Using Real World Data in Pharmacoeconomic Evaluations: Challenges, Opportunities, and Approaches

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Agenda

Overview of Report of ISPOR Real World Data Task Force
A Personal View
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Methodological Issues
Next Steps

Mission—from ISPOR Board

Develop a framework to assist health care decision-makers in dealing with “real world” data and information in “real world” health care decision-making, especially related to coverage and payment decisions.

Definition of Real World Data

“We settled on a definition that reflects data used for decision making that are not collected in conventional controlled randomized trials.”

“This is not to say that data from RCTs are irrelevant or not used by decision makers: indeed, they remain the critical foundation for almost all coverage and reimbursement decisions.”

“For if there is not a belief in the plausibility of the underlying biological mechanism or hypothesis, why should anyone seek further evidence of effectiveness or cost impact in the real world?”

Outline of Draft Paper

1. Why a Real World Data Task Force?
2. Task Force Objectives and Scope
3. Types and Sources of Real World Data
4. Key Findings
5. Conclusions

Section 1. Why Real World Data Task Force?

- Grew out of Medicare Modernization Act of 2003, Section 1013: AHRQ to do “outcomes, comparative clinical effectiveness”
- Other US and non-US efforts: DERP (Oregon), NICE (UK), IOWiG (Germany)
Section 2. Task Force Objectives and Scope

- Mission: Develop framework and action steps
- Focus: Coverage and reimbursement
- Issue: Defining “real world” data
  - Data versus evidence
  - Used in policy circles
- Definition: “data used for decision making that are not collected in rigorously controlled randomized trials”
  - Data from RCTs are important
  - Both drugs and other interventions
  - Both US and ex-US

Section 3. Types and Sources of Real World Data

By type of endpoint:
- Clinical—morbidity, symptoms, mortality
- Economic—resource use and costs
- PRO/QoL—patient-reported symptoms, quality of life

Evidence hierarchies
- Alternative formulations. Move to incorporate benefits.

Sources:
1. Supplementary alongside RCTs—treatments for events
2. Large simple trials—prospective, randomized, variety of settings
3. Patient registries—prospective, observational cohort, all outcomes
4. Administrative claims databases—low cost, resource use
5. Surveys of patients and providers—unbiased, health measures, treatments, representative
6. Electronic health records—real time data on disease

Section 4. Eight Key Findings

1. The importance of RW data
2. Limitations of RW data.
3. Level of evidence required depends on the circumstance
4. Need for good research practices for collecting and reporting RW data
5. Need for good process in using RW data in coverage and reimbursement decisions
6. Need to consider costs and benefits of data collection;
7. Ongoing need for modeling
8. Need for continued stakeholder dialogue on these topics

1. The Importance of Real World Data

- RCTs have many advantages and remain the gold standard
- Decision makers about coverage and payment 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
  - Dosing, compliance, adherence
  - When RCT not possible
  - Confirmatory of RCTs
  - Urgent, life-threatening situation
  - Interim evidence in absence of RCT

2. Recognizing the Limitations of RW Data

- Most significant concern is bias
- Despite sophisticated statistical adjustment techniques, real world data don’t meet the rigor of an RCT
- Can be costly to conduct

3. Level of Evidence Required Depends on the Circumstance

- All types of data can be of variable quality
- Whether good or bad evidence depends on research design and implementation
- For economic data, focus on ‘big ticket’ items
- Training of data collectors is important
4. Need for Good Research Practices

- How RW data are collected and reported is important
- Follow well-established research practices
  - Well-defined questions, appropriate timeframes and sample sizes, informed consent
- Draw inferences from observational data with caution
  - Selection bias is important
  - Other sources of bias: missing variables, measurement error, specification error, simultaneity
  - Statistical tests for "endogeneity bias" exist along with methods for correction

5. Good Process in Coverage and Payment Decisions

- It is important that decision makers follow good process with regard to RW data.
  - Transparency, relevance, fair, consistent
  - Allow stakeholder participation and process for appeal
- Good process increases incentive for greater investment

6. Cost and Benefits of Data Collection

- Critical issue: who pays for RW data collection?
- "Evidence costs money."
- Value of information (VOI) analysis should be used
- In coverage and payment VOI analysis, need to consider:
  - (a) potential benefits lost due to delays and
  - (b) potential adverse consequences of too rapid uptake

7. Need for Modeling

- ISPOR Modeling Task Force:
  - "Models synthesize evidence on health consequences and costs from many different sources, including data from clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys."
- We use bioclinical cost-effectiveness models as an integrative framework
- "Conclusions are conditional upon the assumptions and data on which the model is built." (MTF)

8. Need for Ongoing Dialog

Central policy question: what is the appropriate role of the public sector in producing and judging evidence?
- Who should collect, pay for, and evaluate RW data?

Section 5. Conclusions

- "Real world data are essential for sound coverage, payment, and reimbursement decisions."
- "Randomized controlled trials remain the gold standard for demonstrating clinical efficacy in restricted trial setting, but other designs—such as observational registries, claims databases, and practical clinical trials—can contribute to the evidence base needed for coverage and payment decisions."
- "... need to carefully consider the costs and benefits of different forms of data collection in different situations"
Pharmaceutical Outcomes Research and Policy Program

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Personal Observations on the RWDTF

- There is a subset for health outcomes researchers who hold strongly to the view that RCTs are far superior to real-world data collection.
- There is a subset who think that RCTs are not particularly helpful to understand what economic impacts and PROs are going to show in real world settings for coverage and reimbursement.
  - This tension is reflected in real-world institutions.
  - IQWiG and DERP focus on RCT reviews.
  - NICE uses integrated modeling (Bayesian) approach
  - AMCP guidelines allow modeling approach

Major Challenge

Striking the right balance regarding the value of RCTs versus the value of RW data

What framework?

RWDTF Mission: “Develop a framework to assist health care decision-makers in dealing with “real world” data and information in “real world” health care decision-making, especially related to coverage and payment decisions.”

- We have a framework: the bioclinical cost-effectiveness model
- Need to add
  - Value of information
  - Population level impacts

Pharmacoeconomic Modeling of Drug Therapies

From Surrogate Markers to Economic Outcomes

<table>
<thead>
<tr>
<th>Pharmacoeconomic Modeling of Drug Therapies</th>
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<tbody>
<tr>
<td>Treatment Comparison</td>
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<tr>
<td>Drug Therapy A vs. Drug Therapy B</td>
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<td>Safety</td>
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Evidence-Decision Making Cycle

Pharmaceutical modeling to support decision making should fundamentally be a Bayesian exercise: updating priors and calculating expected gains and losses.
Regulators vs. Payers: Different Standards?

- FDA/EMEA rely heavily on RCT data.
  - BUT post-marketing safety data are largely observational
- NICE and payers are more open to integrative CEA models.
  - BUT carefully examine RCT core
- Not as different as people might think
  - Regulator is certifying product quality
  - Payer is judging value for money

The Regulator’s Role

Incremental Net Health Benefit (INHB) of New Drug (2) vs. Current Therapy (1)

\[ \text{INHB} = (E_2 - E_1) - (H_2 - H_1) \]

where
- Effectiveness E is measured in QALYs
- Harms H can be measured in QALYs

\[ (E_2 - E_1) - (H_2 - H_1) > 0 \]

Favorable benefit-harm balance

These measures are uncertain and would have distributions/variances around them:
1. Need to adjust them for risk aversion
2. Need to use probabilistic sensitivity analysis

Implicit Bioclinical Health Outcomes Model: The Benefits Side

Long-Term Improvements in Surrogate Co-Morbidities:
- Glucose Tolerance
- Cholesterol
- Blood Pressure

Improved Clinical Outcomes:
- Cardiovascular
- Cerebrovascular

Better Health Outcomes:
- Length of Life
- Quality of Life

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PE Models have long lives:
CellCept®—Immunosuppressive for Kidney Transplant

- Started working on this in 1992 (Syntex)
- First built a forecasting model—10 year horizon
  - Three phase III clinical trials were underpowered to measure graft survival.
  - Used acute rejection as a surrogate marker.
  - Economic drivers are the costs and QoL of patients who lose grafts and go on dialysis.
- Total results were for one year, but this is a chronic treatment regime.
- Critical whether the graft survival at one year persists, diminishes, or widens.
- Three-year data were still not powered to measure this.
  - 10 years later (2002-3) ended up in NICE review
  - Developed long-term model (10 years)
  - Argued about correlation of acute rejection and longer term graft survival

Tamiflu for Influenza

- Trials were for treatment and prophylaxis (non-pandemic)
- Probability of diagnosis is critical for cost-effectiveness.
  - How can you do this in an RCT?
- Death is critical in pandemic situation
  - We don’t know what the death rate will be
- Real world decision makers must decide how much to stockpile.
  - Must build a pandemic infectious disease model
Bisphosphonates for Osteoporosis

- Once daily formulations had GI issues.
- Compliance studies from prescription databases highlighted the problem.
- Laid the groundwork for weekly and monthly formulations

Oncology Drugs

- Modeling cost-effectiveness in metastasis use is relatively easy given near complete follow-up
- Crossovers can be a challenge
- Costs during progressive phase are difficult to measure
- Adjuvant treatment (e.g., colon and breast) must project from 3-5 year follow-up data
  - Have good long-term follow-up data from pooled trials in breast cancer
  - Modeling is required for long-term survival projections

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The Economics of Methodology: The Rule of Reason

- What if you could do the ideal real world trial?
  - Head-to-head
  - Large enough to measure impacts on long-term survival and quality of life
  - Large enough to measure costs and outcomes of side effects with precision
  - Would be in multiple practice settings and health systems

- Costs of doing it would be prohibitive?
  - Integrative modeling is the cost-effective way to approach this.
  - Apply value of information: spend your research money where the payoff is greatest.

New (?) Methods

RWOTF did not spend a great deal of time on methods per se.

- Each topic area had its own methodological issues:
  - Clinical, PROs, Economic outcomes
- Each type of data had its own set of methodological issues:
  - Large pragmatic trials, registries, administrative claims, population surveys, trial supplements
- Biggest issue: RW data vs. RCTs: controlling for selection bias and confounders
  - Use propensity scoring, Heckman correction, epidemiological designs
- Value of information: Idea has been around a long time, we are only just beginning to apply it.
  - There is a critical policy question underlying this: who should pay for information—a public good?

Inevitability of Modeling and Using Real World Data

- Some have criticized Markov modeling as that a central approach
  - Markov modeling is relatively simple and straightforward
  - But even simpler methods can be used in many cases
  - Modeling approach and structure should depend on the research question and the data at hand.
- But our projection models used at launch are MODELS: payers will increasingly ask for post-launch measurement of outcomes—*This will require real world outcomes data!*
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- Need to convince some authorities that value for money decisions can not be based on RCT data alone.
  - Issue: Centralized vs. market approach
- Develop checklists by type of data regarding good methodology (ISPOR SIGs doing this work).
- Bring VOI analysis into assessments
- Build more population-level models on health outcomes impact (not just budget-impact models).
- Information as a public good: company vs. government role
  - Role for conditional reimbursement?

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**Thank you!**

**Questions?**