APBG
AUSTRALIAN PHARMACEUTICAL BIOSTATISTICS GROUP
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Real World Evidence

Australian Pharmaceutical Biostatistics Group (APBG)
RWE Seminar July 29th 2015

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Chair of APBG

Lilly

What is the APBG ?

- A not-for-profit association of pharmaceutical industry statisticians in Australia.
- Our mission
  - is to ensure high statistical standards within Australia to assist in the decision processes which provide safe, efficacious and cost-effective health care products produced in a regulated environment for the health and quality of life of people
- Made up of 4 steering committee members:
  - Alan Brnabic (Chair) Annie Solterbeck (vice-chair), Philip McCloud (treasurer), Joanna Leadbetter (secretary)
- Currently ~ 55 members

What is the APBG ?

- To provide professional educational opportunities of specific relevance to statisticians in the regulated health care industry.
  - Past Workshops/Courses:
    - DMC
    - Do pharmacological interventions reduce drugs-related deaths ?
    - Mixed Treatment Comparisons
    - Adaptive Designs for Clinical Trials
- If you want to be on our mailing list speak to Myself or Joanna Leadbetter

Thanks

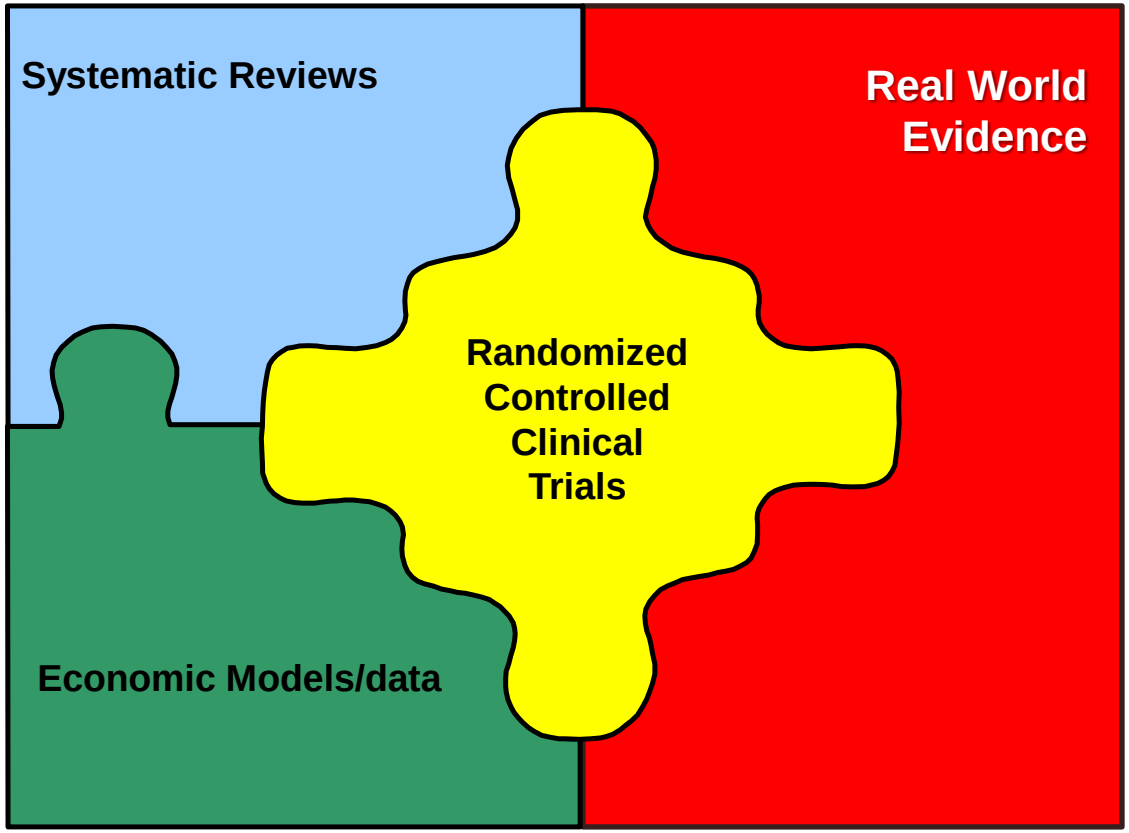
- Thank you to all that helped put this event together
  - Joanna Leadbetter, Annie Solterbeck, Matt Slabbert, Philip McCloud, Laurent Billot, Richard Hutchinson
- Thank you to our speakers
  - David Grainger
  - Laurent Billot
  - John McNeil
- Eli Lilly for hosting the event

OUTLINE

- Introducing TALKS:
  - David Granger: RWE: Policy, Governance and Implications for HTA
  - Laurent Billot: Practicalities of using linked data & statistical applications using Propensity Scoring
  - John McNeil: Clinical Registries, Opportunity and Limitations
- Introduction to RWE
  - What is RWE
  - Why do we need RWE?
  - Analytical Challenges of RWE

What is RWE? - RESEARCH MOSAIC OF EVIDENCE

RWE is complementary to a robust clinical trial program.

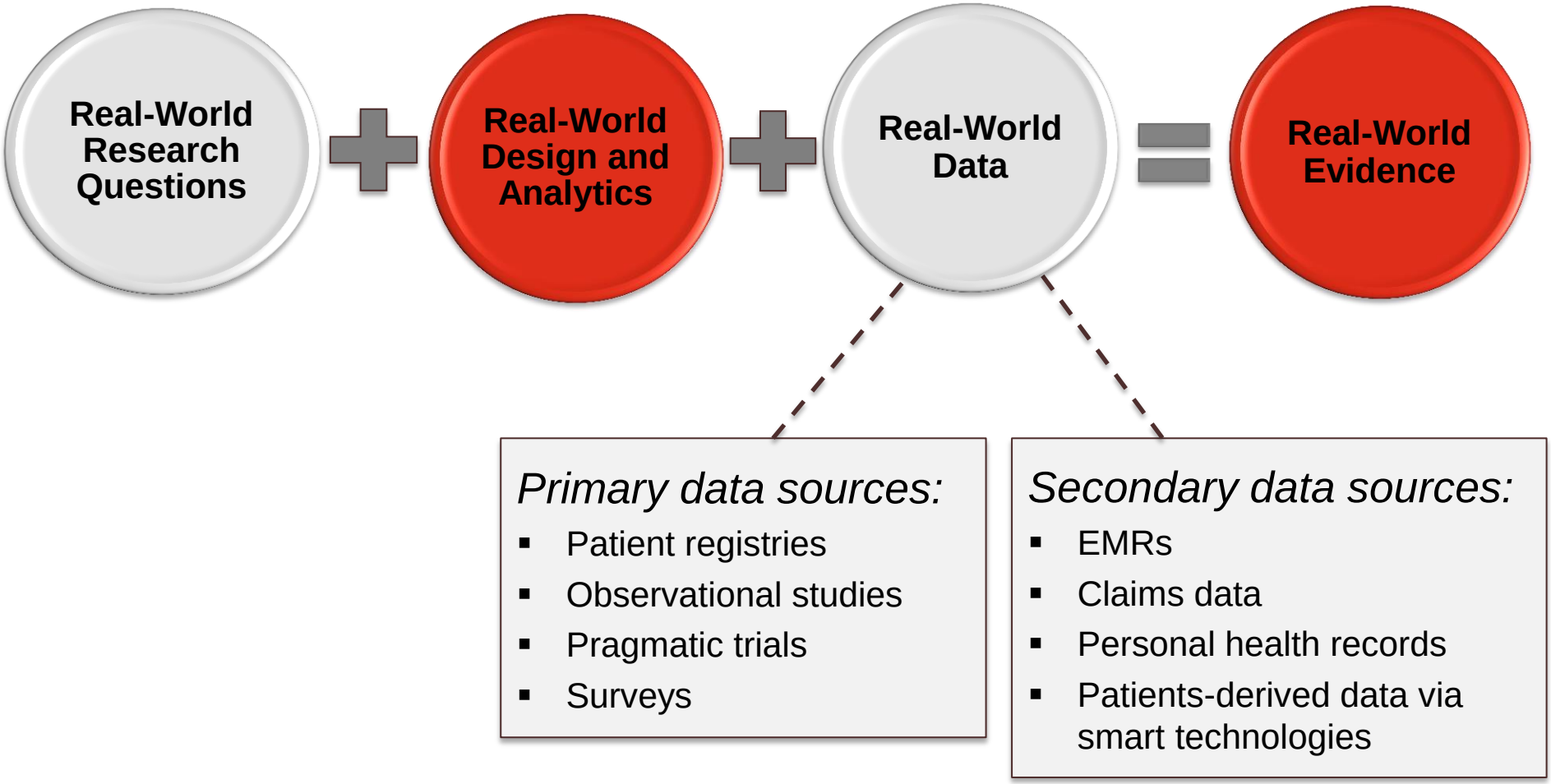


What is RWE? - Definition

RWE is one form of evidence (along with RCT, health economics studies, etc.)

1. **derived from primary or secondary real world data sources**, with appropriate design/analyses, to
2. **provide insights** on diseases, medicines, patient populations and healthcare practices, that will
3. **inform customer and internal decision making**.

What is RWE? - Definition



Why RWE? - INCREASING RWE REQUIREMENTS

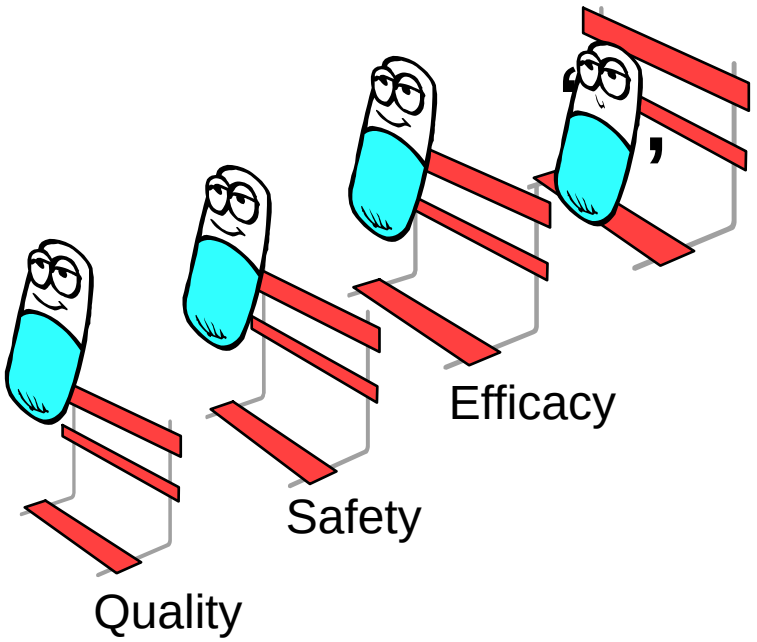
Globally, RWE Research is increasingly required to gain and maintain reimbursement approval and is linked to which populations get access.

Traditional regulatory requirements

- Quality
- Safety
- Efficacy

Emerging requirements

- Clinical effectiveness
- Patient outcomes, e.g. quality of life
- Cost Effectiveness
- Budget Impact
- Benefit-Risk
- Patient subtypes/heterogeneity
- Understand unmet clinical need
- Use of drugs in real life



Taylor RS, et al. *BMJ.* Oct 23 2004;329(7472):972-975.

Why RWE? – A Balance

CAN IT WORK?

Asks different Qs

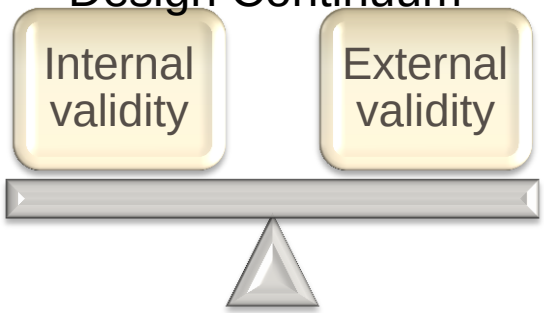
DOES IT WORK?

Randomized Controlled (Explanatory)

Observational (non-interventional)

Pragmatic Trials

Design Continuum



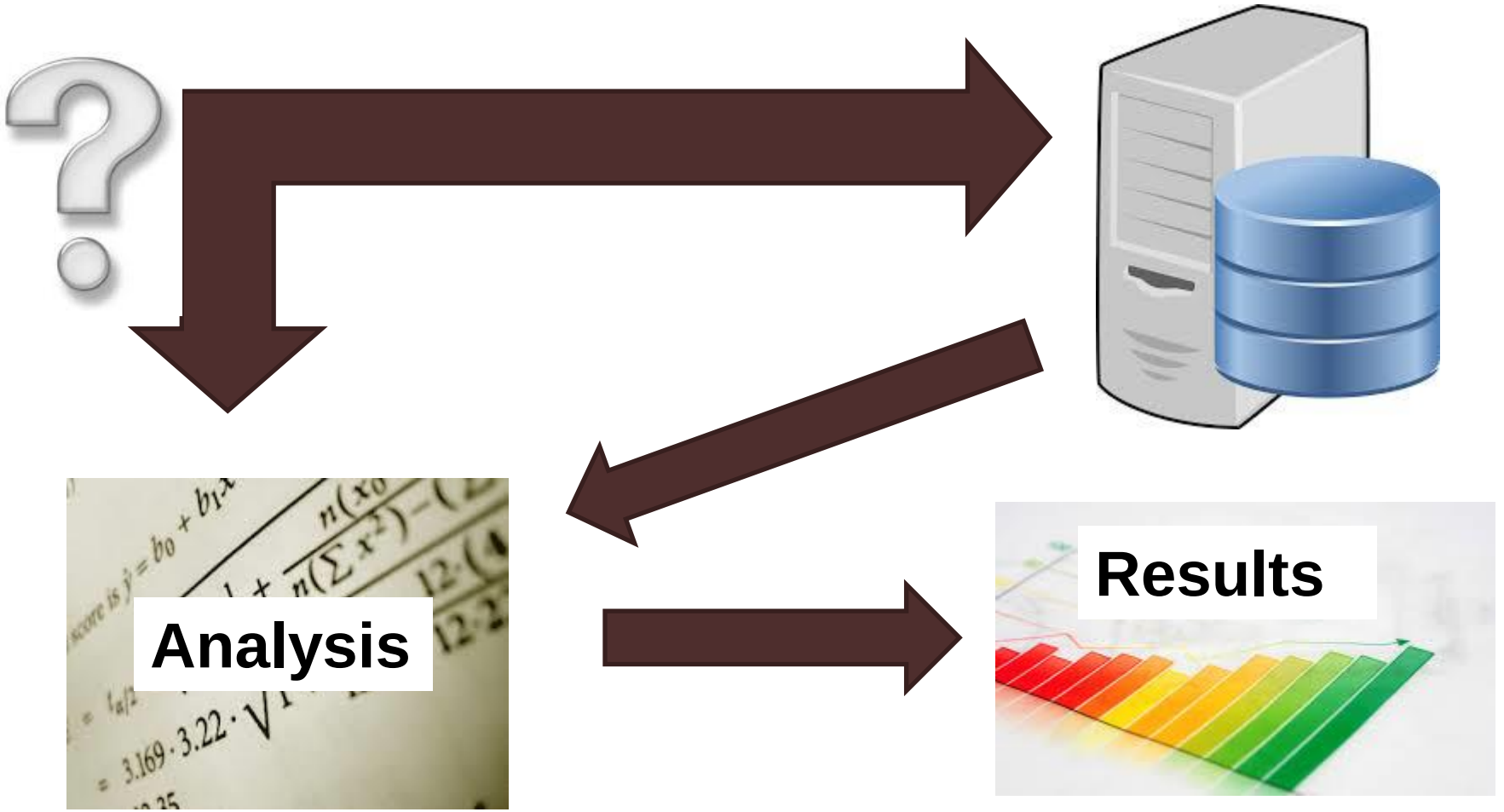
Randomized

Application of RWD

AU Lilly Diabetes/George Institute: EXTEND45 NSW Data linkage Project

Answer RW Questions for patients with Diabetes

RWE – The question!



Statistical Challenges in RWD

- Standard analytic approaches don't work
  → you get biased answers

- No randomisation
  → requires different methodology

- Challenges
  - Selection Bias
  - Unmeasured confounding
  - Reliable Data
  - BIG DATA – all of the above!
  - Mixing RCT & RWD

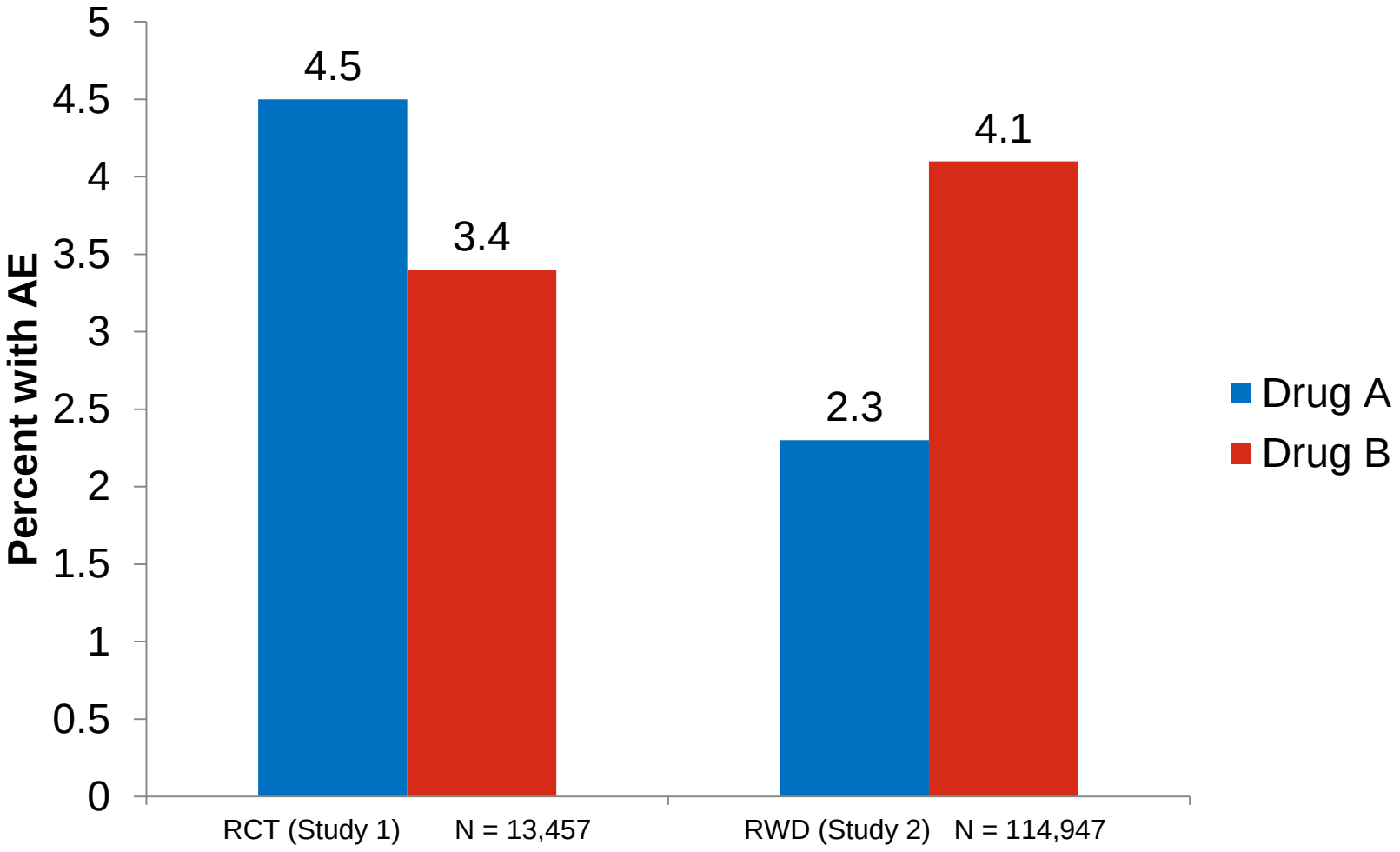
Statistical Challenges in RWD

#1 Issue: Selection Bias / Confounding

- With randomization – standard methods produce estimates of causal treatment effects

- Without randomization – standard methods produce only ‘associations’ …. Treatment groups are NOT comparable at baseline thus comparisons are BIASED

Selection bias: AE rates: RCT vs RWD



Why the difference in Results? =Selection Bias

A confounder is a variable that is associated with both Cohort and Outcome

Study 2 Data Set	Drug A (N=10,448)	Drug B (N=104,499)
Mean Age (years)	57	64
Age > 75 yrs (%)	3.5%	24.9%
Male (%)	75%	66%
Renal Insufficiency	9.3%	19.2%

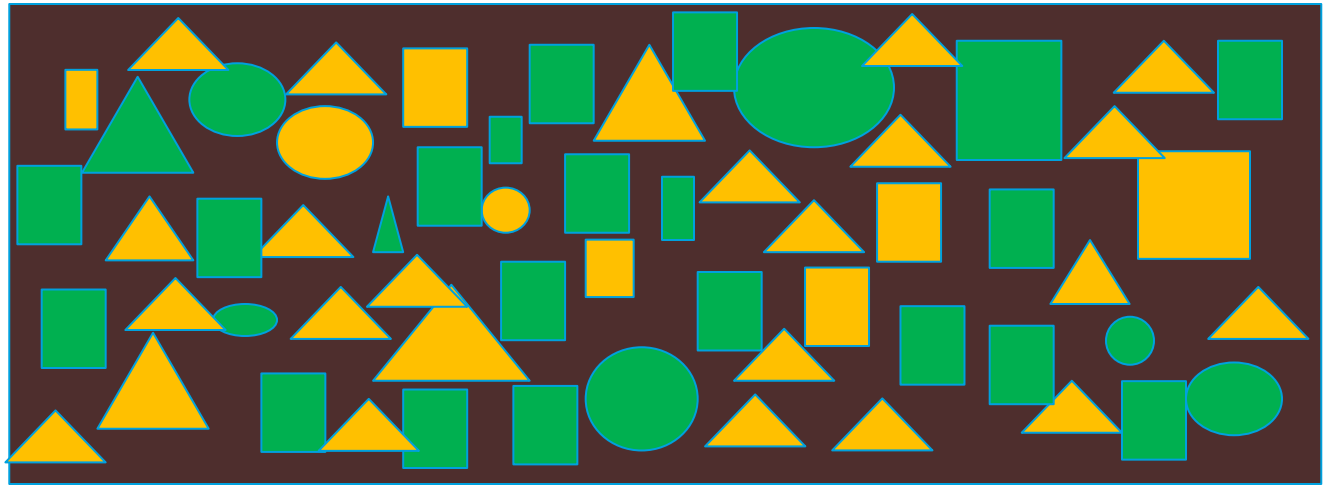
AE Risk Model

Baseline Factors:

1) Older Age
2) Female
3) Renal Insufficiency
4) Blood Pressure
5) History of Bleeding

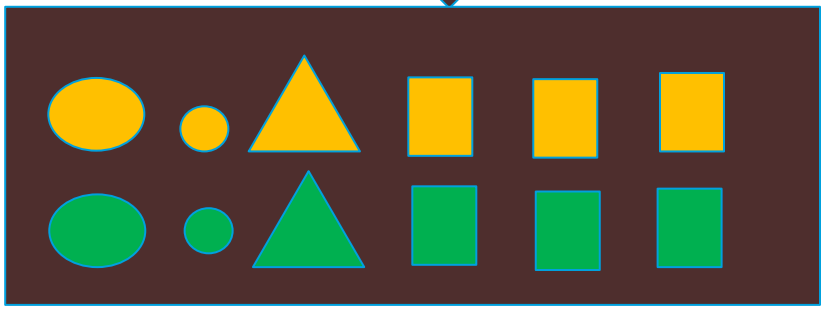
Selection Bias: A solution

Real World Population



Propensity Score:
Probability of being assigned Treatment A

Propensity Matching



BASIC ASSUMPTIONS FOR CAUSAL INFERENCE

Propensity Score adjustments can provide for estimates of the causal group differences under the following assumptions:

#1 **No Unmeasured Confounders**

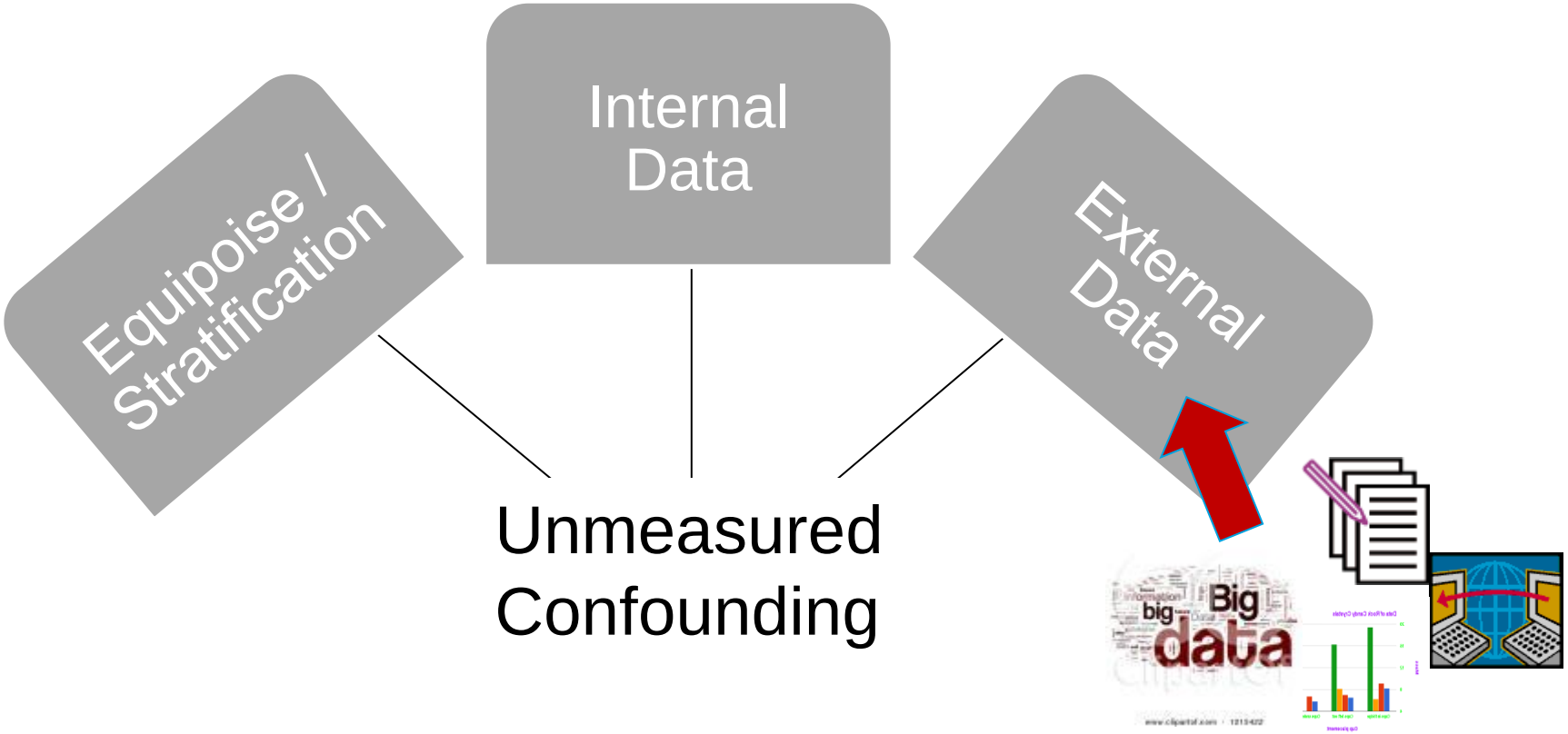
All confounders are in the dataset and analysis

#2 **Sufficient Overlap in Populations**

positivity, no perfect confounding

#3 **Correct Statistical Models**

UNMEASURED CONFOUNDING



Challenges with Data

- Can the data:
  - Answer the question you are asking
    - Collect the information you need e.g. clinical outcomes, capture all costs, Qol
- Is the data:
  - Representative e.g cover all labs in Australia
  - Complete; % missing of variables reasonable, coding correct/consistent
  - Accurate; can be validated with other sources
  - Up to date
  - Can it be linked to other sources

Methods for Analysing BIG RWD

- Focus on Interaction Identification – this identifies relationships that pertain to only certain subgroups
- Traditional DM Machine learning methods include
  - tools used for supervised learning
    - traditional statistical prediction methods like regression models
    - tree-based methods (e.g. classification and regression trees (CART) and random forests)
    - neural networks, discriminant functions and linear classifiers, support vector classifiers and machines (SVM).

Methods for Analysing BIG RWD

- Focus on Interaction Identification – this identifies relationships that pertain to only certain subgroups

CHALLENGE– How to Apply these methods on BIG RWD given the issues of selection bias & unmeasured confounding?

  - neural networks, discriminant functions and linear classifiers, support vector classifiers and machines (SVM).

Mixing RCT & RWD

- Using RWD (e.g. prospective observational studies) to generalise RCT results to the “real world” population (via propensity score or entropy balancing weighting)
- Using IPD and aggregate data (in literature) to match populations better to perform indirect comparisons & network meta analysis (matched adjusted indirect comparisons = MAIC)

Acknowledgements

- Doug Faries
- Tony Zager