ASSESSING LONG TERM LATENCIES FOR NEWLY MARKETED DRUGS: MISSION IMPOSSIBLE FOR THE EPIDEMIOLOGIST?

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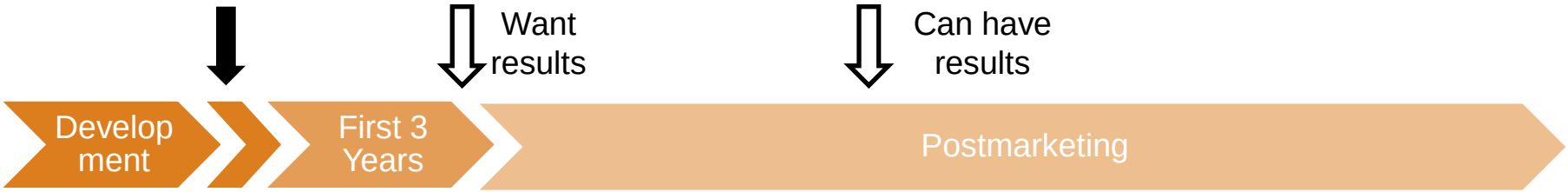
Basel Epidemiology Seminar, 23-Jun-2017

THE PROBLEM

LONG TERM LATENCY IN NEWLY MARKETED PRODUCTS



@ **Launch:** Knowledge gaps

- Long term safety effects (e.g. malignancy)
- Long term efficacy/effectiveness outcomes

Challenges for studying long term latencies at launch of a new product:

- Follow-up time in clinical trials too short to assess outcomes with long latency + study population restricted: limited knowledge about drug-outcome association from development program
- No knowledge about market uptake of the drug, its place in the treatment landscape, and patients' adherence to treatment
- High pressure from different stakeholders, e.g. with respect to timelines
- Paradigm for risks: early detection vs. statistical power

EXAMPLES OF DRUGS APPROVED IN 2016

EMA HUMAN MEDICINES HIGLIGHTS 2016

Innovations advancing public health

Innovation in healthcare brings new opportunities to treat certain diseases and is essential to advancing public health. Therapeutic innovations in 2016 included:

Haematology/ Haemostaseology

Coagadex

replaces the missing factor X, thereby helping the blood to clot and giving temporary control of bleeding in patients with hereditary factor X deficiency

Zalmoxis

an advanced therapy medicine for patients receiving a haploidentical haematopoietic stem cell transplant (HSCT), which contains T cells that have been genetically modified

Metabolism

Galafold

binds to the defective alpha-galactosidase A enzyme and restores its activity in patients with Fabry disease

Immunology

Strimvelis

a gene therapy manufactured from a patient's own immature bone marrow cells that improves their ability to fight infection

Infections

Zavicefta

inhibits the action of beta-lactamase enzymes involved in bacterial resistance to certain antibiotics

Rheumatology

Olumiant

blocks the action of Janus kinase enzymes (JAKs) reducing inflammation and other symptoms of rheumatoid arthritis

Source: ema.europe.eu

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Concern: Long term safety (e.g. immunogenicity, insertional mutagenesis and oncogenesis) and long term efficacy/effectiveness

Action: Obligation to conduct prospective, non-interventional study (15 years follow up)

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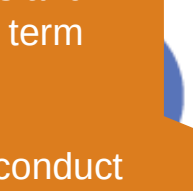

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Concern: Long term safety regarding CV risks and malignancies

Action: Proposed PASS in US insurance database, US and European registries; DUS to evaluate the adherence to risk minimization measures

Source: ema.europe.eu

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Concern: Safety and effectiveness in real clinical practice

Action: Obligation to conduct PASS using the EBMT registry including all patients treated with Zalmoxis

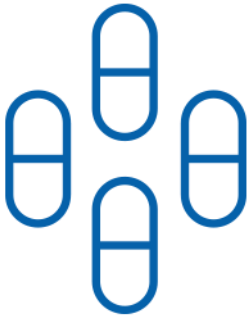
ta-lactamase
cterial resistance

us kinase enzymes
nation and other
d arthritis

Source: ema.europe.eu

TYPICAL SITUATION

BEFORE MARKETING AUTHORIZATION



ABC987Z

- New molecule ABC987Z with significant benefit vs. Standard of Care (SOC)
- Important potential risk: Cancer
- Health authority request to monitor and provide additional data for potential risk

- Strategy needed based on post-marketing data

Adequate study design to refute or confirm risk

Overall strategy addressing all stakeholders' needs

IDENTIFY ADEQUATE STUDY DESIGN

STEP 1: PHRASE THE QUESTION - UNDERSTAND SAFETY CONCERN WITH BRADFORD-HILL

Direct Is there an association?	Experiment • Finding from preclinical data, e.g. from rodent study?	Strength • Large associations → more likely causal	Temporality • Plausible lag time between exposure and disease?
Mechanistic How does the drug cause the outcome?	Biologically plausible • Biological mode of action can explain association	Biological gradient • Is a dose-response relationship to be expected?	Specificity • Which other factors could be causally related to outcome?
Parallel Is this association observed in multiple sources?	Consistency • Multiple studies or data sources report similar association	Analogy • Evidence from another drug within the same class	Coherence • Totality of evidence indicates level of uncertainty

Ref. Howick et al. (2009)

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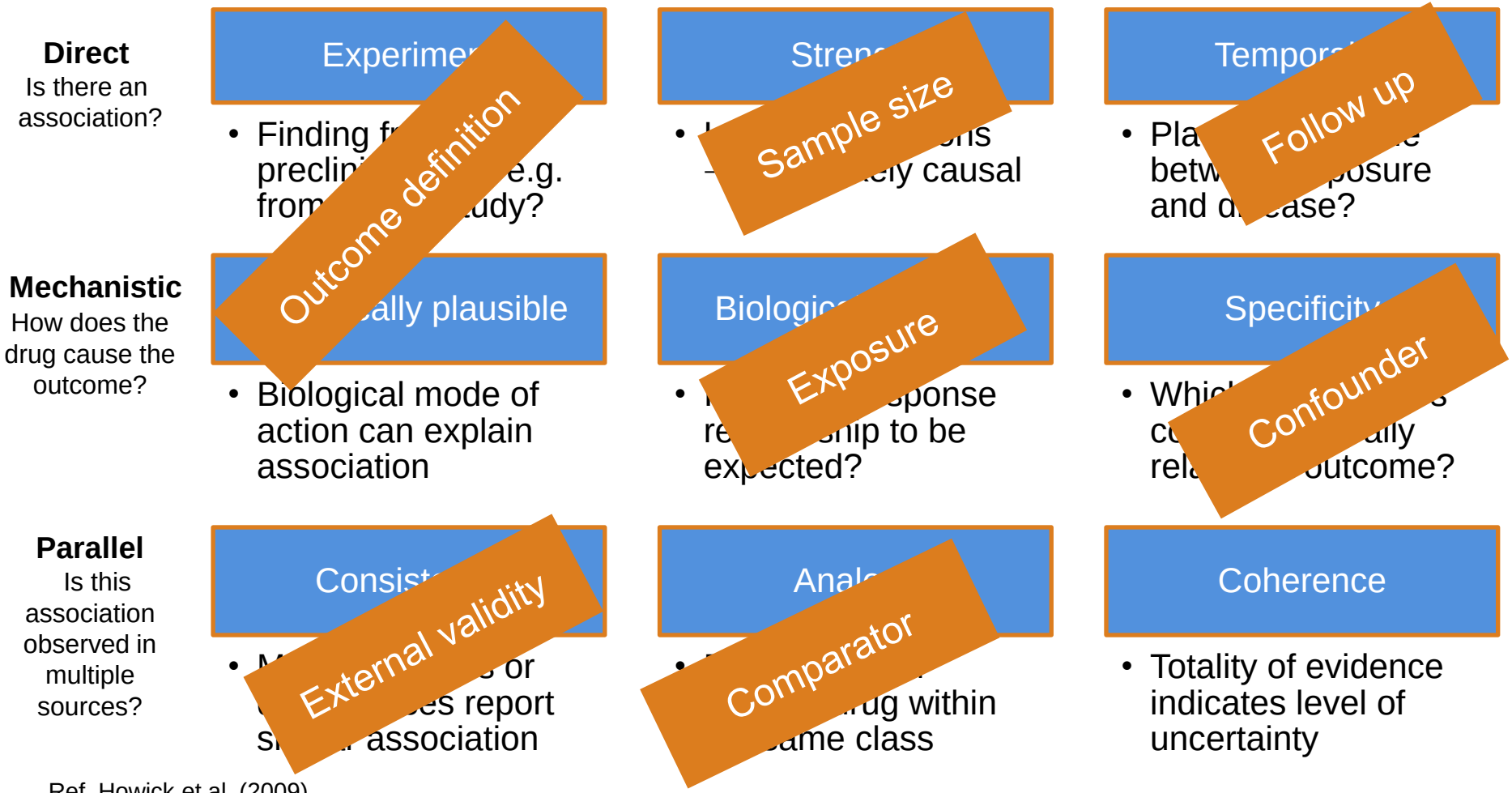

Ref. Howick et al. (2009)

IDENTIFY ADEQUATE STUDY DESIGN

STEP 2: SPECIFY DESIGN AND DATA SOURCE REQUIREMENTS

	DESIGN CONSIDERATION		DATA SOURCE REQUIREMENT
Population	Patients with particular disease who are eligible to receive drug	→	Needs to cover setting in which patients are treated (e.g. hospital, specialists, GP)
Intervention/ Study Drug	Drug use according to clinical practice	→	Complete and longitudinal observation of drug exposure with required details (e.g. dose)
Comparator	Alternative treatment indicated for the same population and not suspected to cause outcome	→	Same process of exposure measurement as for study drug
Outcome	Definition based on suspected mode of action and plausible lag time	→	High specificity of measurement/coding algorithm, non-differential assessment between treatments
Follow-up	Determined by lag time and time to reach sample size (depends on strength of effect)	→	Longitudinal capture of outcomes, exposures and potential confounders
Internal validity	Definition of confounders based on other potential causes of outcome	→	Specific and non-differential measurement of all potential confounders
External validity	Are there country-specific differences in outcome incidence, prevalence of confounders?	→	Inclusion of multiple countries, e.g. multi-study, multi-database study, multiple studies with common protocol
Data quality	Study set-up ensures reproducibility and full traceability	→	Transparent and traceable data generation process, qualified vendors have access to data

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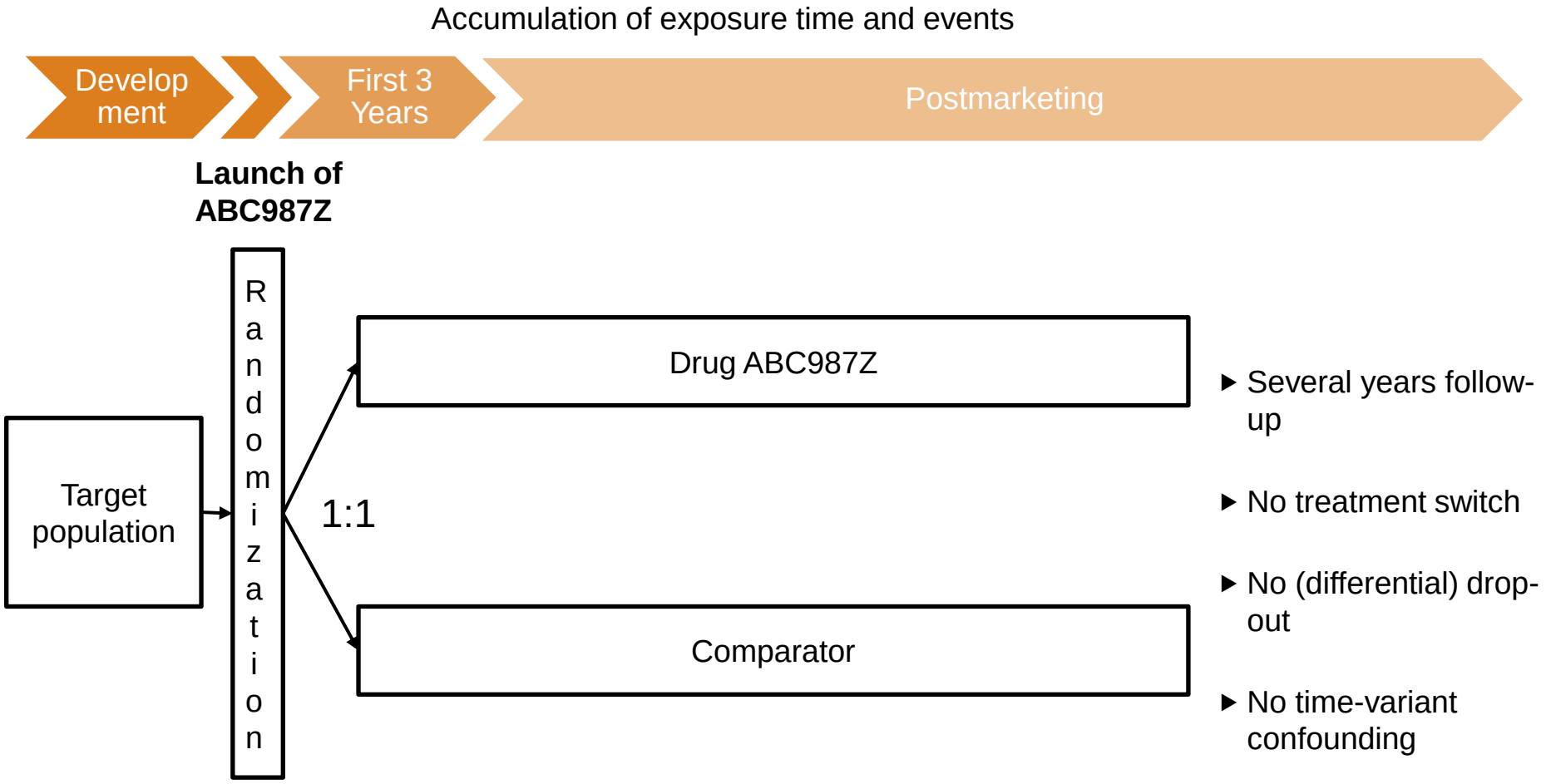
STEP 3: FROM IDEAL-WORLD TO REAL-WORLD DESIGN – INTERVENTIONAL, RANDOMIZED DESIGN



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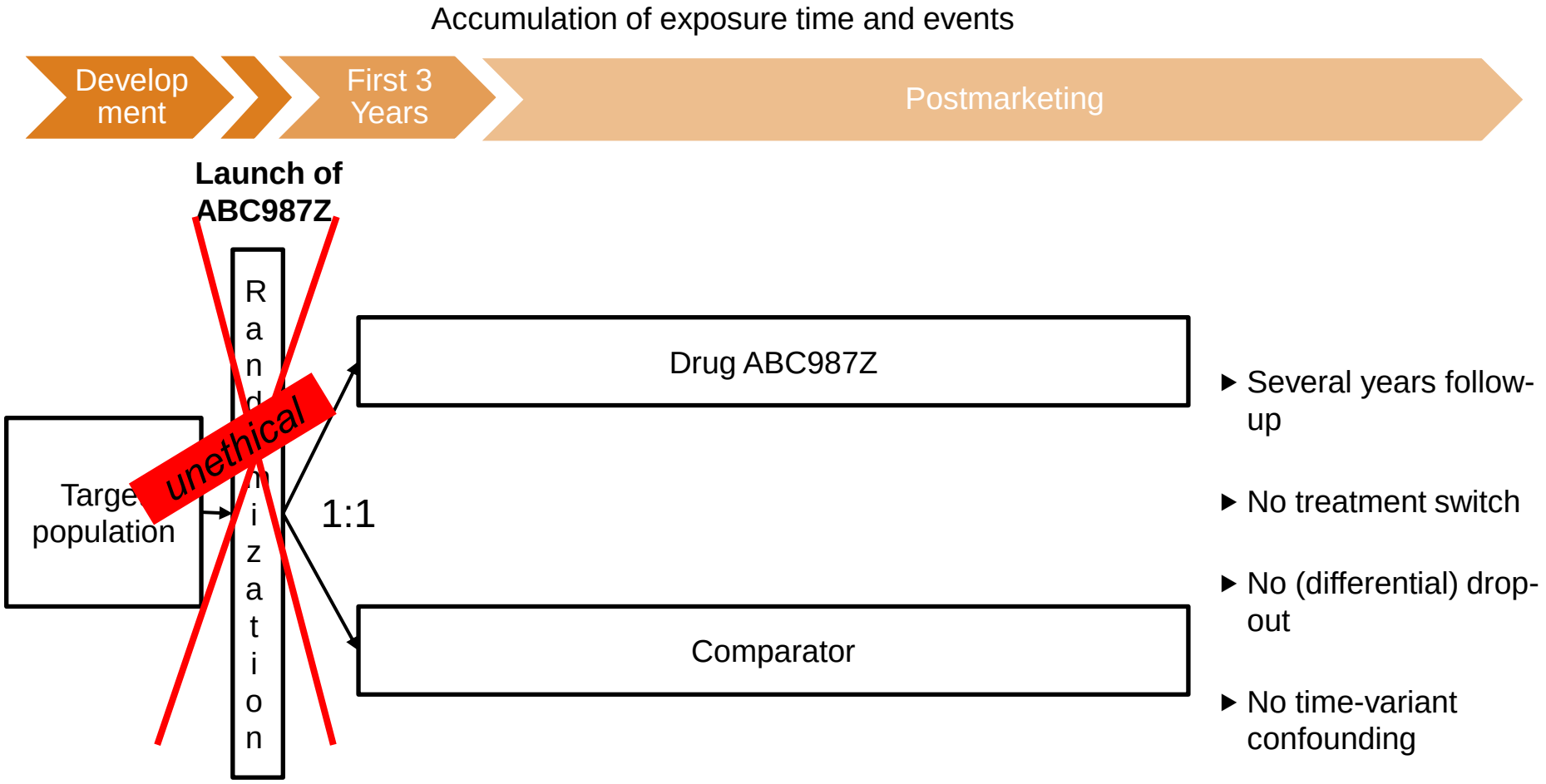

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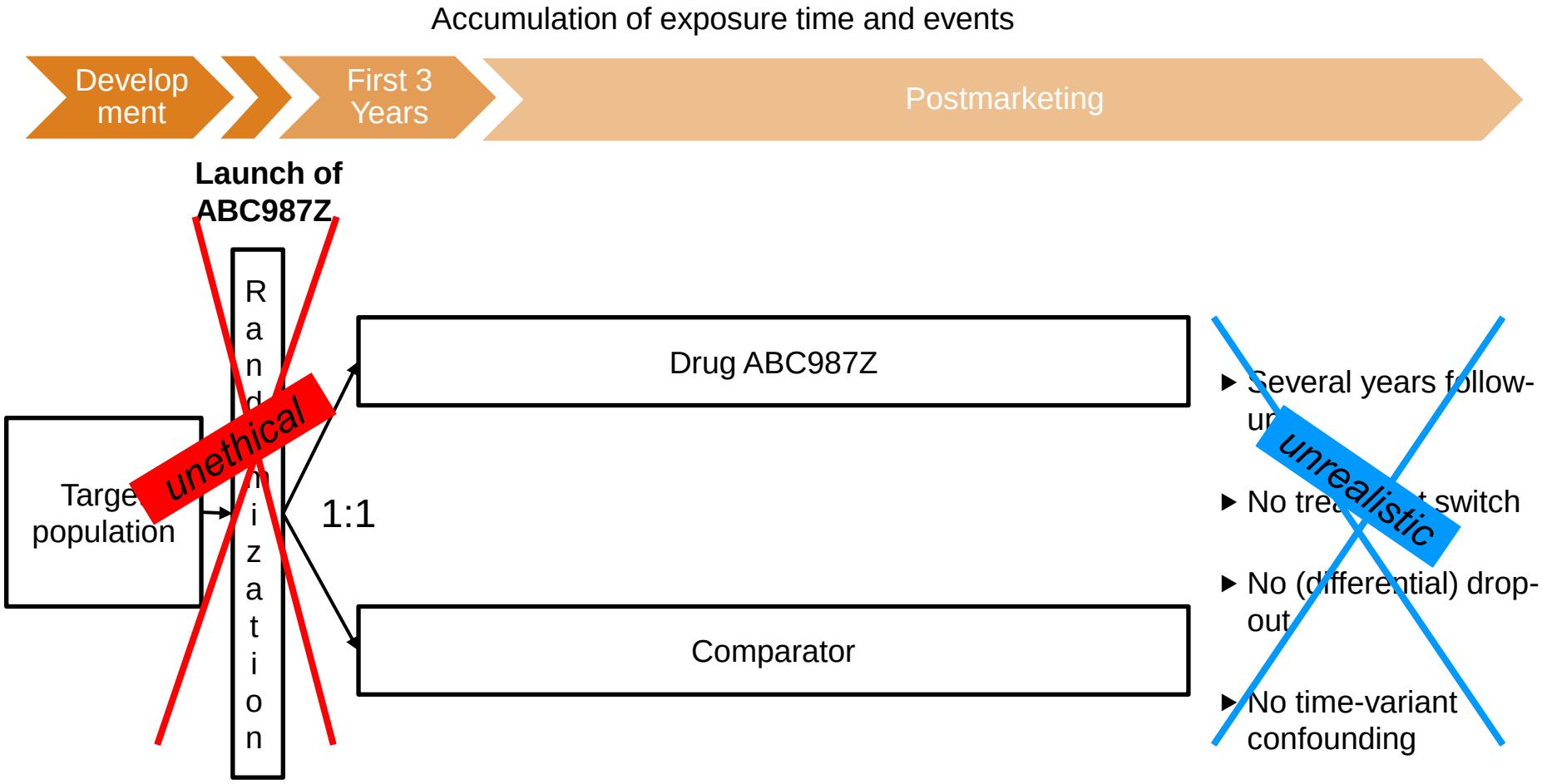

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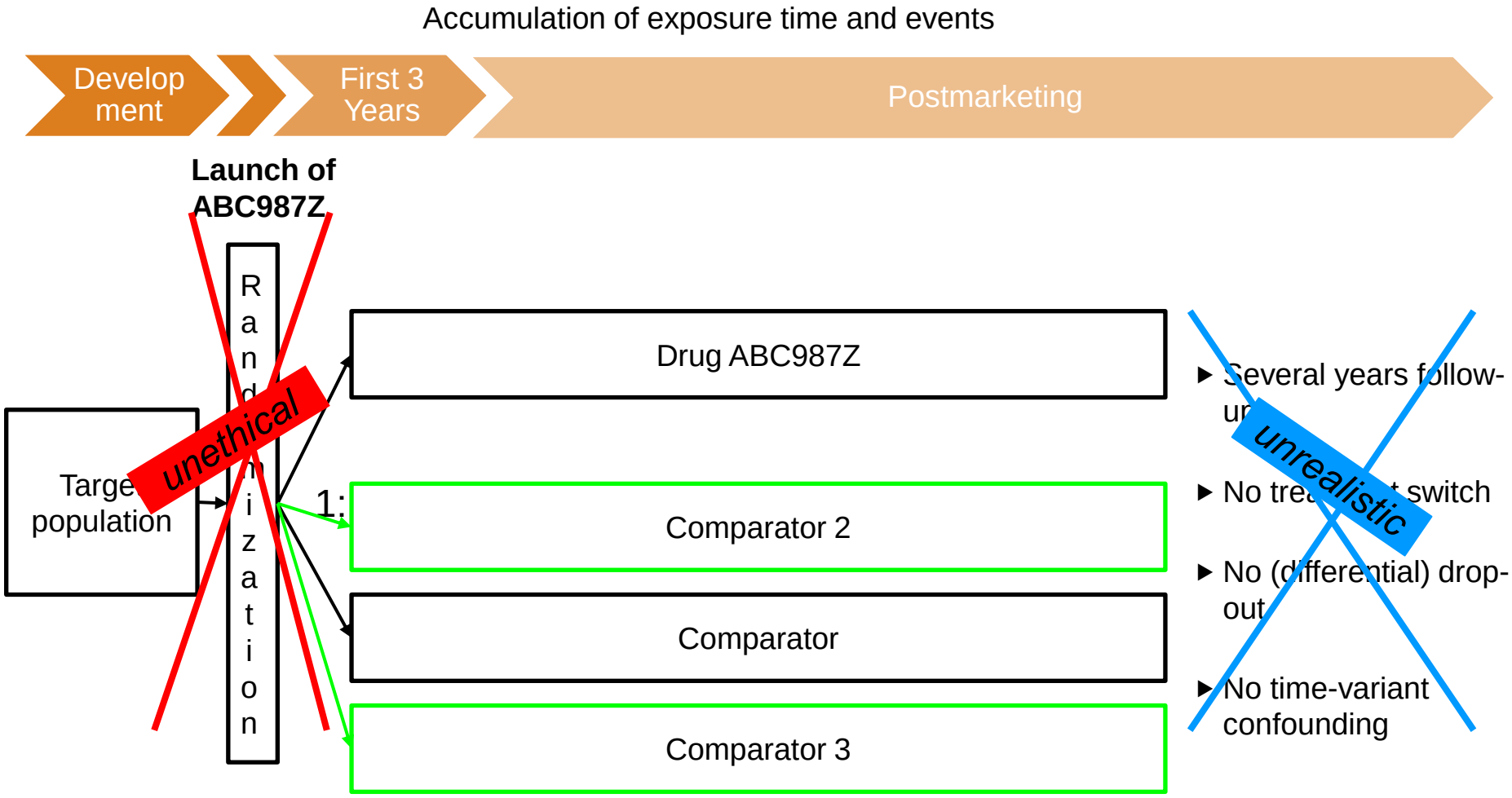
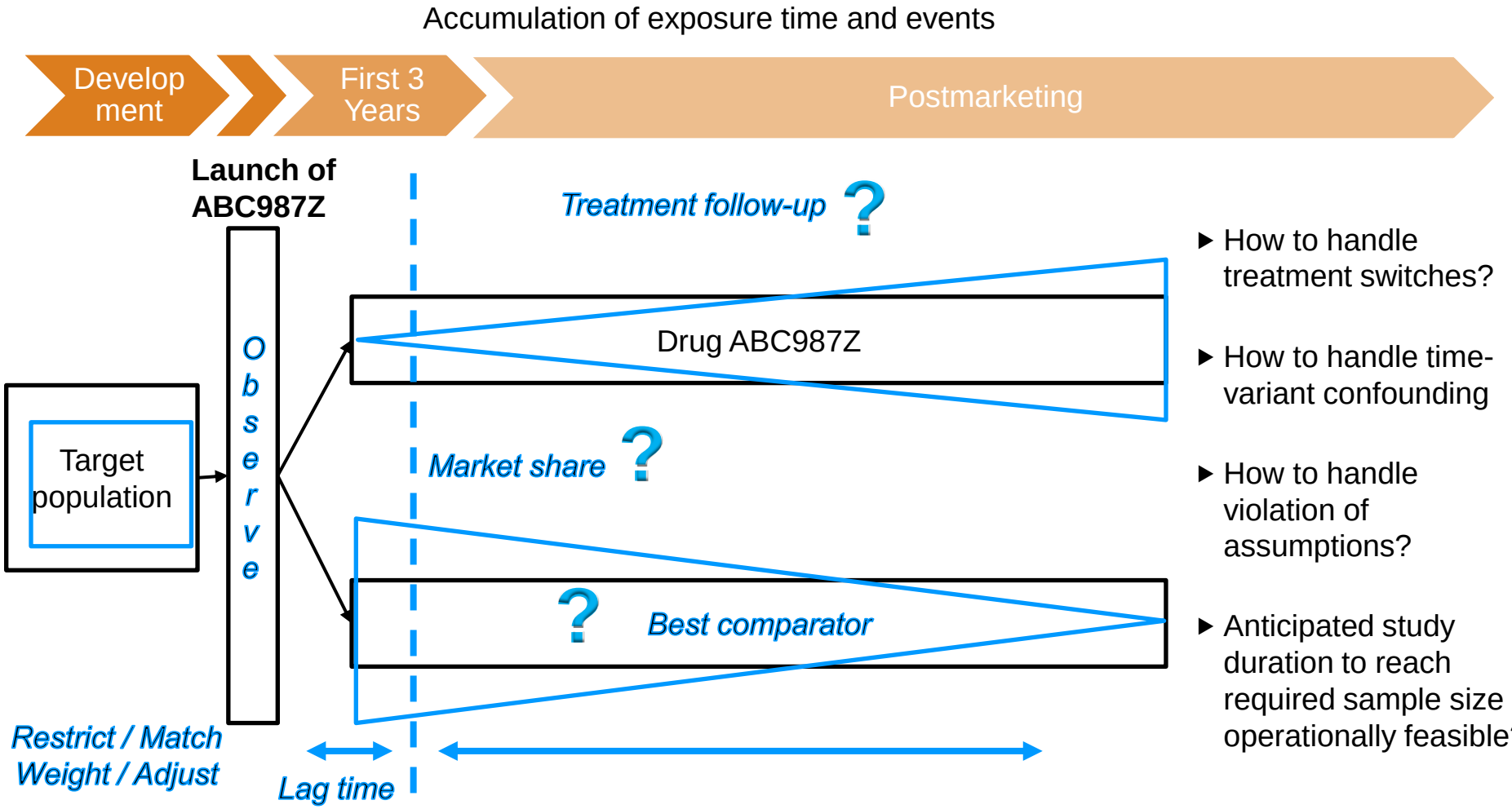


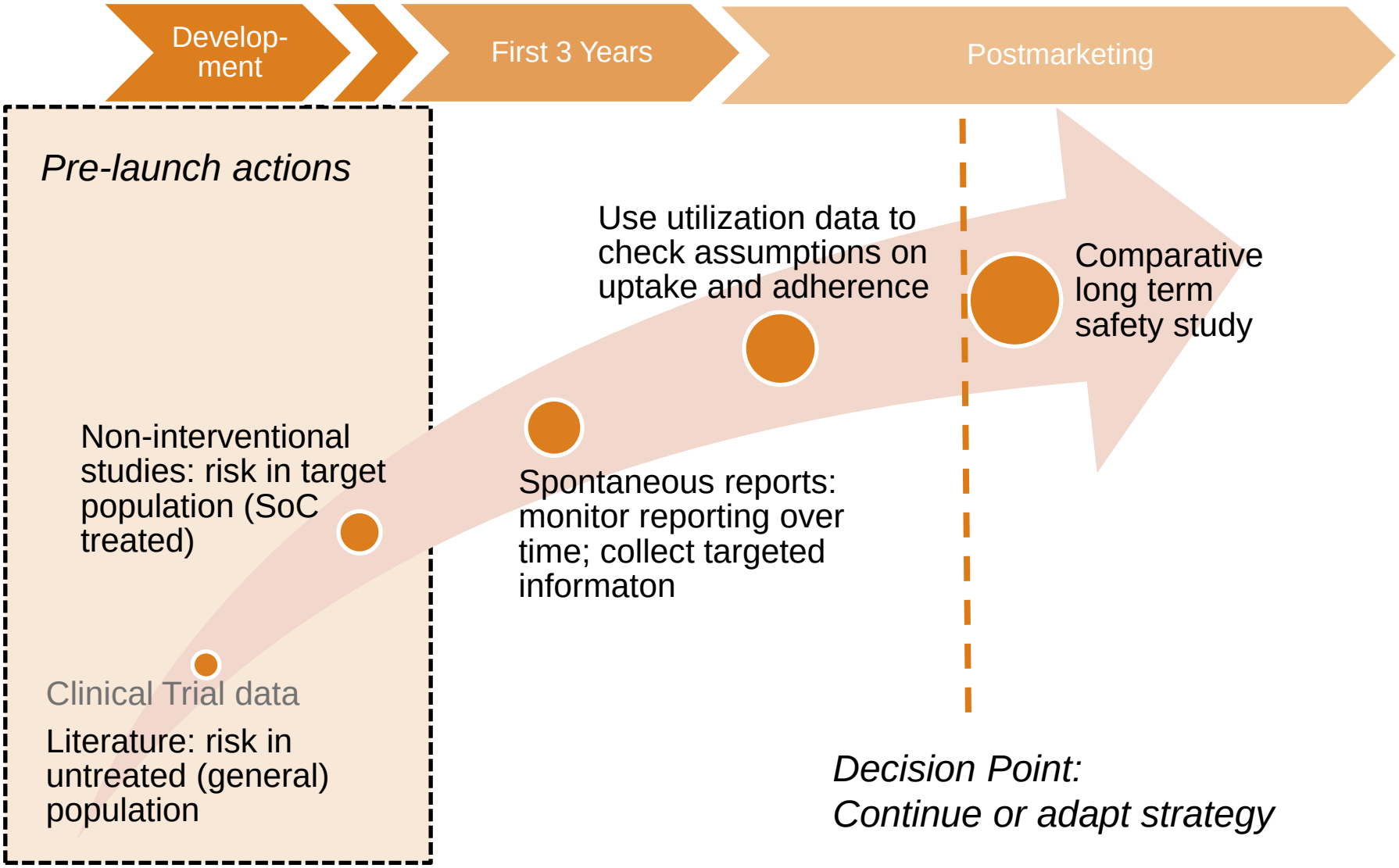
IDENTIFY ADEQUATE STUDY DESIGN

STEP 3: FROM IDEAL-WORLD TO REAL-WORLD DESIGN – ADAPT TO OBSERVATIONAL DESIGN



IDENTIFY ADEQUATE STUDY DESIGN

STEP 4: EMBED STUDY PROPOSAL IN OVERALL STRATEGY



IDENTIFY ADEQUATE STUDY DESIGN

SUMMARY

Best guesses for assumptions

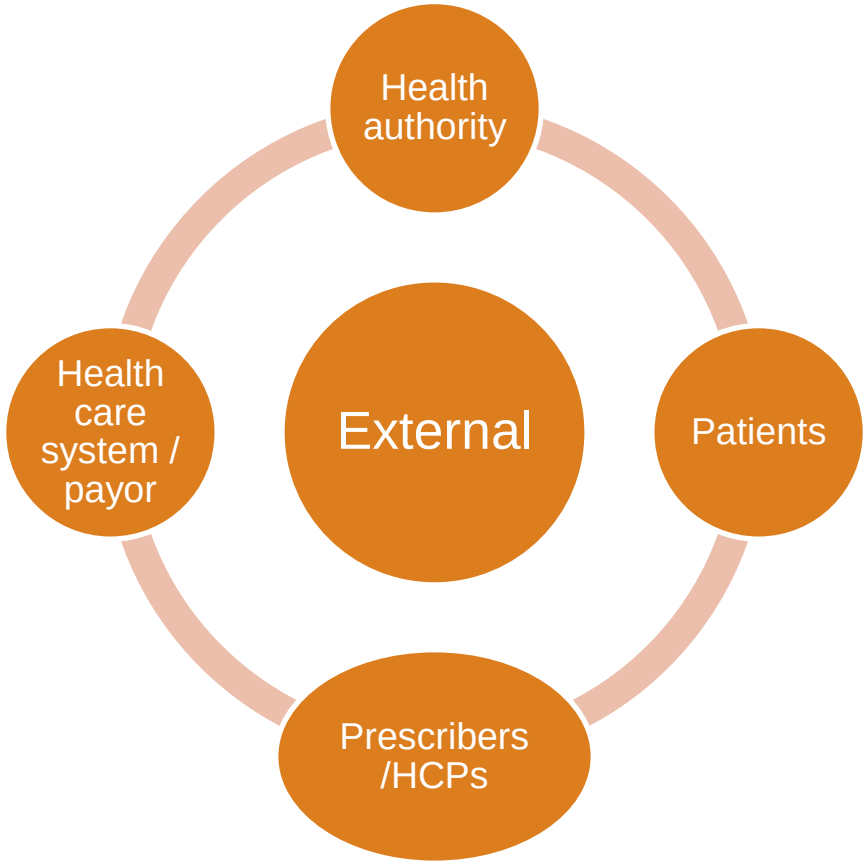
Best choice of data source

Best methods to minimize bias

Study concept

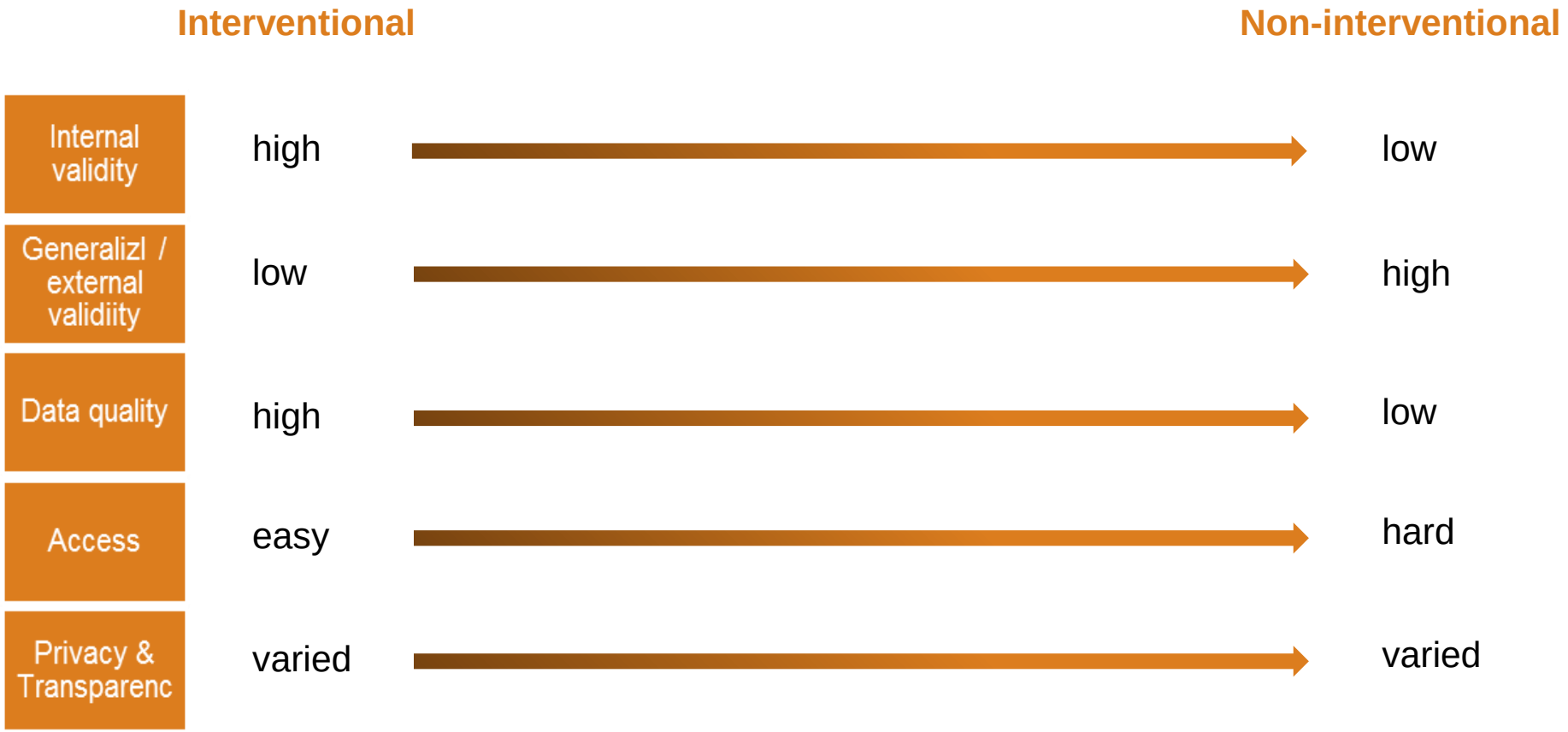
Strategy

STAKEHOLDERS



COMMON STAKEHOLDER PERCEPTION ON STUDY DESIGN ATTRIBUTES (PART 1)

COMMON STAKEHOLDER PERCEPTION ON STUDY DESIGN ATTRIBUTES (PART 2)



SUMMARY

- Questions from internal stakeholders
  - Do you believe the results? Is the data quality high enough ? Not «classical methods» Will the health authority accept analysis methods?
  - What if we do not like the results ?
  - Do we need to publish ?
  - Manage expectation of KOLs ?
- Health Authority perspectives from EMA at «Industry stakeholder platform on research and development support, 25 April 2017»
  - RWD could be acceptable if;
    - If an RCT is not feasible (time , ethics, rarity)
    - Hard endpoints available (to offset bias)
    - Conditions with known and predictable disease progression (note: prospective natural history)
    - Well thought out proposals and trust in reliability and feasiblity

SCENARIO – ALTERNATIVE APPROACH

Challenge

- HIV-exposed uninfected (HEU) infants are increasingly being exposed to newer anti-retroviral (ART) drugs for which less is known regarding both short and long term safety.
- Benefits of combined ART are profound, long term surveillance for potential late effects remain a concern

Action

- Classical clinical longitudinal cohort study initiated but high rates of non-participation and loss to follow-up
- Novel approach to conduct record-linkage between pregnancy registries and national routine data to monitor deaths and cancers in HEU children in England and Wales

Impact

- Despite limitations in fewer outcomes possible, feasible approach to set up record-linkage study at start of cART use

Thorne and Tookey. Front. Immunology. 7: 185. 2016

SCENARIO – DECADES POST EXPOSURE

Challenge

- Safety risk occurs in the next generation, post exposure; children of mother's exposed in utero to diethylstilbestrol (DES). Use in 1940s, use declined in 1950s after CTs showed no efficacy.

Action

- Combined data from 3 cohort studies, 30 years follow-up, n=3796 exposed women, n=1659 unexposed women.

Impact

- "although DES not been prescribed for pregnant women in the US for 40 years, adverse outcomes continue to occur in women exposed in utero, and continued monitoring, as is ongoing in this cohort, for established and unexpected adverse outcomes seems prudent "

Hoover et al. NEJM 365; 14 . 2011.

SCENARIO – RWE EVIDENCE SUPPORTING SAFETY PROFILE ASSESSMENT - IMMUNOLOGY

RECENT EXAMPLE PRESENTED,
«INDUSTRY STAKEHOLDER PLATFORM ON RESEARCH AND DEVELOPMENT SUPPORT, 25 APRIL 2017»

Challenge

- Multiple years after marketing, EMA asked about risk of autoimmune diseases associated with use of drug X in children.

Action

- In collaboration with external investigators, developed retrospective cohort study using population based registries that capture medical and healthcare encounters from birth till death

Impact

- Study results accepted at EMA and CHMP
- Safety questions resolved with minor label changes

SO, IN SUMMARY

- Phrase the question:
  - Understand the safety concern: What is the origin (e.g. preclinical finding)? What do we know about the potential safety risk (definition, epidemiology of disease, strength of association in available data, class problem)?
  - Hypothetical pathway for long term efficacy – effectiveness / outcomes
- Identify appropriate study design (ideal setting)
- Map data source vs. requirements
- Adapt to reality: operational feasibility, costs, timelines
- Propose strategy based on above and convince stakeholders

QUESTIONS