Real World Evidence: Promises and Limitations

Lucinda Orsini, DPM, MPH; Assoc. Chief Science Officer, ISPOR
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What is Real World Data/Evidence?

Retrospective
- Electronic health records
- Data collected from charts
- Insurance claims
- Analysis of data for purpose not originally collected
  - Prospective registries
  - RCT

Prospective
- Active prospective registries
- Observational studies
- Early Access Programs?
- Large Simple Trials?
Figure 1: Conceptual framework of therapeutic research by study design

Source: Roche et al., 2013
Why do we need RWE?

Clinical Trials Answer Benefit/Risk

• Efficacy – does it work:
  • Narrowly defined population
  • Under very controlled conditions
  • Versus: placebo or one active comparator
  • For the duration of the trial

• Safety
  • Can {known} Side Effects and Adverse Events be managed under controlled conditions
Why do we need RWE?

Real-World Evidence Answers:

• Effectiveness – does it work in practice?
  • In broader populations
  • Under uncontrolled conditions
  • Over the long term
  • Versus all current standards of care

• Safety – is it safe in practice?
  • Are {known} side effects
    • reported by patients
    • Treatable in clinical practice
    • Unknown side effects

• Adherence/treatment patterns

• Cost of treatment and side effects
Where is RWE being used

1. Drug Development
2. FDA safety monitoring/safety signals and EMA post approval studies
3. HTA assessments and payer coverage determinations
   1. Initial decisions
   2. Re-assessments
4. Outcomes based contracting
5. Regulatory approval decisions
It’s already happening...

Pfizer uses real-world data to score Ibrance breast cancer nod in males

NHS England Cancer Drugs Fund

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

CMS proposes Coverage with Evidence Development for Chimeric Antigen Receptor (CAR) T-cell Therapy
The Challenge of Real World Evidence

So much data, so much potential information

**but is the evidence derived**

**reliable and trustworthy?**
Today's Random Medical News

Can cause: Hypothermia, Arthritis, Depression

According to a report released today...
Unstructured Data and the AI ‘Frontier’

- Electronic Health Records
  - Doctor’s notes
  - Discharge summary
  - Lab data
  - Image reports
  - 80% unstructured data
- Social media
- Data from apps
- Wearable data
- Patient reported outcomes

Can we trust the algorithms?
RWE Challenges

- Bias and Confounding
- Incomplete Data
- Data Mining or Dredging
- Access to Data
- Universally Accepted Methods to
  - address the above
  - analysis of RWE
Bias and Confounding

• Selection Bias:
  • Selection of subjects isn’t random
  • Mitigate the impact - RWE studies need to be rigorously designed and evaluated
    • describing and adjusting for covariates, matching, or using instrumental variables

• Reporting Bias
  • Some outcomes/datasets are selectively revealed or withheld
  • A mandatory national registry, such as is available for RCTs, could help mitigate this problem
Incomplete Data

- Under-reporting of diagnoses or adverse outcomes/side effects
- Missing Data or Data Gaps
  - Claims – you know what was done to the patient but not the results
  - EHR – depends on what is reported and if you can interpret it
  - Data needed for insurance payment is not what is needed for RWE (US)
  - Relying on self submitted data (patient or physician) may create gaps
- Information bias – from systematic mis-classification
- Mitigation
  - National data repositories
  - Strict reporting guidelines
  - Linking datasets
Data Mining or Data Dredging

- Re-examining datasets to generate new information
- RWE is vulnerable to manipulation via repeat analyses with
  - Continuously using different modelling approaches until one that delivers preferential outcomes is identified
  - Non-disclosure of unexpected results
- Need for *a priori* protocols, analysis plans, and well-defined research questions
Access to Data

- Data sharing is not common in the US
  - Outpatient vs. inpatient
  - Specialist vs. internist
  - Labs, imaging, apps, wearables
- Privacy regulations make it difficult to link patients across data sets
  - Legal frameworks are catching up
  - Trade off between protection of private health information and informing real world research
Lack of Standards

- Universally accepted standards/principles are needed:
  - design,
  - conduct,
  - analysis
  - reporting of RWE

- There have been various best practices/standards developed but lack agreement
Conclusions

• There is a lot of promise in RWD

• The rise of Artificial Intelligence and Large Data Sets is coming – we need to be ready

• The key is -
  • Know the strengths and challenges associated with RWE
  • Design rigorous data collection and analysis plans
  • Be as transparent as possible about what was done with RWD and how it was analyzed
Thank you.