Enhancing the Application of Real-World Evidence in Regulatory Decision-Making

Public Conference
March 3 & 4, 2016
The Washington Plaza Hotel
Regulatory Applications of Real World Evidence:
Observational Data

Jonathan P Jarow, MD
Office of Center Director
CDER
Evidence from Clinical Experience

• Definition
  – Evidence obtained from observational studies or clinical experience
  – Patient registry’s, electronic health records, claims data, social media, etc.

• Uses
  – FDA Regulatory
    • Safety & Efficacy
  – Healthcare economic information: payers
  – Research: academic and drug development
Statutory Basis of FDA Regulatory Standards:
Substantial Evidence

- Efficacy versus safety
- Drugs versus devices
Spectrum of Evidence

- Randomized controlled trials
- Pragmatic trials
- Prospective observational trials
- Retrospective observational trials
- Registries
- Case series/reports
History

• Safety
  – NMEs
  – Sentinel

• Efficacy
  – Rare diseases
  – Devices

• Labeling changes/updates
Use of Registries for Rare Diseases

• Lumizyme for Pompe disease – survival data from an international Pompe disease registry in patients with infantile-onset disease
• Carbaglu for N-acetylglutamate synthase deficiency – data on plasma ammonia level reductions in a case series
• Cholbam for bile acid synthesis disorders – data on growth, survival, and reduction in laboratory parameters of cholestasis in a case series
• Glucarpidase for MTX toxicity - data on a ~20 patient subset within what was essentially a treatment protocol at NIH
• Metreleptin for Leptin deficiency/lipodystrophy - case series out of NIH, similar to glucarpidase, was essentially a treatment protocol
Labeling Changes based on Real World Evidence

• High-dose influenza vaccine versus standard dose
  – Retrospective cohort study of Medicare claims
  – High-dose: 929,730
  – Standard dose: 1,615,545

• Rabies vaccine dose schedule
  – Standard five dose versus four dose used during drug shortage
  – Change in CDC recommendations
CURE-NTD

(Collaborative Use Repurposing Engine)

• Repurposing of drugs for neglected tropical diseases
• Website/mobile app
• Global reporting tool for cases
• Searchable curated database
• Fuel drug development for neglected tropical diseases
Methodology

• Random versus systematic errors versus falsification

• Analysis/review
  – Esophageal cancer and bisphosphonates
  – GPRD database
    • RR 0.96 (0.74-1.25)
    • RR 1.30 (1.02-1.66)

Cardwell JAMA 2010
Green BMJ 2010
Future Needs

• Demonstration projects in US
• Academic research
• Regulatory policy
  – Part 11
  – Part 50
• Federal evidence generation system
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National Medical Evidence Generation System

Melissa Robb
March 4, 2016
Vision

A national medical evidence generation system that allows for integration of clinical care and clinical research (for those systems and patients willing to participate), that would allow for the conduct of observational and interventional research and surveillance (learning) by leveraging and linking information collected by multiple entities.
Call to Action

- Decisions about health and healthcare are best made when informed by high quality evidence
  - Medical product regulation
  - Payment
  - Individual consumer/patient/provider decisions
  - Policies

- Our current system of generating evidence has challenges
  - Generalizability
  - Feasibility
  - Efficiency
  - Sustainability
Partners in a National Infrastructure

- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development
- Other potential partners: disease or treatment-specific networks
Informed by Ongoing Projects, Including:

- FDA
  - Sentinel Initiative
  - National Device Evaluation System
- NIH Health Care Systems Research Collaboratory
- CTSA
- PCORI-PCORnet
- Reagan-Udall Foundation IMEDS Project
- Precision Medicine Initiative
- VA Million Veteran Program
- Coordinating Efforts—ONC, ASPE
Governance Issues Are Key

- Patient Privacy
- Data Security
- Transparency and Confidentiality
- Access
- Conflict of Interest
- Intellectual Property
- Separate governance structures are likely to have different funding models
Crucial Steps to Progress

• Organize operational systems to enable clinicians, patients, consumers, industry, government, and healthcare systems to participate
• Establish a framework for confidentiality and security
• Adopt a common approach to configuring digital healthcare data
• Eliminate barriers that promote complexity, while ensuring appropriate safeguards
• Ensure that each linked group of projects has appropriate governance in place
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Building a Robust 21st Century Evidence Development Infrastructure

Nancy A. Dreyer
Chief of Scientific Affairs
Quintiles Real-World & Late Phase Research

March 4, 2016
Getting to a Better Infrastructure
Integrating Multi-Source Data

- Qualified partners are used on demand
- Health care records and health insurance claims can be individually linked to prospectively collected data
Obtaining real-world evidence: the Salford Lung Study

John P New, 1 Nawar Diar Bakerly , 1 David Leather, 2 Ashley Woodcock

ABSTRACT

We need to assess clinical treatments in real-life settings. A pragmatic clinical trial (pRCT) data can supplement effectiveness information and clinician's decisions. Electronic health records can collect adherence and concurrent safety monitoring, which can be used in randomised study populations in pRCTs. The Salford Lung Study is the world’s first phase III pRCT for asthma and chronic obstructive pulmonary disease (COPD), which aims to randomise over 7000 patients. This paper describes the hurdles overcome and the enormous effort and resource required to establish this comparative effectiveness study of a prelicencing intervention.

GlaxoSmithKline protocol HZC115151
Asthma study clinicaltrials.gov registration NCT01706198
COPD study clinicaltrials.gov registration NCT01551758

Pragmatic trial nested with a health system
Pragmatic Design Compare Spinal Care Algorithm, Usual Care and Rehabilitation-based Therapy

- Direct to Patient
  - Baseline
  - 6 weeks
  - 6 months
  - 12

- Usual Care (n=1345)
- Spinal Care Algorithm (n=1345)
- Physical Therapy (n=1345)

Locations with IDNs & Physical Therapy Sites

Back &/or Neck Pain

E-Consent at site Randomization

Health Care $:
- Opioid Use
- QOL
- Pain
- Able to Work

EMR & Health Insurance Claims

Baseline
6 weeks
6 months
12
COMPASS: COMparative effectiveness and PATient Safety & Surveillance

~8 million unique current* patients; ~21 million patients total

*current = a physician encounter within the past 18 months

As of December, 2015
Patient as a Reporter: PROTECT validation study*

Self-reported medication use in pregnant women / pregnancy outcomes

**Objective:** To assess the extent to which data collected directly from pregnant women provides information on medication use and other potential risk factors throughout pregnancy, and is suitable for research purposes

- Tested Internet v IVRS
- 2 v 4 weeks data collection
- How much medication usage (eg OTC or prescribed but not taken,) is not recorded in electronic health or prescription records?
- Are there additional risk factors not typically recorded?

**Conclusion**

- 83% used ≥ 1 non-pregnancy-related medication during pregnancy or the preceding month; 24% reported using OTC medications; 7% reported not using prescribed medications
- Additional risk factors not found in EHR were reported.
- Validation of clinical outcomes of special interest may be warranted

*Dreyer et al. Direct-to-patient research: piloting a new approach to understanding drug safety during pregnancy. *JMIR Public Health & Surveillance* 2015; 1(2); e22. doi:10.2196*
Using Existing Data Standards & Unique Patient Identifiers Allows Quick Generation of Evidence-Based Information*

*Data standards have already been developed & other modern countries are using unique patient identifiers
21st Century Robust Evidence Development

Key Challenges

• Knowing the limitations of existing data sets and when supplementary data are required
• Maintaining a system for re-identification of patients, providers and institutions
• Determining when informed consent is needed
Contact Information

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RWEB INFRASTRUCTURE
A FOCUS ON OUTCOMES

Duke-FDA Symposium:  RWE in Regulatory Decision-Making
Sean R. Tunis, MD, MSc
March 4, 2016
What is Patient-Centered CER?

- Involves patients, consumers, other stakeholders in conducting and disseminating the research
- Compares two or more options for prevention, diagnosis, or treatment (can include “usual care”)
- Conducted in real-world populations and real-world settings
- Considers the range of clinical outcomes relevant to patients
- Attends to differences in effectiveness (both benefits and harms) and preferences across patient subgroups
- Often requires randomized trial design
DMARD trials for rheumatoid arthritis

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WHO/ILAR core set
RA clinical trials

- global assessments patient & assessor
- pain
- painful joint count
- swollen joint count
- physical disability
- acute phase protein

- in studies ≥ 1 year: X-rays hands & feet
Improvements over time (Kirkham et al, *Trials* 2013)

Studies reporting full RA COS (%)

- 1985: 0%
- 1990: 20%
- 1995: 40%
- 2000: 60%
- 2005: 80%
- 2010: 100%

Mean number of clinical outcomes

- Drug studies:
  - 1985: 0.0
  - 1990: 6.0
  - 1995: 6.5
  - 2000: 7.0
  - 2005: 6.5
  - 2010: 7.0

- Non-drug studies:
  - 1985: 0.0
  - 1990: 6.0
  - 1995: 6.0
  - 2000: 6.0
  - 2005: 6.0
  - 2010: 6.0

WHO/ILAR RA COS guideline

EMA guideline

FDA guideline
Core outcome set

• An agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care
Developing a Core Outcome Measurement Set

Core Domain Set

- Literature review
  - List of candidate Measurement Instruments per Domain

For each Domain:
- covered by at least one Instrument?
  - no
  - yes

Document applicability
  (for each available instrument: is it Truthful, Discriminative and Feasible?)

- no
- yes

When all Domains have at least one applicable instrument:

Preliminary Core Outcome Measurement Set

- consensus

Draft Core Outcome Measurement Set

- consensus

Develop new Instrument(s)

Validation studies

Core Outcome Measurement Set

agreement on how to measure at least one applicable Instrument per Domain
Year of COS publication
Core Outcome Measures in Effectiveness Trials

www.comet-initiative.org
A PROBLEM WITH STANDARDS

“Standards are like toothbrushes: everybody wants one, but nobody wants to use anybody else’s.”

Jerry Sheehan, NIH/NLM
(citing Doug Fridsma, AMIA)
Developing the PCORI Methodology Standards

- Congressional Requirements - Patient Protection and Affordable Care Act, Subtitle D, Paragraph (6)(C)(i)

“(C) FUNCTIONS.—Subject to subparagraph (D), the methodology committee shall work to develop and improve the science and methods of comparative clinical effectiveness research by, not later than 18 months after the establishment of the Institute, directly or through sub-contract, developing and periodically updating the following:

“(i) Methodological standards for research. Such methodological standards shall provide specific criteria for internal validity, generalizability, feasibility, and timeliness of research and for health outcomes measures, risk adjustment, and other relevant aspects of research and assessment with respect to the design of research.
PCORI Methodology Committee

“Select outcomes based on input directly elicited from patient informants, people representative of the population of interest, either in previous studies or in the proposed research.”
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