Use of Real-World Data and Real-World Evidence for Regulatory Decisions: Opportunities and Challenges

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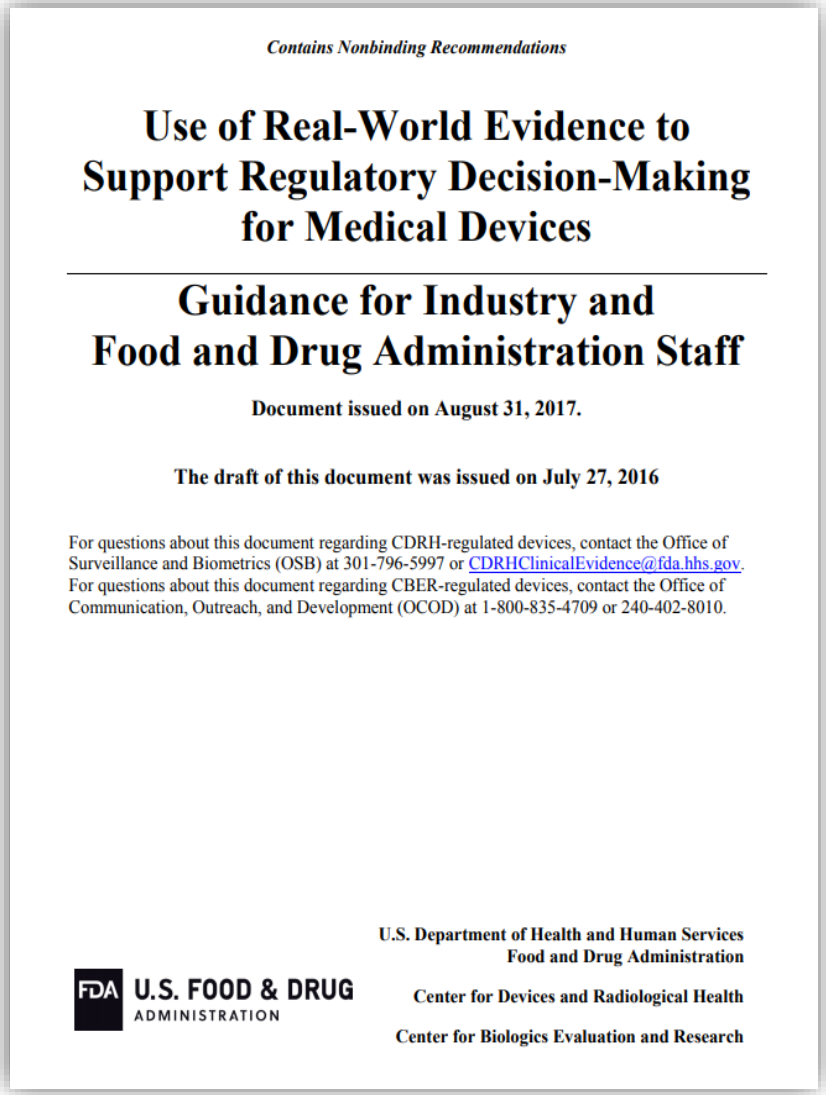
Outline

- State of leveraging real-world data (RWD) and real-world evidence (RWE) in the medical product regulatory decision making
- Opportunities and case studies of leveraging RWD/RWE in pre- and post-market medical device evaluations
- Major statistical and regulatory challenges
- Concluding remarks

FDA/CDRH & CBER

RWE Guidance

Aug. 31, 2017



Contains Nonbinding Recommendations

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Definitions from the Guidance

Real-World Data (RWD)

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE)

Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Real World Data Source Examples

- Electronic health records (EHRs)
- Insurance claims and billing data
- Patient Registry (product or disease)
- Personal data., e.g., patient-reported outcomes
- Laboratory test database

General Potential Use of RWE

- High quality RWE has the potential to
  - Complement the knowledge gained from traditional clinical research to answer scientific and clinical questions.
  - Support applications, including therapeutic development, outcome research, patient care, quality improvement, medical product surveillance, and well-controlled effectiveness studies.
  - Allow researchers to answer healthcare questions efficiently, with saving in both time and cost, and for broader patient populations.

Why Use RWE in Regulatory Decisions?

Traditional clinical trials

- Evaluate medical product performance in controlled setting.
- Benefits include:
  - Control over the study design and protocol
  - Control for confounding
- Limitations include:
  - Usually, expensive and time-consuming
  - May be difficult to collect rare endpoints
  - How generalizable are results?

Why Use RWD/RWE in Regulatory Decisions?

Potential benefits of real world data sources include:

- Understand medical product performance in real-world environment to inform benefit-risk.
- Collect endpoints not feasible in traditional clinical trials,
  - performance in diverse patient populations and subgroups
  - long-term outcomes
  - larger data sets to assess rare endpoints
- Bring off-label use "on label"
- Opportunities to partner w/patients (patient reported outcomes, mobile medical apps, wearable devices, user experience, etc.)
- Reduced time/cost to market

What is FDA's Role for RWE?

Support Sentinel & NEST

- Engage in broad collaboration and discussion

Work with sponsors

- Consider new and flexible approaches

Develop and clarify policy

- RWE guidance
- Outreach

FDA Guidance

Use of Electronic Health Record Data in Clinical Investigations- Guidance for Industry

July 2018 by FDA/CDER & CBER & CCDRH

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm501068.pdf

FDA Voice by Commissioner Scott Gottlieb, M.D.

https://blogs.fda.gov/fdavoice/index.php/2018/07/fda-budget-matters-a-cross-cutting-data-enterprise-for-real-world-evidence

FDA Budget Matters: A Cross-Cutting Data Enterprise for Real World Evidence

Posted on **July 10, 2018** by **FDA Voice**

By: Scott Gottlieb, M.D.

Over time, as our experience with new medical products expands, our knowledge about how best to maximize their benefits and minimize any potential risks, sharpens with each data point we gather. Every clinical use of a product produces data that can help better inform us about its safety and efficacy.

The FDA is committed to developing new tools to help us access and use data collected from all sources. This includes ways to expand our methodological repertoire to build on our understanding of medical products throughout their lifecycle, in the post market. We don't limit our knowledge to pre-market information, traditional de novo post-market studies, and passive reporting. Newer methodologies enable us to collect data from routine medical care and develop valid scientific evidence that's appropriate for regulatory decision making to help patients and health care providers prevent, diagnose, or treat diseases.

RWD/RWE Use in Regulatory Settings

- Post-market medical product surveillance
- Pre-market medical product evaluations
- Today's topic - Pre-market medical device evaluations
  - Opportunities
  - Case studies
  - Challenges

Opportunities in Leveraging *High Quality* RWD/RWE in *Pre-market* Medical Device Studies

- *Creating efficiencies* for evaluating *investigational* medical devices.
  - Inform prospective investigational study design
  - Provide supplemental evidence to investigational clinical study
- *Expanding knowledge* for *already approved* devices
  - Labeling update of safety and effectiveness
  - Labeling extension (expanded indications for use)

Case Studies

1. Cardiac device – a *national device registry leveraged* for indication expansion

2. Sequencing assay – a *public NGS database used* for pre-market claim clearance

Case Study 1 - Leveraging a National Registry for Indication Expansion

- Investigational device – Percutaneous transluminal angioplasty (PTA) Drug-coated Balloon Catheter
- Study design – Comparative study for pre-market approval of an indication expansion
- RWD source – Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) , a national device registry
- Use of RWD – external control group formulation for the indication expansion approval and post-market surveillance
- Statistical method – Propensity score adjustment

https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010S015B.pdf

Case Study 2: Leveraging a RWD Database to Enable Pre-Market Claims

- Two sequencing assays were cleared for variants/variant combinations associated with cystic fibrosis using a public next-generation sequencing (NGS) database.
- In lieu of clinical trials, an established publicly-maintained database hosted by the academic institution was used to support clinical validity of the test.
  - Database used as a source of valid scientific evidence to establish which variants/ variant combinations were causal for the target disease.
  - Additional relevant patient information, e.g. sweat chloride, lung function, pancreatic status, and *Pseudomonas* infection rate, associated with each variant/variant combination were included in the evaluation.

https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf

Major Statistical and Regulatory Challenges

- RWD relevance and reliability
- Novel statistical approaches used to design, conduct and analyze investigational studies when leveraging RWE
  - Bias introduced in the investigational studies
  - Scientific validity of investigational study design, and interpretability of study results.

FDA Voice by Commissioner Scott Gottlieb, M.D.

https://blogs.fda.gov/fdavoice/index.php/2018/07/fda-budget-matters-a-cross-cutting-data-enterprise-for-real-world-evidence

Improving Clinical Trials

The development of such a tool can also make the entire clinical trial process much more efficient. And it can enable us to enroll more patients from more diverse backgrounds into trials.

For example, real world data can be used to more efficiently identify and recruit patients for a clinical trial. Key design considerations, such as randomization, can be integrated across clinical care settings, introducing a much more diverse population into the clinical trial system. Innovative statistical approaches — such as Bayesian and propensity scores methods — can combine information from different sources and potentially reduce the size and duration of a clinical trial while expanding the scope of healthcare questions that we're able to evaluate. This will enable a modern clinical trial system that improves upon trials being conducted in large medical care centers. It could enable more clinical trials at smaller community-based health care providers. Such a system can expand the number of patients we're able to evaluate, and broaden the information that we're able to collect, while at the same time reducing the cost of developing this information. We can have more and better information, and a less costly process.

Today's Highlight

- Use RWD to form an external control group for a comparative study in the safety and effectiveness evaluation of an investigational medical product.
  - Bias introduced in the investigational studies
  - Scientific validity of investigational study design

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Bias

- In the investigational comparative study leveraging RWD,
  - ➢ Potential systematic difference in the distribution of baseline covariates between different data sources, due to possible heterogeneity in
    - Patient population
    - Collection of important baseline confounding covariates
  - ➢ Potential systematic difference in the collection of clinical outcome data between different data sources in
    - Definition and adjudication of clinical outcomes
    - Length of follow-up
  - ➢ Possible temporal bias with a non-concurrent control
- Lead to bias in treatment effect estimation and compromise the objectivity of resulting causal inference!

Propensity Score Methodology for Bias Reduction

- A ground-breaking statistical innovation for the *design* and *analysis* of observational studies, developed by Rosenbaum and Rubin in 1983 (Rosenbaum and Rubin, 1983).
- Propensity score (PS): Conditional prob. of receiving treatment A rather than treatment B, given a collection of observed baseline covariates (Rosenbaum and Rubin, 1983).
- Replace the collection of confounding covariates with one scalar function of these covariates: the propensity score.
- Goal: Simultaneously balance many observed covariates between the two treatment groups, and then reduce bias in treatment comparison with respect to outcomes.

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Propensity Score Methodology (cont.)

- PS estimation: often estimated using a logistic regression model where the response is the treatment assignment and predictors are baseline covariates.
- With estimated PS, observational study design and outcome analysis can be performed.
  - Mimic some of characteristics of RCT
- Often used propensity score methods
  - Matching on propensity scores
  - Stratification on propensity scores
  - Inverse probability weighting using propensity scores

Propensity Score Utilization

- Unique and critical feature of these PS methods:
  - Can be used to separate study design and outcome analysis
    - Study design - create distribution balance of covariates between treatment groups (PS estimation and covariate balance assessment), without access to any outcomes (outcome-free)
    - Outcome analysis – compare treatment groups on outcomes, adjusting for PS.

Rubin: For Objective Causal Inference, Design Trumps Analysis, Ann. Appl. Stat. 2008, 2(3), 808-840

- Regarding the utilization of PS, a fundamental distinction between an exploratory study of general research and a regulatory confirmatory study is the necessity of outcome-free study design in the regulatory settings.

Bias Reduction
Using Propensity Score Methodology (cont.)

- Adopted first by FDA/CDRH in 2002, for pre-market *confirmatory* observational medical device studies.
- Utilized for post-market safety evaluation of drugs and devices (Levenson and Yue, 2013).
- Applied for leveraging "big data", such as a high-quality national/international registry database for pre-market medical device studies.

Scientific Validity of Study design

- A principle is to prospectively plan on the use of RWD and objectively design a comparative study to avoid data dredging excise for the evaluation of an investigational product.

- One strategy is to approximate randomized clinical trial, using statistical methodology.

- Some sophisticated statistical methods exist for such studies, e.g. propensity score methods.

Objective Study Design Using PS

- Using propensity score methodology
  - Select a comparable control group from RWD.
  - Approximate RCT and balance covariates.
- Design study without access to any outcome data.

Rubin, D. B. (2001). Using propensity scores to help design observational studies: Application to the tobacco litigation. *Health Services & Outcomes Research Methodology* 2:169–188.

Yue et al (2014). Designing pre-market observational comparative studies using existing data as controls: challenges and opportunities. *Journal of Biopharmaceutical Statistics* 24:994-1010.

Yue et al (2016). Utilizing National and International Registries to Enhance Pre-Market Medical Device Regulatory Evaluation. *Journal of Biopharmaceutical Statistics 26,* 1136-1145

Objective Study Design – 1st Stage

Initial planning on a study by sponsor

- Mimic RCT planning.
- Begin before the investigational study starts.
- Identify an independent statistician who is masked to the outcome data of both treatment groups and will design the study in the 2nd stage.
- Establish firewall to mask outcomes of both treatment and control groups.

Objective Study Design – 2nd Stage

Accomplished by the independent statistician identified

- The 2nd study design stage should start as soon as all patients with the investigational product are enrolled.
- Select a comparable control group from RWD.
- Approximate RCT using PS to create distributional balance of covariates between the two treatment groups.
- Specify a statistical analysis plan for the treatment effect estimation on outcomes.
- Design study without access to any outcome data from either treatment group.

Concluding Remarks

- High quality real world data and evidence have potential to play an important role in the regulatory decision making.

- Statisticians' role is to
  - Transfer data to evidence
  - Develop and apply appropriate statistical methods which play a key role in the transformation.

- We, statisticians, can make a significant difference!

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Thank You!