

Using Real World Data in Pharmacoeconomic Evaluations:

Challenges, Opportunities, and Approaches

Andreas M. Pleil, PhD

Senior Director

Worldwide Medical and Outcomes
Research

Pfizer, Inc., La Jolla, CA





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Many thanks to Lou Garrison for allowing me to steal many of these slides shamelessly

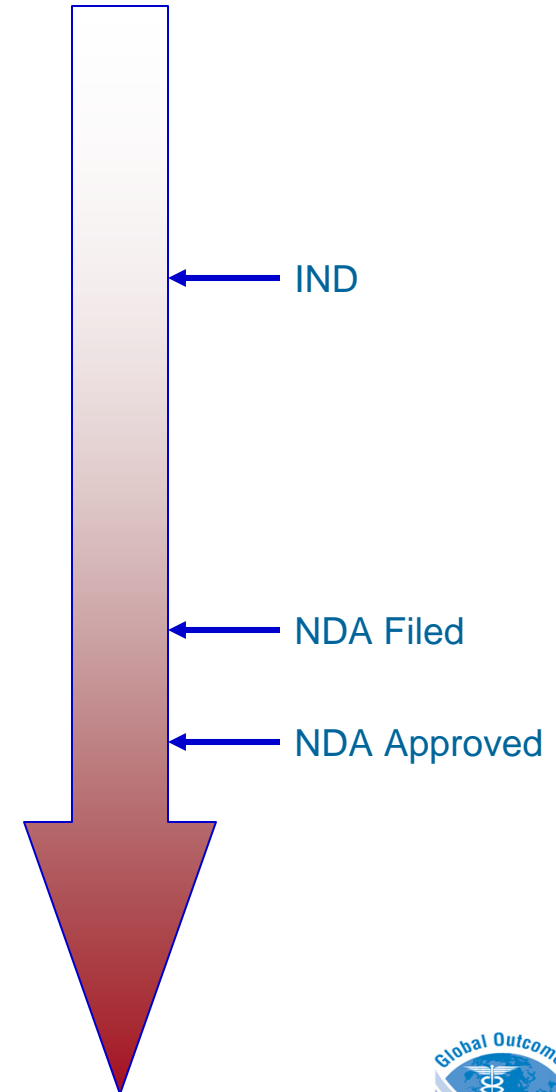


- Overview of the Landscape
 - Where do data come from
- Report from the Task Force
 - What was their charge
 - Who did the charging
 - What did they conclude
- Discussion points
 - Is the RWTF sufficient
 - Are there gaps in our knowledge
 - What should we do next
- Applications from your world
- Group Project

Where do “Data” Come From?



- **Pre-clinical studies**
 - Provides a first assessment of the expected safety and efficacy of a compound using proven animal models
- **Early Phase Clinical trials**
 - Safety focus and the beginnings of efficacy, dose ranging, and tolerability
- **Pivotal Clinical trials**
 - Demonstrate safety and efficacy in well controlled (generally masked) randomized studies sufficient for market authorization
- **Phase IIIB**
 - Expanded trials in different use situations or populations
- **Phase IV**
 - Post marketing safety or “new” indications
- **Real World Data**
 - Evaluations of safety, effectiveness and outcomes in “routine” clinical practice



Who uses “Data”?



- Companies making internal decision regarding drug development
- Regulators responsible for controlling drug development and approval of new treatments
- Ethics boards interested in protecting human subjects
- Physicians making prescribing decisions
- Payers making reimbursement and formulary status decisions
- Health care systems making resource allocation decisions regarding access and reimbursement for treatment
- Governments making public policy decisions regarding health and health priorities



What are “Data” used for?



- Identifying potential new medical treatments
- Informing the design of clinical programs
- Supporting the clinical efficacy and safety of new interventions
- Establishing the clinical value and role of a new treatment
- Informing prescribers about the features and benefits of a medical treatment
- Establishing the economic value of treatment in usual care environments
- Differentiating one treatment from another for commercial purposes
- Assessing the long term safety of medical interventions





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.



Task Force Structure and Membership



Co-Chairs

Peter Neumann ScD,
Tufts University School of
Medicine

Lou Garrison PhD,
University of Washington
Dept. of Pharmacy

Working Groups

**PATIENT REPORTED
OUTCOMES**

**ECONOMIC
OUTCOMES**

**EVIDENCE
HIERARCHIES**

**CLINICAL
OUTCOMES**

Chair: Penny Erickson PhD, O.L.G.A.

Jamie Banks PhD, Abt Associates
Richard Chapman PhD, ValueMedics
Mary A. Cifaldi, Ph.D, RPh., MSHA, Abbott
Andreas Pleil PhD, Pfizer Inc.

Chair: Lou Garrison PhD, University of Washington

Jens Grueger PhD, Novartis
Penny Mohr, CMS
Les Noe RPh, Ovation Research Group
Bill Crown, i3 Innovus

Chair: Dan Mullins PhD, University of Maryland

Joe Jackson PhD, Bristol-Myers Squibb
Phil Sarocco MSc, RPh, Boston Scientific
Jennifer Elson-Lafata PhD, Henry Ford Center for Health Services

Chair: Deborah Marshall PhD, i3 Innovus

Marc Berger MD, Merck & Company Inc.
Gurvaneet Randhawa MD, MPH, AHRQ
Bruce Carleton PhD, Children's and Women's Health Centre of British Columbia
Anne Smith, Children's and Women's Health Centre of British Columbia



Task Force Timeline



Spring 2004:	Institutional Council recommends “Real World Data” TF
Summer 2004:	ISPOR board approves
Fall 2004 to Spring 2005:	Working groups
June 2005:	Comments on CMS CED
August 2005:	Draft Report
Sept-Oct 2005:	Feedback from Working groups
November 2005:	TF meets at European ISPOR
December 2006:	Revised Draft for Task Force Review
April 2006:	Revised Draft sent to Reference Group
May 2006:	Presentation at Philadelphia ISPOR Meeting
August 2006:	Revised Draft Posted on www.ISPOR.org
September 2006:	ISPOR Member Comments (>75!) Received
November 2006:	Draft Report to be Submitted for Publication;
September 2007:	Published report

Garrison LP and Neumann PJ (co-chairs); Erickson P, Marshall D, Mullins CD. *Using real world data for coverage and payment decisions: the ISPOR real world data task force report.* Value in Health 10(5): 326-335. September, 2007.



- Why a Real World Data Task Force?
- Task Force Objectives and Scope
- Types and Sources of Real World Data
- Key Findings
- Conclusions

- 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), IQWiG (Germany), CMS (Coverage with Evidence Development)

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

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

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

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.

“Evidence” infers a degree of actionability whereas data are just the facts

- Data are objective observations
- Evidence is the organization of observations to be informative
- Evidence is normative and as such conditioned on subjective interpretation
- Data provides the foundation on which we build reasoning
- Evidence drives the decision based on the interpretation of the data

In general, “real world evidence” is what happens to data. Building the evidentiary portfolio requires the systematic unbiased collection of data. The validity of the evidence is dependent on the accuracy of the data and the appropriate organization to allow interpretation, analysis, and conclusions.

“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?”

- Coverage and payment focus (P&R)
 - Includes public policy as well
 - Excludes patient level decisions and regulatory (safety/efficacy) decision making

- Pharmaceutical technology emphasis
 - Familiar space, but the data can be applied to other medical technology decisions or comparisons

- US-Centric with global reach
 - Though the MMA was a driver, the implications are global

By type of endpoint

- Economic—resource use and costs
- Clinical—morbidity, symptoms, mortality
- Humanistic—patient-reported symptoms, quality of life

Evidence hierarchies

- Are RCT's always the “strongest”?

Data Sources

- Datasets
- Databases

- 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
 - Guidances abound but guidance is fleeting

The strength of the evidence (EBM) is determined by its internal validity and then its generalizability

The hierarchy of data:

- Meta-analysis of RCT data
- The single or replicate RCT
- The non-randomized interventional trials (quasi-experimental)
- Observational studies
- Non-experimental studies (case-studies)
- Expert opinion

Balanced by the quality of the design

- A well designed non-randomized trial may (often does) provide better quality data than a poorly designed (or small sample) RCT

The secret is in the flexibility of the interpretation not the inflexibility of the order used to define the hierarchy

Datasets

- Supplementary alongside RCTs
 - ◆ 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

Databases

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

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 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
 - 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
 - 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)



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
- There may be a lag between the time when a decision needs to be made and when the data are available – a “Catch 22”



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



- 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 bio-clinical 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?
- Why should these data be collected?
 - Confirm RCT's?
 - Focus on safety, not efficacy?
 - Rationalize rationing?
 - Can these data help at the patient level to improve individual outcomes?

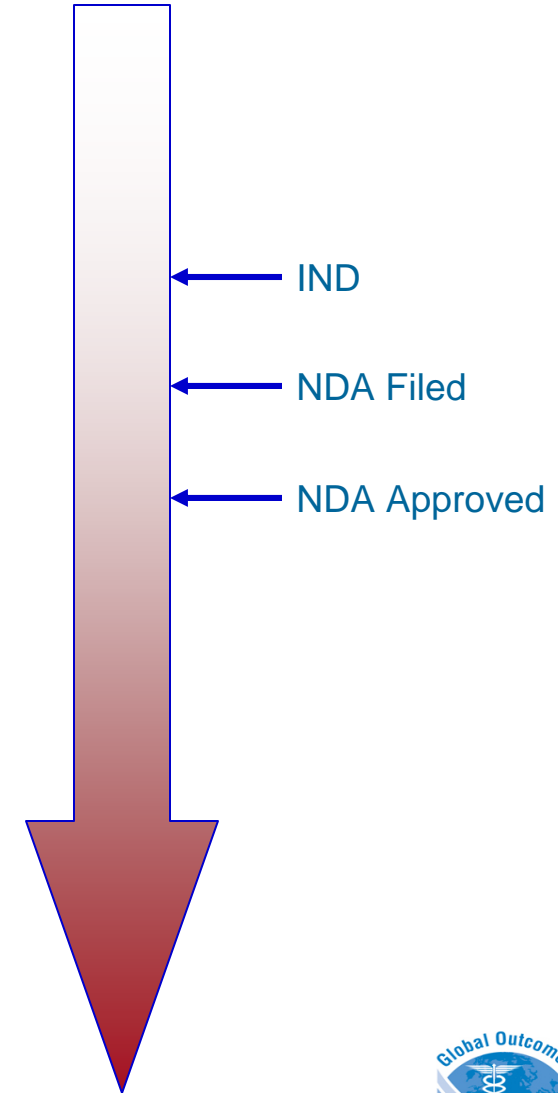


- “Real world data are essential for sound coverage, payment, and reimbursement decisions.”
- “Randomized controlled trials remain the gold standard for demonstrating clinical efficacy in restricted trial setting, but other designs—such as observational registries, claims databases, and practical clinical 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”

- Should regulators and payers have a different set of 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
 - ◆ The issue of the “fourth” hurdle (or fifth)

- If “real world” data are informative, is it reasonable to change the criteria for regulatory approval (two well controlled studies?)

- Not as different as people might think
 - Regulator is certifying product quality
 - Payer is judging value for money



Thank you!

Questions?