U.S. FOOD & DRUG ADMINISTRATION

Postmarketing Drug Safety and Risk Assessment Studies Using Real-World Data

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Disclaimer

- This talk reflects the views of the author and should not be construed to represent FDA's views or policies.

Background

- FDA approves effective and safe drugs when used as specified in the labeling.
- FDA may be aware of information at the time of approval, or become aware of information in a postapproval setting that necessitates further assessment.
- Under section 505(o)(3) of the FD&C Act, FDA has statutory authority to require certain postmarketing studies and clinical trials.

Purposes

- Postmarketing studies and clinical trials may be required for any or all of the following three purposes*:
  - To assess ***a known serious risk*** related to the use of the drug
  - To assess ***signals of serious risk*** related to the use of the drug
  - To identify **an *unexpected serious risk*** when available data indicate the potential for a serious risk

**See section 505(o)(3)(B) of the FD&C Act.*

Postmarketing Studies

- Clinical trials: Any prospective investigations in which the applicant or investigator determines the method of assigning the drug(s) or other interventions to one or more human subjects.
- **Studies**: All other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., **observational epidemiologic studies**), animal studies, and laboratory experiments.

**Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry*

Relevance

Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources that can inform on health status, such as mobile devices

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

General Framework (1)

Principles of (any) studies using RWD in regulatory decisions:

1. Data Fit-for-Purpose
2. Appropriate Study Design
3. Appropriate Study Conduct

which are also consistent with "*framework for FDA's real-world evidence program*".*

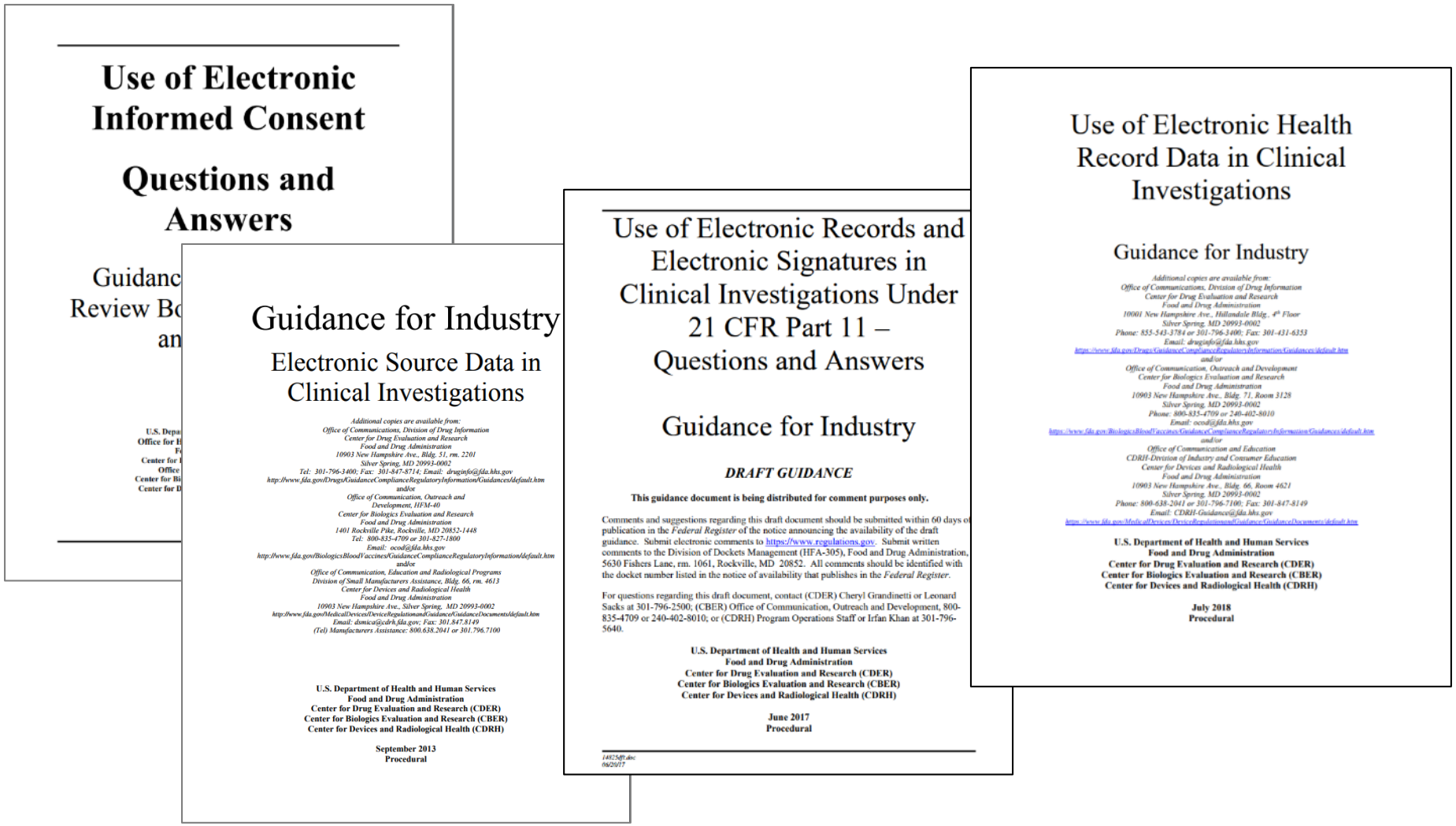
**https://www.fda.gov/media/120060/download*

RWD Fitness for Use

- Assessing data reliability and relevance*
- Reliability example:
  - Medical claims: the assessment ICD codes
  - EHR: the assessment of laboratory data
- Relevance example:
  - Exposure, outcome, and covariate ascertainment
  - Multi-sites, common data model (e.g., Sentinel): whether contains the critical data elements and whether available analytic tools are sufficient

** Framework for FDA's real-world evidence program*

Resources for Use of Electronic Source Data (1)



Use of Electronic Informed Consent

Questions and Answers

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Review Bo
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Guidance for Industry

Electronic Source Data in Clinical Investigations

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; Email: druginfo@fda.hhs.gov
http://www.fda.gov/DrugsGuidanceComplianceRegulatoryInformation/Guidances/default.htm
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Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2013
Procedural

Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Cheryl Grandinetti or Leonard Sacks at 301-796-2500; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff or Irfan Khan at 301-796-5640.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2017
Procedural

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06/20/17

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

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July 2018
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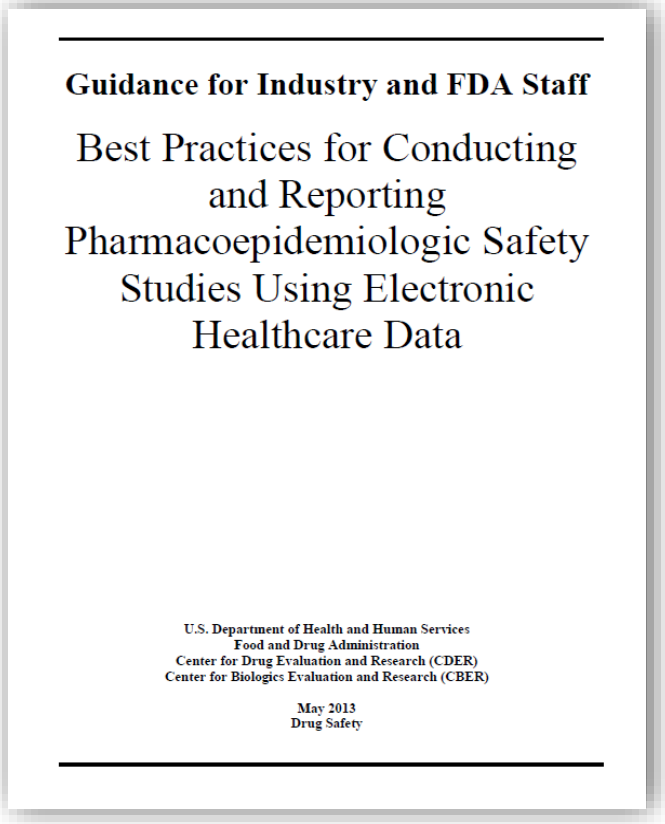
Resources for Use of Electronic Source Data (2)



Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

Real-World Data: Assessing Electronic Health Records and Medical Claims Data for Regulatory Purposes

Guidance for Industry

Forthcoming!

General Framework (2)

- Randomized clinical trial (RCT) is the gold standard → we have no choice but using RWD (unethical, practically infeasible, …)

- First thing: What we would have done if we could have designed a RCT → target trial

- Then try to emulate the target trial using RWD

Study Design

Study protocol of target trial*

1. Eligibility criteria
2. Treatment strategies
3. Randomized assignment
4. Start/end of follow-up
5. Outcomes
6. Causal contrast
7. Analysis plan

Can we replicate all of the specified components using RWD?

**Hernan and Robins. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. AJE 2016.*

Study Design: Breast Cancer Example

Study Protocol of Target Trial	
Eligibility criteria	Insulin naïve, older female patients (age≥65)
Treatment strategies	Initiate glargine or NPH.
Randomized assignment	Participants will be randomly assigned to either glargine or NPH at baseline.
Start/end of follow-up	Starts at randomization and ends at breast cancer, loss to follow-up, or end of follow up.
Outcomes	Breast cancer
Causal contrast	Intention-to-treat effect
Analysis plan	Intention-to-treat analysis

**Bradley et al. Similar Breast Cancer Risk in Women Older Than 65 Years Initiating Glargine, Detemir, and NPH Insulins. Diabetes Care 2020*

Study Design: Breast Cancer Example

Study Protocol of Target Trial		Study Protocol of Observational Study
Eligibility criteria	Insulin naïve older female patients.	Female Medicare beneficiaries aged ≥65. No study insulin prescription in the 270 days prior to the first prescription of study insulin date (index date).
Treatment strategies	Initiate glargine or NPH.	Initiate glargine or NPH.
Randomized assignment	Participants will be randomly assigned to either glargine or NPH at baseline.	Propensity score adjusted glargine or NPH groups using baseline (index date) confounding information
Start/end of follow-up	Starts at randomization and ends at breast cancer, loss to follow-up, or end of follow up.	Starts at the index date and ends at breast cancer, loss to follow-up (disenrollment, switching, death), or end of follow up (May 2017).
Outcomes	Breast cancer	Breast cancer identified via a validated algorithm using ICD-9 codes
Causal contrast	Intention-to-treat effect	Intention-to-treat effect
Analysis plan	Intention-to-treat analysis	Intention-to-treat analysis

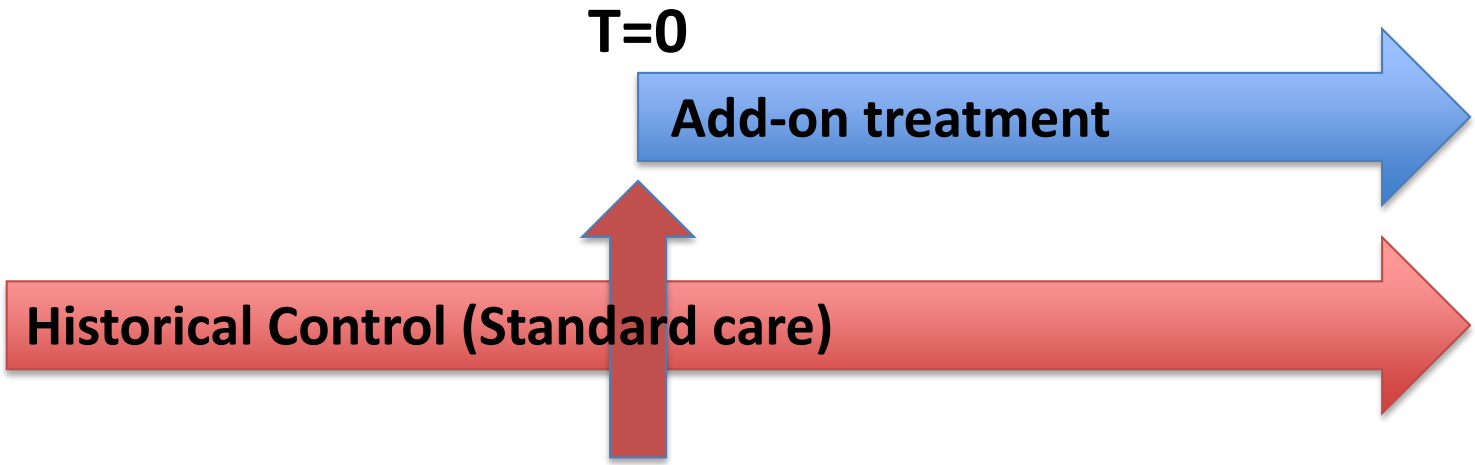
Study Design: Considerations

Study protocol of target trial

1. Eligibility criteria
2. Treatment strategies
3. Randomized assignment
4. Start/end of follow-up
5. Outcomes
6. Causal contrast
7. Analysis plan

What if we can't replicate some of these components?

Study Design: Considerations



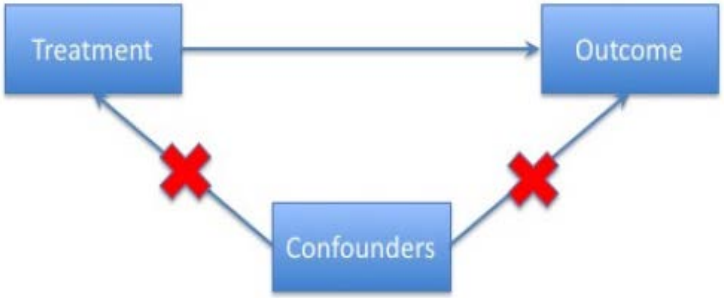
- What is T=0 (time zero) for historical control?
- What if there is no visit at T=0?
- What if patient characteristics at T=0 are different between treatment and control groups? ➔ Methodologic considerations

Methodologic Considerations

- Major challenge: Two groups (treatment vs. control) might not be comparable.
- Design and method considerations:
  1. Identification of sources of bias and confounding
  2. Methods to control for the bias and confounding
  3. Diagnostics of bias/confounding control
  4. Key limitations and interpretation of study findings

Methodologic Considerations

- Confounding can be accounted for by statistically "breaking" one or two relationships



- Propensity score methods: attempt to break (treatment-confounder) relationship
- Outcome regression-based methods: attempt to break (outcome-confounder) relationship
- Doubly-robust methods: attempt to break both

Summary

- General framework, design and methodologic considerations for postmarking observational studies using RWD.

- Every rare disease application is unique.
  - No general recommendation for design and analysis can be made. Discuss with the review division.

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Comments and Questions?

hana.lee@fda.hhs.gov