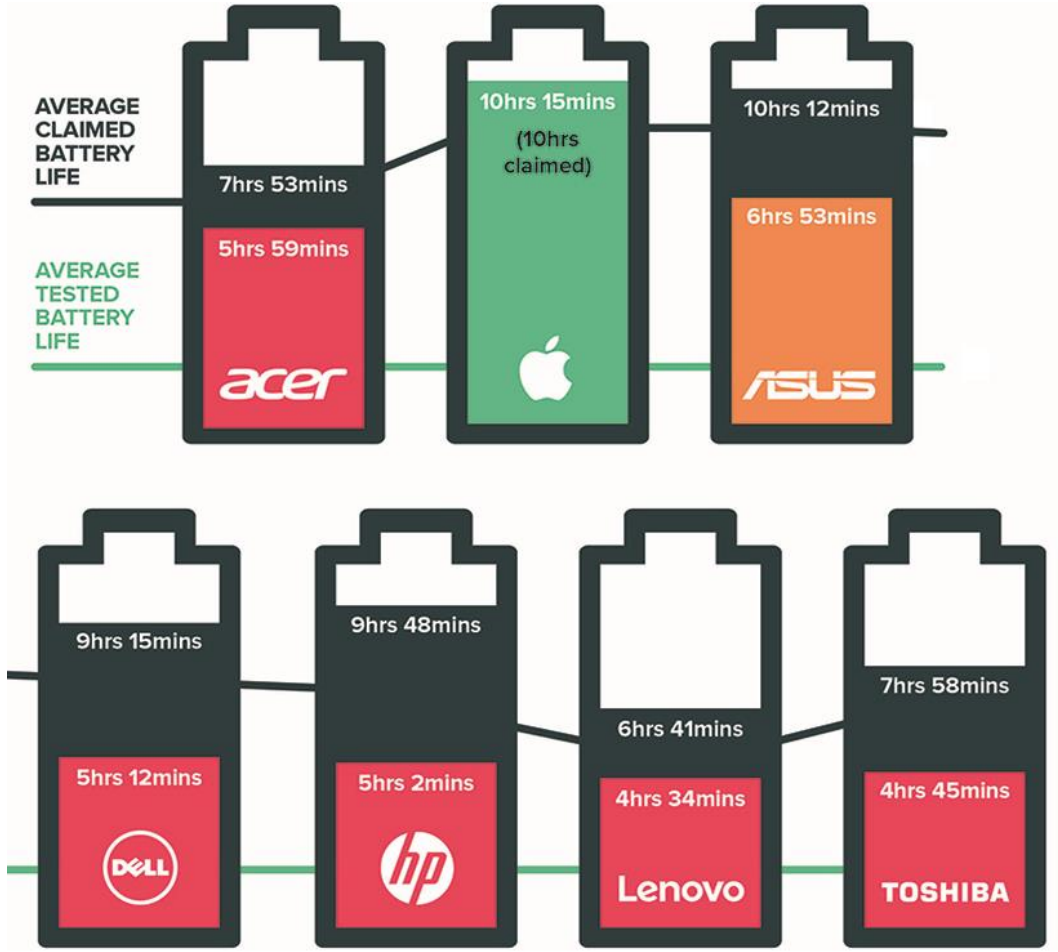
Seeking the True Value

- When buying something, we depends on the available information to make decision.

- **What if the information is false/ not the same?**

We would **endeavor** to ensure the **information** we received is **accurate and real** to make better judgement on value and investment.



Where are the Values? In Search of Real World Evidence for Outcomes

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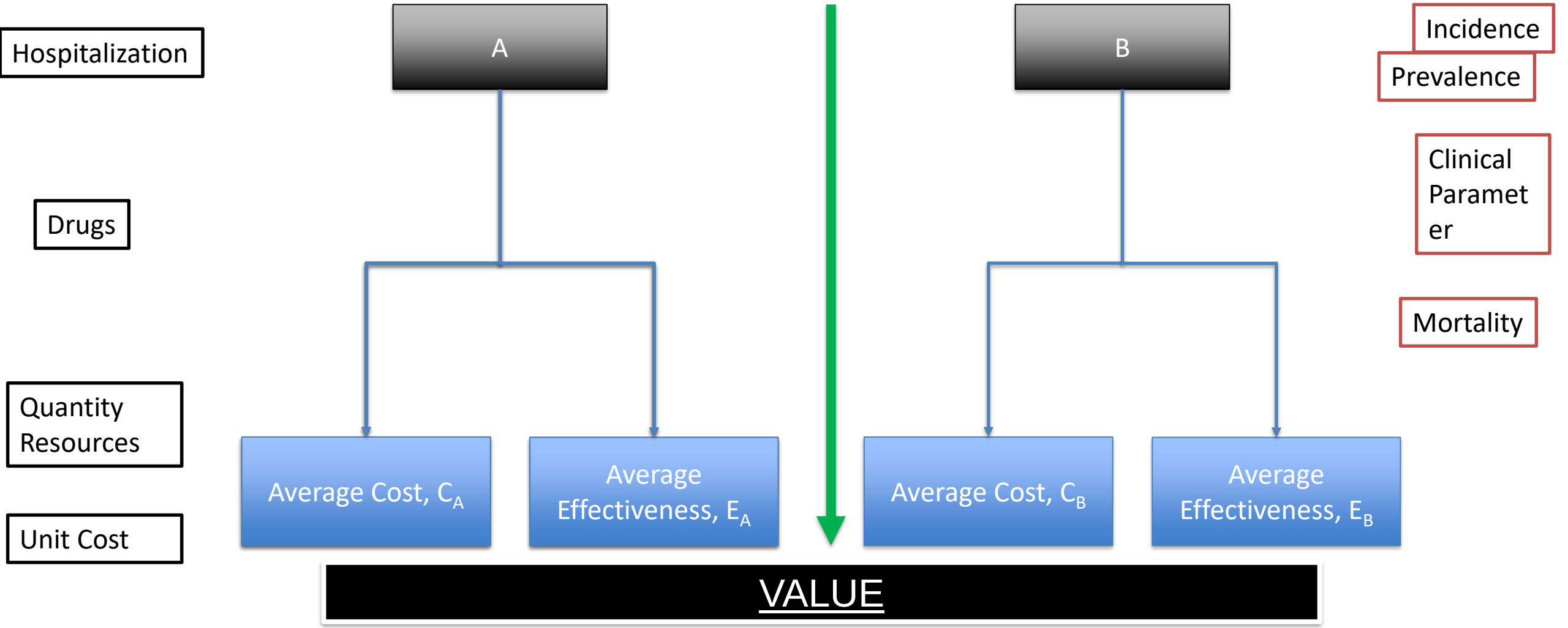
Outline (45 min)

- Why do we need RWE
- What is real world evidence (RWE)?
  - Current RWE example
- Why RWE?
- Challenge in using RWE
- Way forward

What Did We Collect to Determine Value?

Value and Data



Type of Outcomes- ECHO

Economic

- Resource use
- Numerator of the “cost-effectiveness” ratio
- May be direct medical, direct non-medical, or indirect
- Need to be aware of the “cost” of benefits

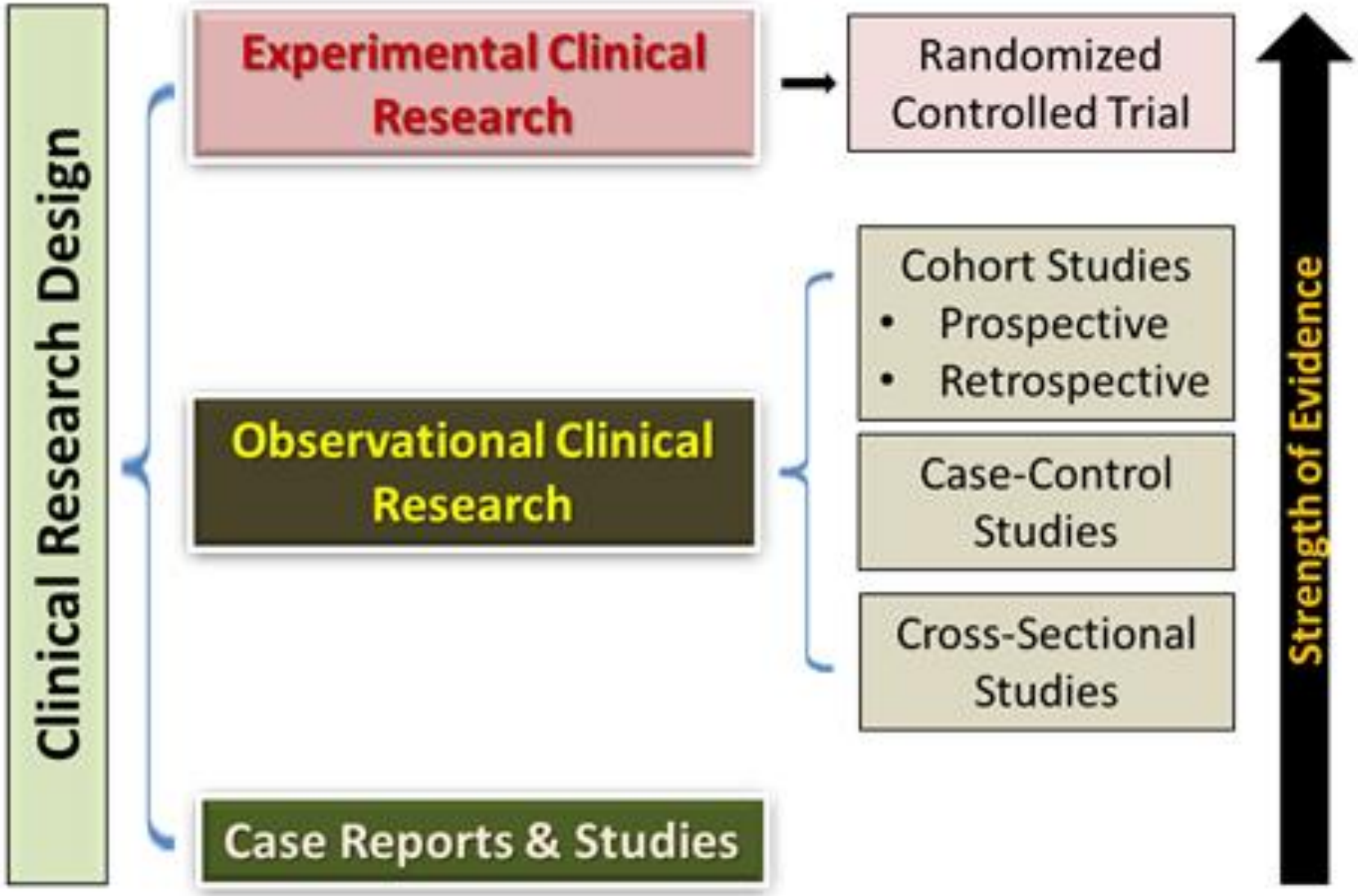
Clinical

- Morbidity and (perhaps) mortality
- Use of surrogates
- Avoid confusion with “ health” outcomes (e.g. QoL)
- A clinical outcome may become a resource cost

Humanistic

- PRO-based
- Acceptance of data is variable
- Guidance abound but guidance is fleeting

How Do We Get the Data?



What is Real World Data?

data *used for decision making that are not collected in conventional controlled randomized trials."*

What are “Real World Data”

“Real World” data is anything OTHER than RCT generated data… data derived from:

- Prospective observational studies
  - Non-interventional studies
- Database studies
  - Prospective registries create a database
  - Retrospective databases created for other reasons
- Medical records
  - Data abstraction

In general, “real world evidence” are observations of effects based on what happens after a prescriptive (treatment) decision is made where the researcher does not or cannot control who get what treatment and does not or cannot control the medical management of the patients beyond observing outcomes

Data Sources – a priori

Datasets

- Supplementary alongside RCT
  - Events and resource costs (morbidity, mortality)
  - PRO endpoints
- Large simple trials – prospective, randomized, variety of settings
  - Greater generalizability
  - Limited protocol influence
  - Closer to real world
- Patient registries – prospective, observational cohort, all outcomes
  - Safety focused
  - Long term
  - Lack of control over intervention
  - Data gaps possible

Data Sources – post priori

Databases

- Administrative claims databases – low cost, resource use focused
  - May be complete, may be not
  - Missing lab data (lab was done but what was the value?)
- Routine surveys of patients and providers – unbiasees, health measures, treatments, representative
  - Recall bias, past experience
- Electronic health (medical) records – real time data on disease and treatment

The Non-Interventional Study

The European Medicines Evaluation Agency defines **clinical trials** in 2001/20/EC and then EXEMPTS non- interventional trials from the regulations

The term “non-interventional study” (or non-interventional trial) is a study where the medicinal product(s) is/are prescribed in the usual manner in accordance with the terms of the marketing authorization.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by the trial protocol but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the patient in the study.

No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

	RCT	Real World Data
Type of Trial	Experimental	Observational
Primary Focus	Efficacy, safety, and quality	Effectiveness
Patient population	Narrow and restricted	Wide and unrestricted
Monitoring	Intense	Not required
Cost	High	Regularly less expensive
Randomization & Blinding	Yes	No

Why Do We Need RWE?

Efficacy vs Effectiveness

- Efficacy
  - Howe well a medication works as established through rigorous & controlled clinical investigation

- Effectiveness
  - Usefulness of a medication under condition of actual clinical practice.
  - = Efficacy + Tolerability + Adherence + Ease of Use

The Importance of Real World Data

- Decision makers looking to make coverage and payment decisions may rely on multiple sources of real world data, as well.
- Benefits of RW data:
  - Effectiveness vs. efficacy
  - Multiple interventions
  - Long-term benefits and harms
  - Diverse population
  - Broader range of outcomes
  - Resource use
  - More relevant
  - Retrospective later to collect than ideal
  - Dosing, compliance, adherence
  - When RCT not possible
  - Confirmatory of RCTs
  - Urgent, life-threatening situation
  - Interim evidence in absence of RCT
  - More robust
  - Prospective longer to conduct than ideal

Who Use RWD?

- **To public payers and evidence assessment agencies:** Payers must balance the need to provide improved health outcomes and access to new technologies with budgetary considerations. Clinical trials developed for regulatory purposes may be insufficient to resolve payer uncertainty.

- **To researchers:** Techniques and tools to analyze data for RWE have become increasingly widespread and accessible to researchers. Researchers are now able to answer an increasing number of important health services and policy questions without the considerable expense, length of time, and complication of conducting high-cost experimental studies.

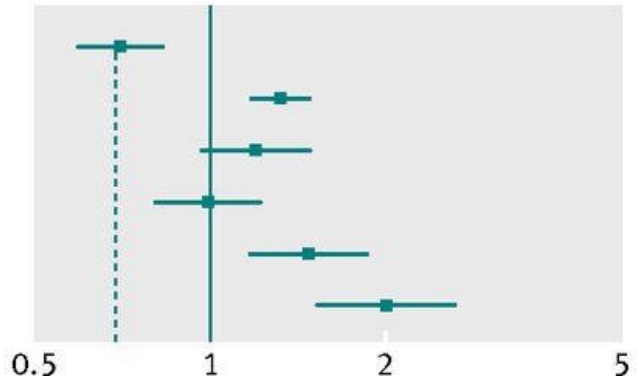
- **To industry**: Industry views RWE as an additional opportunity to demonstrate the value of medicines, for both the patient and the health system. It may also provide new opportunities for industry to work with payers to advance novel approaches to pricing and reimbursement.

Challenges in Using RWD

Limitations of RW Data

- Most significant concern is bias
  - Typically there is a selection bias in treatment decisions and this bias can lead to differences in outcomes (rather than due to treatment)
- Despite sophisticated statistical adjustment techniques, real world data don't meet the "scientific" rigor of an RCT
- Can be costly to conduct
  - (e.g. prospective non-interventional studies)
- Can be complicated to conduct
  - (e.g. medical record abstraction)
- Can be difficult to interpret
  - (e.g. large retrospective databases)
- Data accessibility/sharing
- Data accuracy, completeness
- Fragmented healthcare

	No of events	No of participants	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)
RALES 1999	670	1663		<0.001	0.70 (0.60 to 0.82)
Overall propensity score matched analysis	1285	4412		<0.001	1.32 (1.18 to 1.47)
Propensity score quartile >75% to 100%	369	1103		0.085	1.20 (0.98 to 1.47)
Propensity score quartile >50% to ≤75%	388	1103		0.91	0.99 (0.81 to 1.21)
Propensity score quartile >25% to ≤50%	298	1103		0.001	1.46 (1.16 to 1.83)
Propensity score quartile ≤25%	230	1103		<0.001	2.01 (1.54 to 2.63)



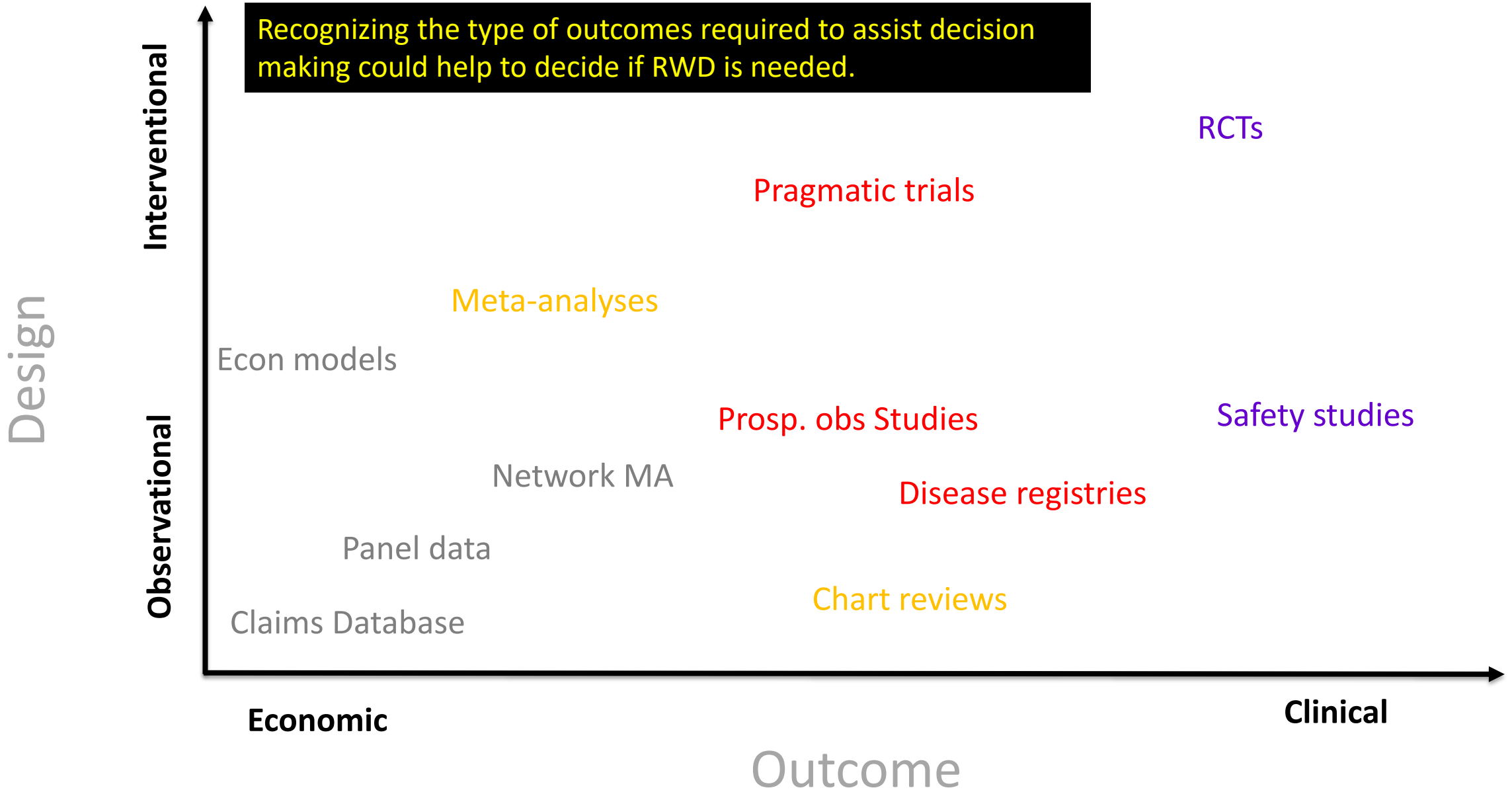
- attempt to replicate the findings of landmark randomised controlled trials in heart failure, using a sophisticated propensity score approach in real-world data
- massively biased estimate providing a qualitatively opposite (and incorrect) result to that found in the randomised controlled trials.

Freemantle et al *BMJ* 2013;347:f6409

Conclusion

- Real world evidence can be used for developing medical products and informing healthcare practice and policy making.
  - support for identification of unmet medical needs
  - design of registered clinical trials
  - post-approval drug safety assessment and pharmacovigilance
  - payment and coverage decisions
  - healthcare quality improvement
  - new indications of medical products
  - assessment of healthcare technologies
  - clinical practice guideline development
  - exploration of clinical research questions other than healthcare interventions, such as disease burdens, prognoses, and clinical predictions.

Types of outcomes and typical study design supporting required outcome



Conclusion

- better to **push the pharmaceutical industry** from the very start of the **approval procedure** for new drugs to produce evidence on comparative efficacy with those already marketed and therapeutically overlapping, then setting prices according to their incremental efficacy

Way Forward

- **regulations** to deal with concerns about data sources, such as confidentiality, privacy protection, data sharing, and ethical approval.
- **research community** to foster collaboration across institutions and stakeholders must be developed urgently.
  - public and private collaborations such as the Observational Medical Outcomes Partnership in the US and China REal world evidence ALliance, ChinaREAL

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