U.S. FOOD & DRUG ADMINISTRATION

Real-World Evidence Use at the Center for Biologics Evaluation and Research

Jennifer L. Kirk

September 25, 2019

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

DISCLAIMER

This presentation represents my views and does not represent FDA position or policy.

OVERVIEW

1 Real-World Evidence Use at CBER

2 Emerging Issues in Real-World Evidence Use

1

REAL-WORLD EVIDENCE USE AT CBER

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

Regulates a wide range of products:

- Vaccines & Allergenics
- Blood Derivatives & Components
- Human Tissue & Cellular Products
- Gene Therapies
- Xenotransplantation Products

PRIOR RWD/RWE EXPERIENCE

1. Sentinel
2. Center for Medicaid and Medicare (CMS) Data
3. Post-marketing Studies

SENTINEL

- National safety surveillance program
- Focused on signal detection in claims data from ≈ 225 million people
- CBER Specific Programs
  - PRISM: vaccines, ≈ 170 million persons
  - BloodSCAN: blood products

SENTINEL

- CBER conducts
  - Large epidemiological studies
  - Rapid assessments
- CBER projects:
  - **Intussusception risk after rotavirus vaccination**
  - **Febrile seizure risk after flu vaccination in children**

ORIGINAL ARTICLE

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

Article Figures/Media Metrics

33 References 127 Citing Articles

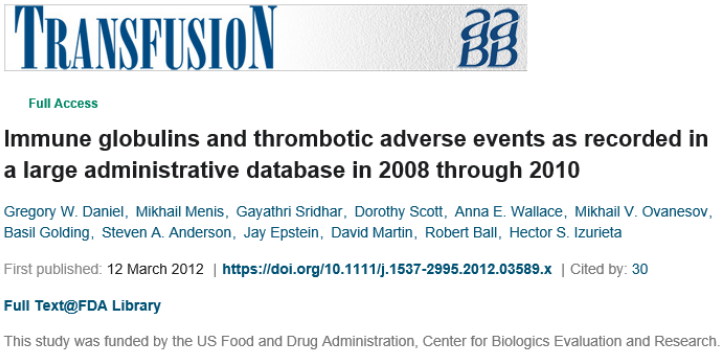
February 6, 2014
N Engl J Med 2014; 370:503-512
DOI: 10.1056/NEJMoa1303164

CMS DATA

- Claims data from ≈ 50 million people ≥ 65 years old
- CBER conducts
  - Large epidemiological studies
  - Rapid assessments

CMS DATA

- CBER projects:
  - **Immunoglobulins and thrombotic events (Transfusion 2012)**
  - High-dose verses standard dose flu vaccine (Lancet Infect Dis 2015, JID 2017)
  - Herpes zoster vaccine effectiveness (CID 2017)



TRANSFUSION

Full Access

Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010

Gregory W. Daniel, Mikhail Menis, Gayathri Sridhar, Dorothy Scott, Anna E. Wallace, Mikhail V. Ovanesov, Basil Golding, Steven A. Anderson, Jay Epstein, David Martin, Robert Ball, Hector S. Izurieta

First published: 12 March 2012 | https://doi.org/10.1111/j.1537-2995.2012.03589.x | Cited by: 30

Full Text@FDA Library

This study was funded by the US Food and Drug Administration, Center for Biologics Evaluation and Research.

CURRENT RWD/RWE EFFORTS

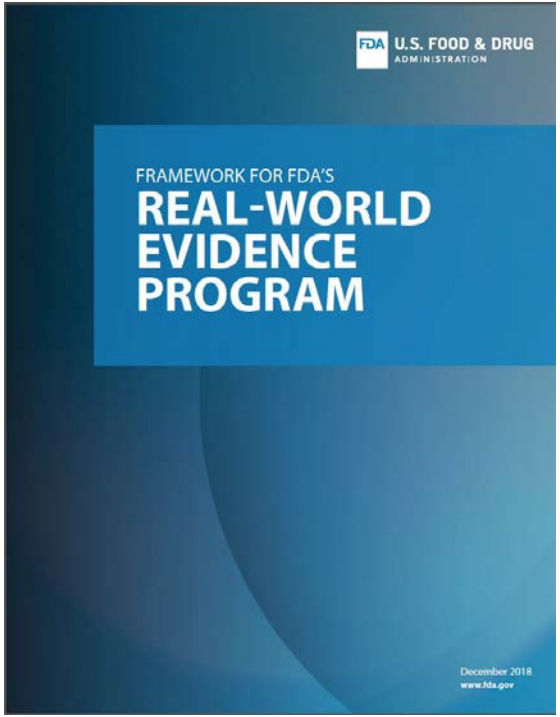
1 **FDA** Programs

2 CBER working group

3 BEST Program

CURRENT RWD/RWE EFFORTS

- **FDA** RWD/RWE
  - Guidances
  - Public Meetings
- CBER RWD/RWE working group



CURRENT RWD/RWE EFFORTS

BEST: Biologics Effectiveness and Safety Program

- Launched September 2017
- Electronic health records: > 20-40 million
- Better address CBER's regulatory needs

2

EMERGING ISSUES WITH RWD/RWE

EMERGING ISSUES

1 Mitigating Study Failures

2 Addressing Data Reuse

3 Role of Published Studies

MITIGATING FAILURES: EXAMPLE

- Post-marketing safety study of a vaccine in a large health-care system
- Sample size calculations accounted for
  - changing incidence over time (secular trends)
  - changing incidence by age
- Study seemed well powered, but the incidence was half of assumed:
  - Analysis models were numerically unstable and were changed post-hoc
  - Covariates were not included or included with less fine adjustments
  - Wide 95% confidence intervals for the outcome of interest
- Study could not answer the question it was designed to answer

MITIGATING STUDY FAILURES

Randomized Clinical Trials

- Well-defined population
- Standardized treatments
- Consistent data collection
- Simple analyses rely on study design for validity

Real-World Evidence Studies

- Unclear population
- Non-standardized treatment
- Inconsistent data collection
- Complex analyses to compensate for limitations

MITIGATING STUDY FAILURES

- Real-world evidence studies
  - Have much less control over the data content and quality
  - Rely on complex analyses to overcome limitations
- Given this, how do we prevent a study from failing?

MITIGATING FAILURES: SOLUTIONS?

- Pre-specify alternative analyses
  - Cannot address every possible failure
  - Might address common or extremely important ones
- Exploit statistical monitoring methods from RCTs
  - Group sequential methods
  - Blinded adaptations

DATA REUSE

Randomized Clinical Trials

- Focused on development program's specific needs
- Pre-specify analyses for regulatory use
- Used by a single sponsor for essentially one purpose

Real-World Evidence Studies

- Broad and rich source of data not collected for regulatory use
- Analyses not pre-specified and accumulate over time
- Used by many sponsors, as well as others

DATA REUSE

- Concerns about the reuse of databases
  - By the same sponsor for the same or similar indications
  - By different sponsors in the same or similar products
- How do we ensure that the results of RWD analyses are not influence by related analyses?

ROLE OF PUBLISHED STUDIES

Regulatory Studies

- Completed by sponsor for regulatory purposes
- FDA provides feedback throughout design and conduct
- Extensively documented

Published Studies

- Completed by a variety of people for many purposes
- FDA does not have an opportunity to comment on design and analysis
- Documentation requirements vary

ROLE OF PUBLISHED STUDIES

- Received multiple requests to label based on published studies
    - randomized pragmatic trials
    - observational studies in large databases
- What is the role of published studies if we are labeling real-world evidence?

ROLE OF PUBLISHED STUDIES

Many issues to address for an appropriate published study:

- Are the statistical methods documented in sufficient detail?
- Who can answer CBER's questions about the study?
- What access can CBER have to the study data?
- Are there limitations on the analyses that can be performed?

ROLE OF PUBLISHED STUDIES

Published studies present further unique challenges:

- Should we label all studies of similar design and quality?
- What if similar studies have conflicting results?
- What if the results from similar studies change over time?

CONCLUSIONS

- CBER is actively using RWD/RWE and participating in the **FDA** efforts

- Many issues to resolve that could be exciting areas of research


FDA
U.S. FOOD & DRUG
ADMINISTRATION