
SAT as basis for approval

On the down-side - single-arm trials (uncontrolled studies) are associated with substantial uncertainties in benefit/risk (B/R) assessment:

- Impact of the selected trial population on the magnitude of effect.
  (in RCT a control arm can be used to 'calibrate' the trial)
- No/Limited data on prognosis in biomarker defined subset
- Size of the treatment effect (relative to standard of care)
- Acceptability of the safety profile compared to (a) standard of care

So - B/R assessment based on uncontrolled studies is complex due to lack of context - can this be "fixed" by external controls?

ICH E10 – on control groups

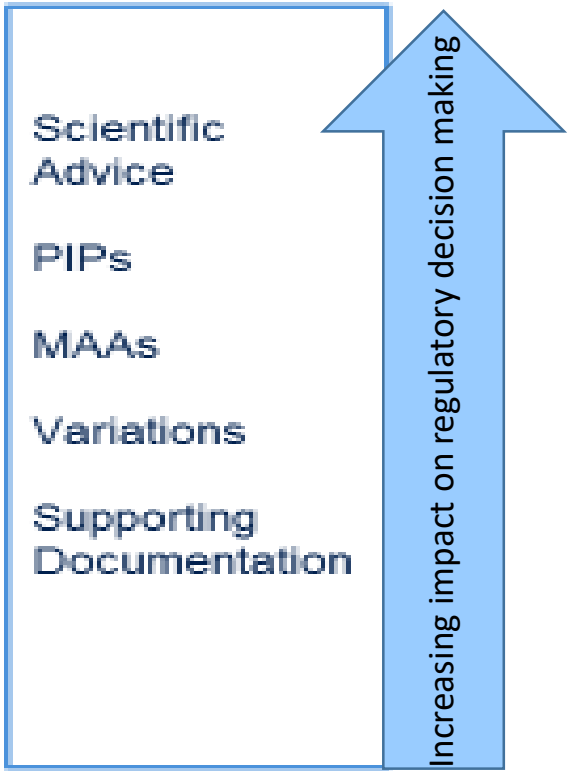
"The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized."

So yes, it can be "fixed", but only in specific cases and only to a certain extent …

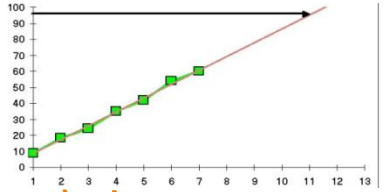
If not RCTs, then what? Modelling and Simulation

Powerful tools to study effect modifiers:
- at the patient level
- at the level of the healthcare system?

Be wary of post-hoc modelling



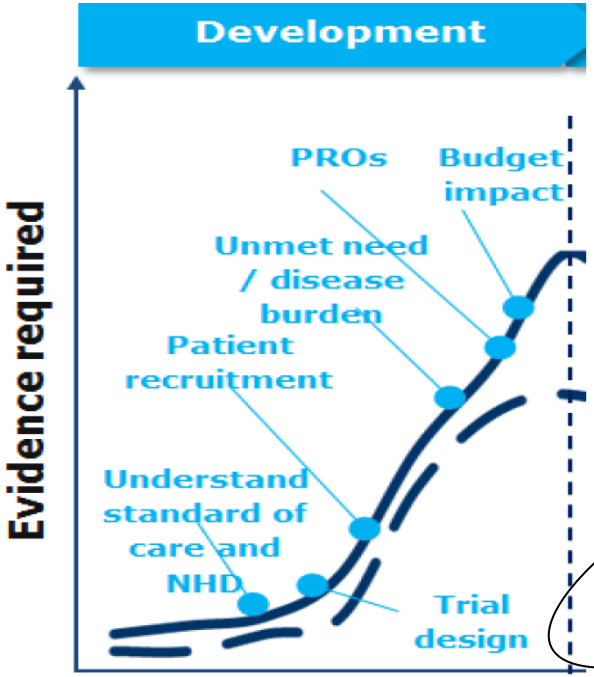
If not RCTs, then what? Extrapolation



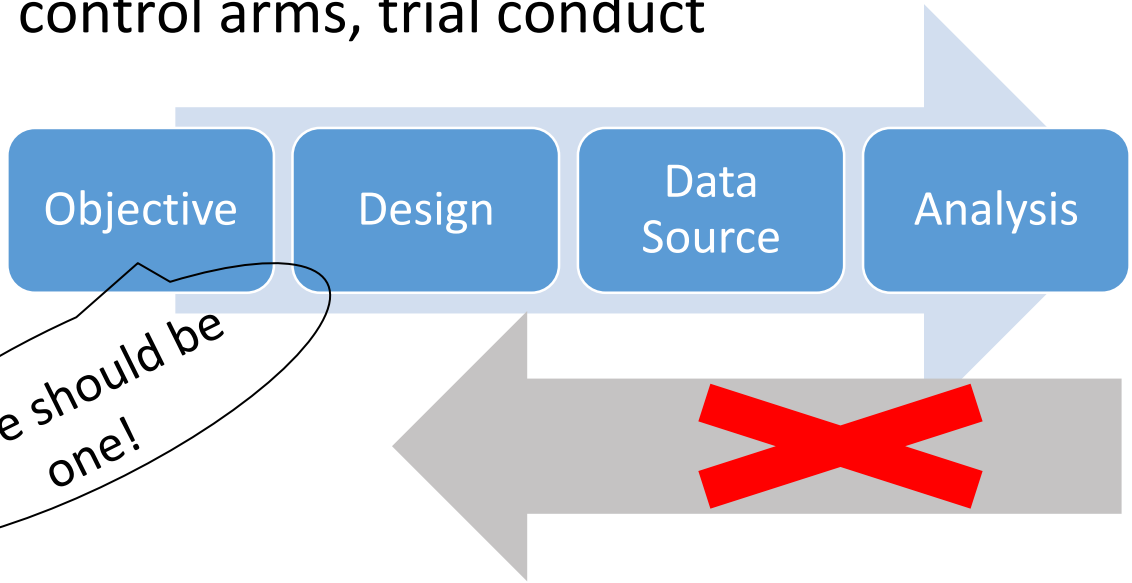
- Extrapolation concept
  - What evidence is available that elicits this question?
  - Under what conditions will conclusions in (predictions from) the source population hold true (be valid) in the target population?
- Extrapolation plan
  - Prospective evidence generation to demonstrate that conditions hold
  - Supportive evidence on efficacy and safety directly

Interesting – but both M&S and extrapolation are best used to answer complementary questions when robust controlled trial (CT) data are available

If not RCTs, then what?
Real World Evidence

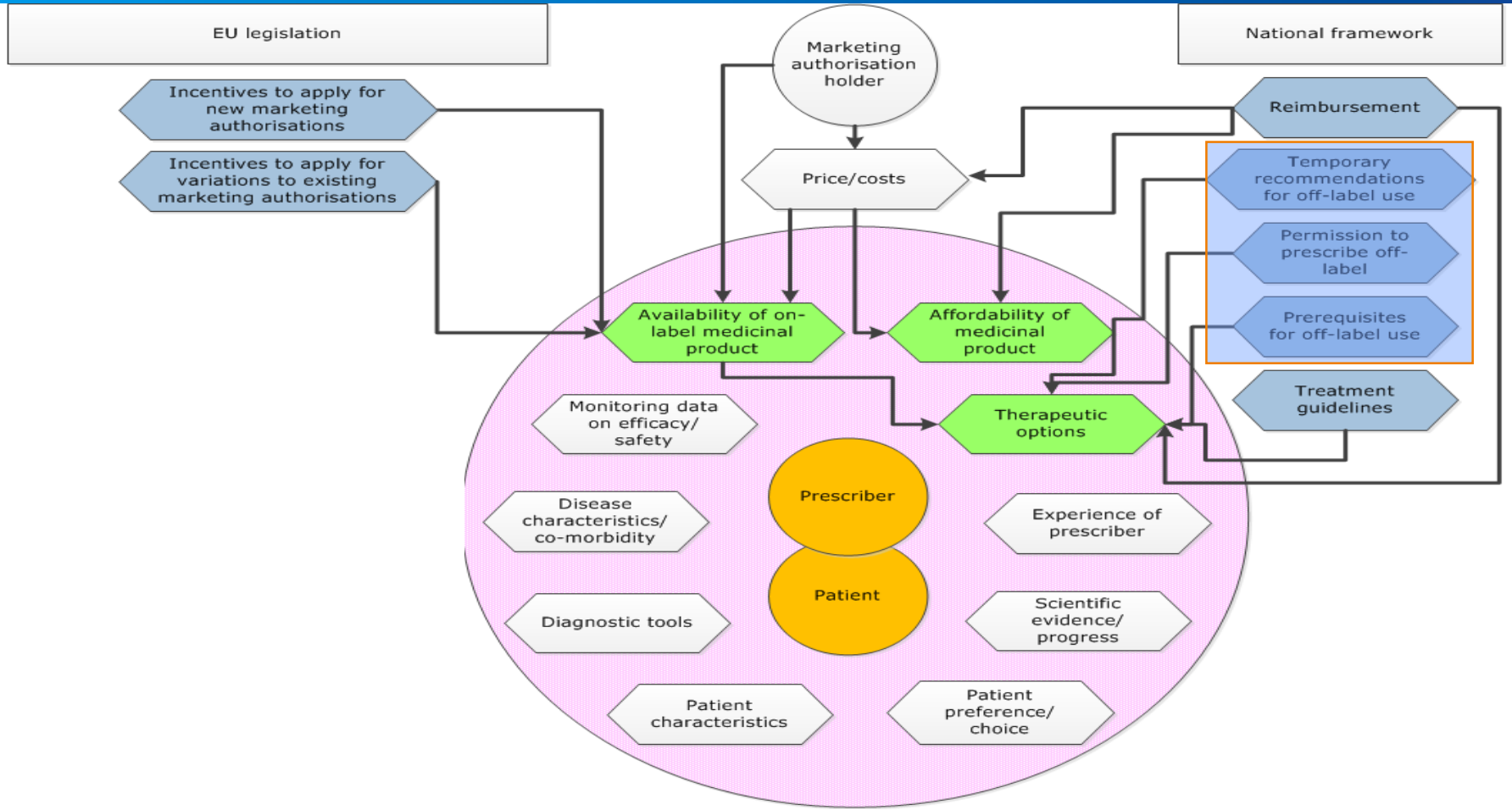


For use for RWE we need understanding of epidemiology, trial planning, external control arms, trial conduct



And we have not even discussed yet …

- Umbrella trial
  - molecular marker-driven
  - histology-driven
- Basket trial
- Adaptive (“seemless”) trial
- “Window-of-opportunity” trial



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Available regulatory tools for early dialogue and early patient acess

Stage of regulatory evaluation	Characteristic	EMA	FDA
Marketing authorization (benefit/risk evaluation)	Early and continuous dialogue	Adaptive pathways	Fast track Breakthrough therapy designation
	Faster evaluation	Accelerated assessment	Fast track Priority review
	Less evidence	CA Exceptional circumstances	AA
Market access (relative effectiveness/ cost-effectiveness evaluation)	Early market access (limited to EU market)	Managed entry agreements ~~Cancer Drugs Fund (UK)~~ EAMS (UK) Joint HTA advice	Payers decisions, rebates and negotiations (plus Medicare/ Medicaid)

PRIME

"we should remember that most regulations in this area *(i.e. drug development)* had followed huge public health disasters jeopardizing the health of thousands of people, and, indeed, **patients' safety and wellbeing should be in the foreground in all stakeholders' agendas**"

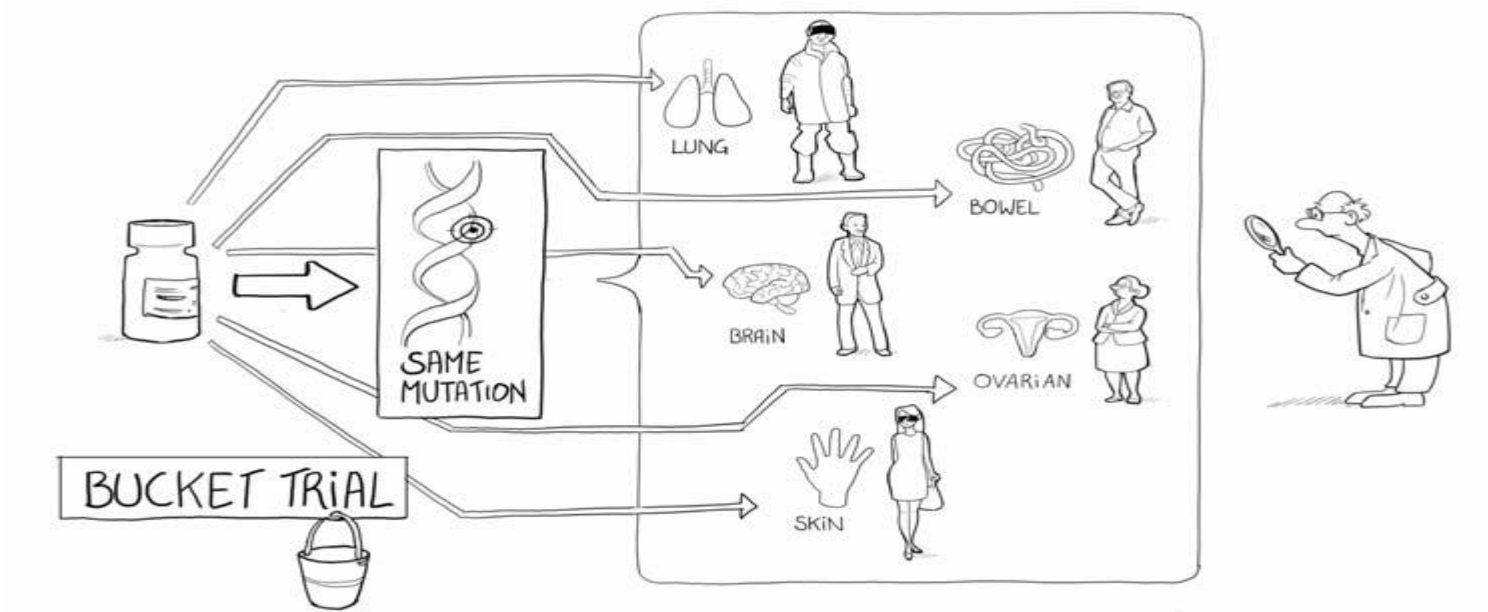
Leyens et al Public Health Genomics 2015

Take home message

- Have a clear development plan
- **Remember** –
  - controlled trials (CT) are the backbone for evidence on treatment effects
  - other routes to evidence generation provide important complementary evidence to support planning, interpretation and extension of CT data
- Ask for regulatory advice on development strategy
- Ask for (combined) scientific advice
- Involve patients, physicians and HTAs early

Thank you

Roche – you tube



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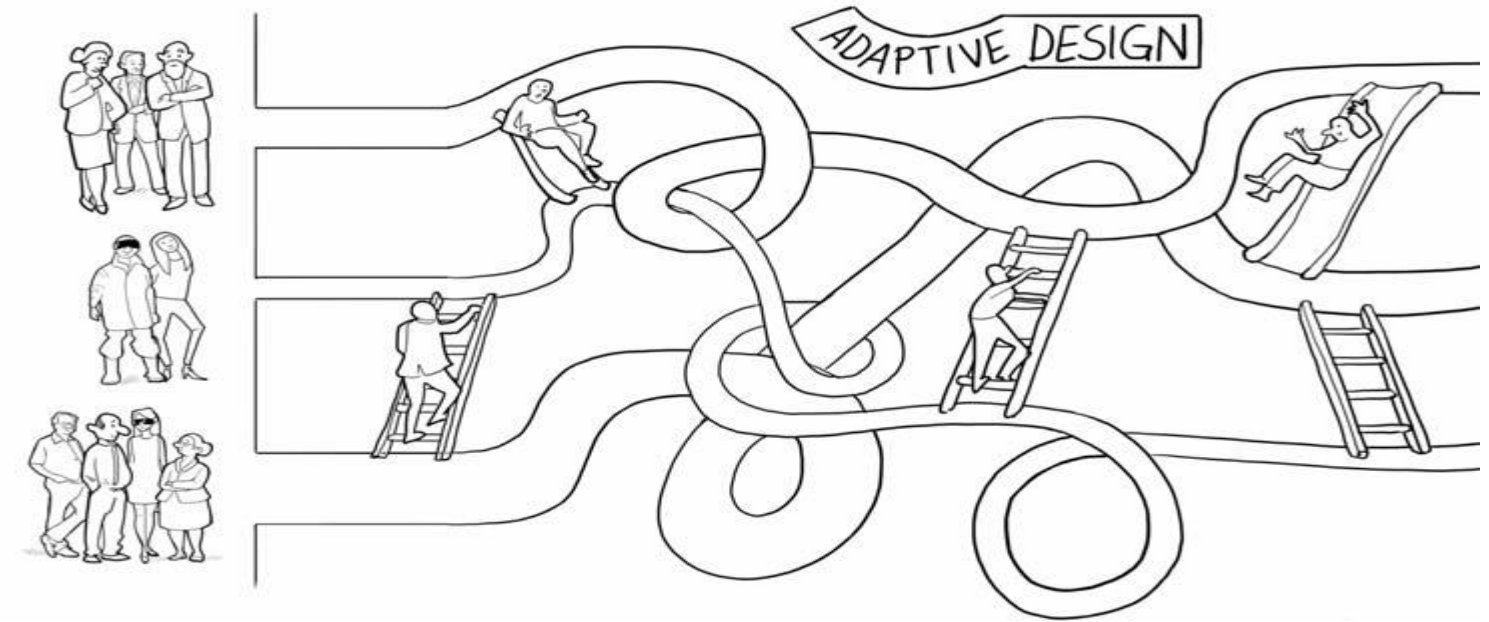

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