Pfizer GLOBAL HEALTH & VALUE

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Real-World Evidence Generation and Evaluation of Therapeutics

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Real World Evidence

RWE Usually Proves to be True

- Lower blood pressure with drugs
- Lower LDL cholesterol with statins
- Aspirin to prevent MI and stroke
- Beta-blockers and ACE inhibitors for CHF
- Diagnostic tests:
  - Mammography for breast cancer
  - CT for lung cancer
  - Ultrasound for abdominal aneurysm

Sometimes not…

- Vitamins to prevent cancer/CVD (failed)
- Anti-arrhythmic drugs (higher death rate)
- HRT(breast cancer, failed CHD)
- Back surgery, kyphoplasty (little benefit)
- Aggressive glucose reduction to prevent MI
- Stents *after* myocardial infarction
- Bone marrow transplantation for breast cancer (higher death rate)

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review)

Anglemyer A, Horvath HT, Bero L

THE COCHRANE COLLABORATION®

Our results provide little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, inclusion of pharmacological studies, or use of propensity score adjustment. Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies.

But when is RWE “good enough” and for what purposes?

- Understanding the epidemiology of disease / unmet medical need
- Informing Precision Medicine (drug discovery and development)
- Informing healthcare benefit design
- Informing quality improvement / efficiency improvement efforts
- Informing Health Technology Assessments / Decisions regarding access to and pricing of new therapies
- Assessing the incidence / prevalence of adverse events associated with marketed medications to inform Regulatory Labelling

- Informing Bedside Shared Decision-Making between patient and provider
- Informing Regulatory Decisions regarding indications, dosing, etc.

Not All RWE is Created Equal
When is it “good enough” to inform regulatory decisions?

- Pragmatic Clinical Trials
  - Randomization to deal with bias
  - PCT vs Large Simple Trials (enforced treatment assignment)
    - Fully Pragmatic PCT’s are observational studies on Day 2
  - A good solution → will never meet all the needs of a Learning Health Care System
- Observational Studies
  - Prospective (ex Registries)
    - Used for rare diseases
  - Retrospective
    - Existing databases: EHR, Claims, Linked EHR-Claims, Other
    - Used commonly by FDA for pharmacovigilance
    - Has been used by FDA for alternative dosing schedules

How can increase the credibility of RWE from observational studies?

Put them on the same footing as RCT's

ISSUE	ACTION
Publication Bias	Pre-registration of studies
Torturing the data until it confesses	Pre-specified protocols and data analysis plans
Substantial Evidence	Typically require at least 2 studies from different data sets
Substantial Evidence	Adoption of rigorous methods to assess and address bias / confounding*

*Newer approaches are enhancing ability to detect residual bias in observational data sets (ex. empirically derived null distributions, use of positive and negative controls)