Gaps and Opportunities: Methodologic challenges in post-market safety surveillance.

Susan Gruber
Reagan-Udall Foundation for the FDA

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Overview

Part I: Why Observational Studies are Here to Stay, and Why We Need to Get Them Right

Part II: Issues in Post-Market Safety Surveillance using Observational Data

Part III: What IMEDS Can Do for You

Innovation in Medical Evidence Development and Surveillance
a program of the Reagan-Udall Foundation for the FDA
PART I

Why Observational Studies are Here to Stay, and Why We Need to Get Them Right
Pre-approval studies

• Typically underpowered for rare adverse events (AE)

• May lack sufficient follow-up time for detecting AEs with long induction or latent periods

• Findings may not generalize to post-market exposed population
  – higher number of co-morbidities
  – off-label use
And Yet...

Public demands access to new drugs ASAP

Tension

- Thorough Risk Assessment
- Reduce Delay in getting much needed drugs to physicians and patients
Risk-Benefit approach to regulatory decision-making

Methodologic Challenges

- Incomplete information
- Reasoning in the face of uncertainty
- Risk – Benefit tradeoff (one size does not fit all)

Risk-Benefit trade-off

• Opportunity for periodic re-evaluation
  – supported by ongoing accumulation of evidence
  – relative to new alternatives

• Information can inspire different types of regulatory action
Range of post-market regulatory actions

- Additional post-market requirement
- Safety warning
- Black box label
- Withdrawal
  - either failure or success of the system
  - success of the system
The Bottom Line

1. Pre-approval studies cannot provide all the answers.

2. Ethical considerations aside, not enough time, money, or manpower to run RCT for every post-market question.

3. Thus, observational studies (OS) may be the best, or only, source of knowledge.

Challenge #1: How can we make best use of observational data to improve post-market safety monitoring?
PART II

Post-Market Safety Surveillance using Observational Data
What, exactly, do we want to know?

• **Signal Detection:** For all exposures and outcomes of interest, identify exposure–outcome pairs where exposure increases risk for the outcome (*classification task*)

• **Signal Refinement:** Estimate the causal effect of a pre-specified exposure on a pre-specified outcome (*estimation task*)
Reality makes things complicated

• The risk profile may not be constant over time.
• Relevant comparison group depends on scientific question of interest
  – relative to active comparator (Drug A vs. Drug B)
    • clinical decision-making
    • risk/benefit analysis
  – relative to no exposure
    • biological pathway discovery
    • joint replacement, device implantation
Example: Does exposure to Drug $A$ increase risk for Outcome $O$?

\[
\begin{align*}
\text{RR}_{AB, \text{6months}} &= 2/3 \implies \text{No} \\
\text{RR}_{AC, \text{6months}} &= 2 \implies \text{Yes}
\end{align*}
\]

If $A$ doubles the risk, $B$ triples the risk, and $C$ is unrelated to $O$, both RR estimates are correct.

- This phenomenon is not due to an inherent flaw in observational studies
  - It is independent of the quality of the data
  - It is not a failure of the analytical approach
  - We’d see the same thing in an ideal RCT

- Ask a precise question

- Understand which parameter corresponds to the scientific question you care about
Challenge #2: What are the right questions to ask when monitoring drug safety?

- Estimate an absolute risk?
- Estimate risk relative to available treatment options?
- Is risk above a certain threshold? (Yes or No)
- Over what time period?
- For what set of outcomes?
Statistical analysis of observational electronic healthcare data

• False positives are a regulatory concern
  – Further investigation wastes scarce resources
  – Regulatory action could unnecessarily reduce exposure
  – Publicity might reduce adherence

• Bias is a major issue
  – Lack of randomization
  – Unmeasured confounders
  – Exposure and outcome misclassification
  – Missing data
  – Censored data
Challenge #3: How to deal with bias in the analysis of observational electronic healthcare data?
Options for addressing bias in causal effect estimation

• **Approach 1: Unbiased estimation of causal effect**
  – Handle confounding in the statistical analysis
    • outcome regression modeling, propensity score matching, inverse probability weighting
    • instrumental variables approach
    • self-controlled design

• **Approach 2: Quantify the bias**
  – External domain knowledge
    • is it correct?
    • does it generalize to target population?
  – How large would it have to be to change qualitative conclusion?
Options for addressing bias in causal effect estimation

• Approach 3: Attack bias at its source
  – Outcome misclassification
    • chart review
    • develop algorithms to better distinguish cases/non-cases
  – Exposure misclassification
    • patient-reported data
      – adherence patterns
      – capture OTC drug use
  – Improve EHR systems

• Approach 4: Change the question
  – Estimate bounds on effect size
  – Aim to detect changes in risk patterns over time (signal detection)
Challenge #4: How to interpret heterogeneous results from multiple studies?

Potential sources of heterogeneity include

- Study inclusion/exclusion criteria
- Coding practices, formularies
- Different sources of bias (strength, direction)
- Violation of assumptions underlying the analytical approach
- Incorrectly comparing “apples” and “oranges” (different statistical estimands)
Challenge #5: Characterize Uses and Limitations of the Data

Can we characterize scenarios where we are confident that the results provide reliable evidence to inform regulatory action?

Scenario = (question, exposure, outcome, data, study design)
PART III

What can IMEDS do for you?
What is IMEDS?
http://imeds.reaganudall.org/

• A program within the Reagan-Udall Foundation for the FDA
• Three components: Education, Evaluation, Methods
• IMEDS-Methods
  Mission is to facilitate methods research aimed at monitoring safety of marketed medical products.
### IMEDS-Methods

**Challenges**

#1: How can we make best use of observational data to improve post-market safety monitoring?

#2: What are the right questions to ask when monitoring drug safety?

#3: How to deal with bias in the analysis of observational electronic healthcare data?

#4: How to interpret heterogeneous results from multiple studies?

#5: Characterize Uses and Limitations of the Data

IMEDS sponsors research to address these challenges (and more)
IMEDS Research Laboratory

• **Computing Platform**
  - Secure computing platform housing research tools and healthcare datasets
  - Amazon.com's Elastic Cloud Computing (EC2) technology
    - virtual computers based on predefined configuration
    - quickly scale capacity to reflect changes in computing requirements

• **Data**
  - De-identified pursuant to HIPAA standards
  - Formatted to conform to OMOP and Mini-Sentinel Common Data Model
  - GE Centricity, Truven MarketScan *Commercial Claims and Encounters*, *Multi-State Medicaid*, *Medicare Supplemental Beneficiaries*, *Lab Supplemental*
  - In discussion with PatientsLikeMe to bring de-identified patient-reported data into the lab

• **Investigator groups from FDA, NIH, industry, academia**

IMEDS Research Laboratory

Examples of Methodologic Research carried out in the IMEDS Lab
http://imeds.reaganudall.org/LabUsers

• **OHDSI Investigator Group**: Develop software and infrastructure to support post-marketing evidence generation by creating summary statistics for associations between all combinations of medical products and outcomes.

• **GlaxoSmithKline R&D**: A methodological comparison across data sources, common data model approaches, and epidemiological designs. This research will evaluate the performance of Mini-Sentinel (MS) and Observational Medical Outcomes Partnership (OMOP) analytical tools.

• **NIH Investigators**: Analyzing and measuring the comprehensiveness of Electronic Health Record (EHR) in a given Integrated Data Repository.

• **RAND Corporation**: Discover discriminative sequential treatment patterns between patients with better than expected and worse than expected outcomes at given health status at incident diagnosis with a chronic condition.

• **UCLA David Geffen School of Medicine, Department of Biomathematics**: Integrate Bayesian methods and high performance computing to achieve better identification of drug risk.
What IMEDS-Methods can do for you

• Provide access to the IMEDS Research Lab data + software + parallel computing platform
• Supports internally and externally funded projects
• IMEDS Community
  • Discussion group
  • Webinars
• Upcoming
  • Open Comment Period on 2015 DRAFT Research Agenda (late Fall, 2014)
  • IMEDS Competition for identifying the occurrence of health outcomes from claims data
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IMEDS Community
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