REAGAN-UDALL FOUNDATION FOR THE FDA

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry

Real-World Evidence Webinar Series

November 4, 2021
1:30-2:30 pm Eastern Time

This webinar is part of a series hosted by the Reagan-Udall Foundation for the FDA, in collaboration with the U.S. Food and Drug Administration (FDA). This series is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of $56,097 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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Welcome

Susan C. Winckler, RPh, Esq.
Reagan-Udall Foundation for the FDA

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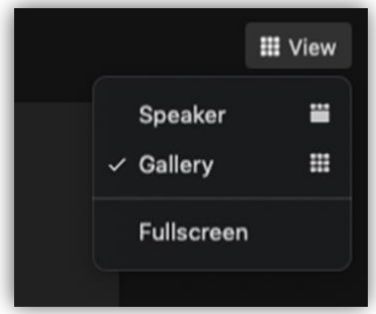
Thank you for joining

This webinar is being recorded. The slides and video recording will be available after the meeting.

If you'd like to ask a question, you may enter it in the Zoom Q&A. We will get to as many questions as time allows.

For the best viewing experience during the panel, we recommend selecting the Gallery view (in the upper right-hand corner).



Speakers and presenters cannot address questions regarding any pending regulatory action.

Submit either electronic or written comments on the draft guidance by November 29, 2021 to Docket Number FDA-2020-D-2307 ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

Agenda

1:30 pm	**Welcome**
1:35 pm	**Opening Remarks**
1:40 pm	**Overview of Draft Guidance**
2:10 pm	**Question and Answer Panel**
2:25 pm	**Closing Remarks**
2:30 pm	**Adjourn**

All times listed in Eastern Time

Why Are We Here Today?

Provide an overview of recent draft guidance and address questions from the public about the draft guidance titled *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products*

Submit either electronic or written comments on the draft guidance by November 29, 2021, to Docket Number FDA-2020-D-2307 ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

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Opening Remarks

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Public Webinar

Real-World Data: Assessing EHR/Claims Data to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry

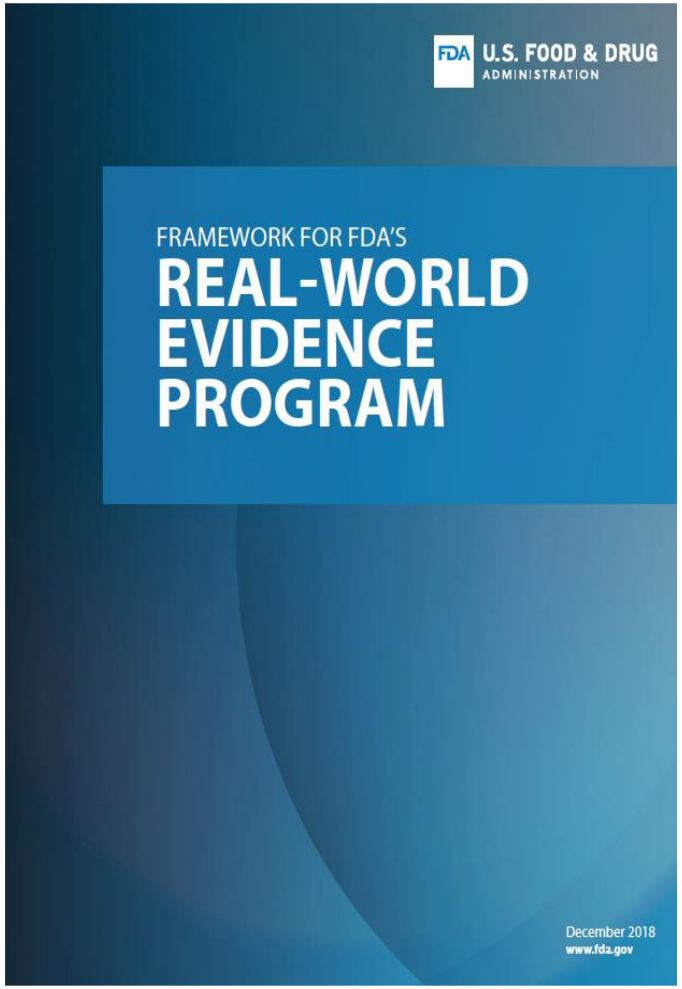
4 November 2021

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics
Office of Medical Policy, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

21st Century Cures Act of 2016 – *status as of 2021*

- **FDA *has established* a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Standard for substantial evidence *remains unchanged*; commitments under Prescription Drug User Fee Act (PDUFA) VI**
- **Draft framework *issued December 2018***
  - **Describes sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry *issued September 2021***
  - **'EHR/Claims' guidance; others in development**

FDA RWE Framework (2018)



- **Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)**
- **Multifaceted program to implement RWE:**
  - **internal processes**
  - **external stakeholder engagement**
  - **demonstration projects**
  - **guidance development** ←

CDER-CBER RWE Guidance Series

CDER Guidance Agenda
New & Revised Draft Guidance Documents
Planned for Publication in Calendar Year 2021[1]

CATEGORY – Real World Data/Real World Evidence (RWD/RWE)[2]

- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

[1] Final guidance documents planned for publication in calendar year 2021 are not included on this list. CDER is not bound by this list of topics, nor required to issue every guidance document on this list. We are not precluded from developing guidance documents on topics not on this list.

[2] New category added since the January 2021 posting

‘EHR/Claims Data’ Guidance

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

September 2021
Real World Data/Real World Evidence (RWD/RWE)

Michael Blum, MD, MPH
Deputy Director, Office of Pharmacovigilance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

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Overview of Draft Guidance

Wei Hua, MD, PhD, MHS, MS
Supervisory Associate Director in Oncology and RWE, Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

FDA Draft Guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (September 2021)

Michael D. Blum, MD, MPH
Deputy Director, Office of Pharmacovigilance and Epidemiology

Wei Hua, MD, PhD, MS, MHS
Supervisory Associate Director in Oncology and RWE,
Division of Epidemiology I

Office of Surveillance and Epidemiology, CDER

FDA Draft Guidance on *RWD: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making* (September 2021)

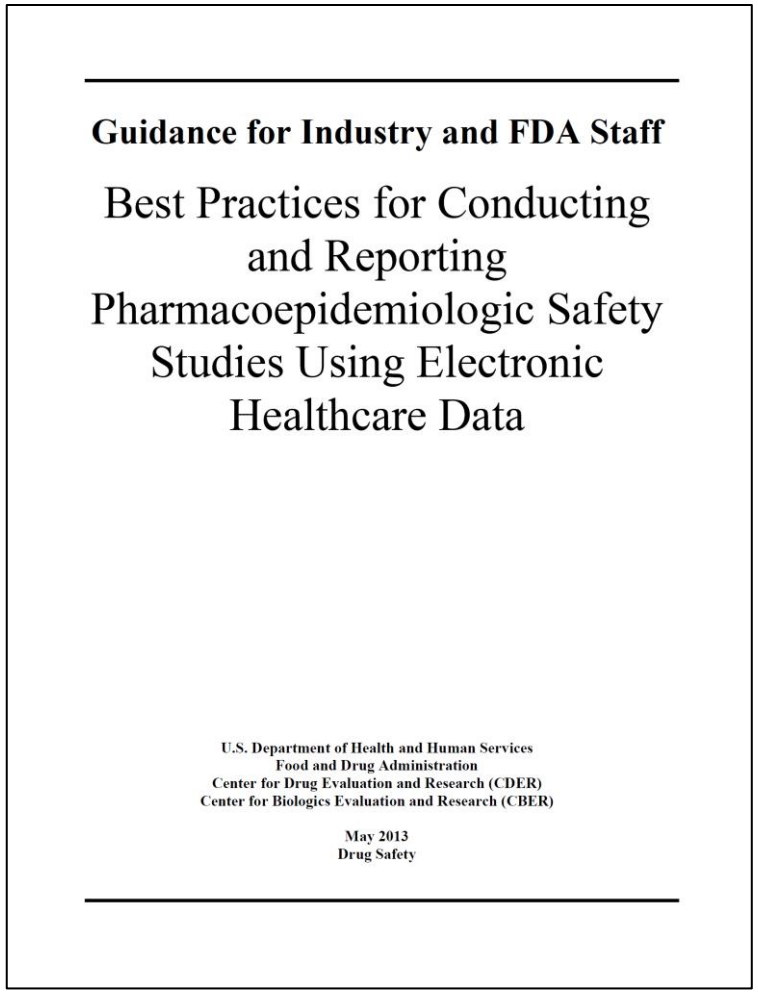
Scope of the Guidance:

- **Selection of data sources** that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key covariates
- **Development and validation of definitions** for study design elements (e.g., exposure, outcomes, covariates)
- **Data provenance and quality** during data accrual, data curation, and into the final study-specific dataset

This guidance does not provide recommendations on choice of study design or type of statistical analysis, and it does not endorse any type of data source or study methodology. For all study designs, it is important to ensure the reliability and relevance of the data used to help support a regulatory decision.

FDA Draft Guidance on *RWD: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making* (September 2021)

- Complements the May 2013 FDA Guidance on *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013)
  - Expands on certain aspects relating to the selection of data sources
  - Provides additional guidance for evaluating the relevance and reliability of both EHRs and medical claims data for use in clinical studies, including those evaluating product effectiveness


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

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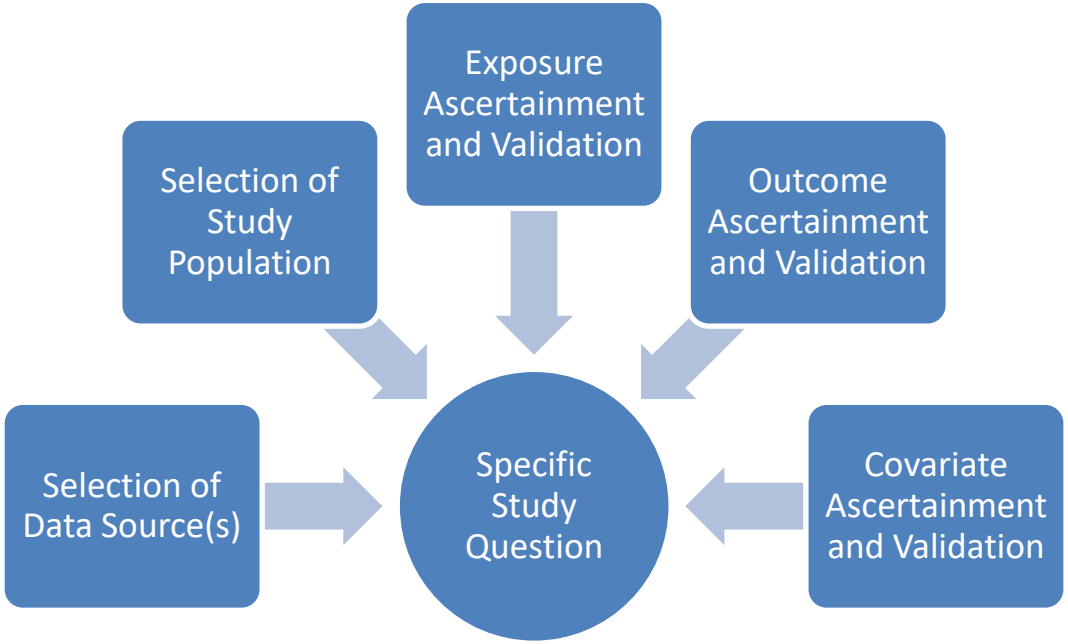
Contains Nonbinding Recommendations

Draft — Not for Implementation

September 2021
Real World Data/Real World Evidence (RWD/RWE)


Exposure Ascertainment and Validation
Selection of Study Population
Outcome Ascertainment and Validation
Selection of Data Source(s)
Specific Study Question
Covariate Ascertainment and Validation

SECTION IV. DATA SOURCES

FDA does not endorse one data source over another or seek to limit the possible sources of data that may be relevant to answering study questions

A. Relevance of the Data Source

- FDA recommends providing:
  - The reason for selecting the particular data sources to address the specific hypotheses
  - Background information about the health care system from which the data are derived
  - A description of prescribing and use practices in the health care system (if available)
  - For non-U.S. data sources, an explanation of how all of these factors might affect the generalizability of the study results to the U.S. population

B. Data Capture - General

- FDA recommends addressing:
  - Continuity of coverage (enrollment and disenrollment)
  - Comprehensiveness of the data sources in capturing aspects of care and outcomes that are relevant to the study question (e.g., settings of care, labs, nonprescription drugs)
  - How all relevant populations, exposures, outcomes, and covariates will be captured during the study period

SECTION IV. DATA SOURCES

B.2 Data Linkage and Synthesis

- Data linkages can be used to increase the breadth and depth of data on individual patients over time and provide additional data for validation purposes
- For studies that require combining data from multiple data sources or study sites, FDA recommends:
  - demonstrating whether and how data from different sources can be obtained and integrated with acceptable quality, given the potential for heterogeneity in population characteristics, clinical practices, and coding across data sources
  - considering and documenting the type of curation performed to address duplication or fragmentation issues and documenting approaches taken to address issues that cannot be fully rectified by curation

B.3 Distributed Data Networks

- Before using a Common Data Model (CDM)-driven network, data elements collected by the CDM should be considered to determine suitability for the study and whether identified deficiencies can be addressed by supplementing with customized study-specific data elements, collecting additional data, or using other data elements present in the dataset that are reasonable proxies for the missing information

SECTION VI. DATA QUALITY DURING DATA ACCRUAL, CURATION, AND TRANSFORMATION INTO THE FINAL STUDY-SPECIFIC DATASET

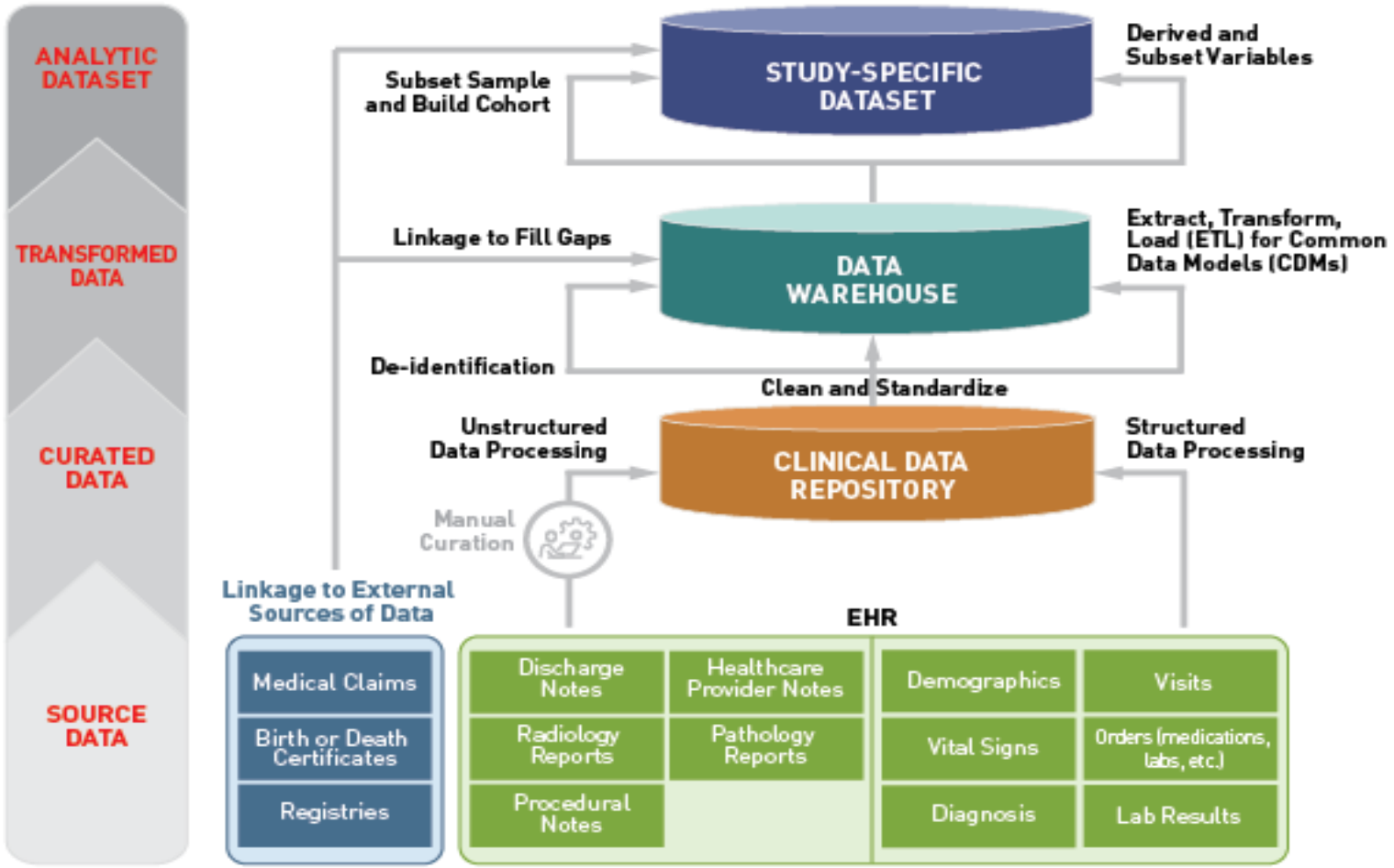


Figure 1: Illustrative Example of the Life Cycle of EHR Data

SECTION V. STUDY DESIGN ELEMENTS

Key Messages

- The study questions of interest should be established first, and then the data source and study design most appropriate for addressing these questions should be determined.
- The study should not be designed to fit a specific data source, because the limitations of a specific data source may restrict the options for study design and limit the inferences that can be drawn.
- For all studies using EHR or claims data that will be submitted to FDA to support a regulatory decision, sponsors should submit protocols and statistical analysis plans before conducting the study.
- All essential elements of study design, analysis, conduct, and reporting should be predefined.
- For each study element, the protocol and final study report should describe how the element was ascertained from the selected RWD source, including applicable validation studies.

Key Study Design Elements

Conceptual and Operational Definitions

	Concepts

Conceptual definition	• Intended to minimize the effect of variability in practice by different physicians and over time
	• Current medical and scientific thinking regarding the variable of interest, such as:
	  ○ clinical criteria to define a condition for population selection or as an outcome of interest or a covariate, or
	  ○ measurement of drug intake to define an exposure of interest
	• Might vary by study

Operational definition	• Developed based on the conceptual definition to extract the most complete and accurate data from the data source, such as:
	  ○ code-based electronic algorithm using structured data elements,
	  ○ derived from extracting relevant information from unstructured data or constructing an algorithm that combines structured and unstructured data elements, or
	  ○ through additional data collection, e.g., patient survey

Ascertainment: General Considerations

- Operational definition using diagnosis and procedure codes, laboratory tests and values, or unstructured data, should be developed based on the conceptual definition

- Consider the impact on misclassification when selecting coding system and information to construct the operational definition

- Performance (e.g., positive predictive value) of an operational definition may vary substantially by data source and study scenario, and over time. If the performance has been assessed in prior studies, the applicability to the proposed study should be justified

Validation: General Considerations

- Because operational definitions are usually imperfect, a resulting misclassification can lead to false positives and false negatives and may bias the association between exposure and outcome

- Understanding the implications of potential misclassification for study internal validity and study inference is the key step in determining what variables might require validation and to what extent
  - Whereas internal validity should always be optimized, some misclassification might be tolerable depending on the study question and regulatory purpose (e.g., quantifying drug effect for effectiveness or safety versus signal detection)

- FDA recommends using standardized validation processes (e.g., standardized tools, documentation, training); this approach is critical for minimizing intra- and inter-rater variability, especially for multi-site studies

Extent of Validation

Complete Verification

- Complete verification of a study variable for every study subject is considered the most rigorous approach
- Through complete verification of each subject (both positive and negative subjects), the adjudicated subjects are assigned an accurate value of the variable to minimize misclassification and improve study internal validity

Extent of Validation

Assessing Performance of Operational Definition

- Although sensitivity, specificity, and predictive values reflect performance, they don’t ensure accurate classification of cases and non-cases; rather, these measures inform the degree of misclassification and facilitate interpretation of results in the presence of misclassification
- Based on the concern of false positives and false negatives, consider whether validating the variable to a greater extent (e.g., all positives or all negatives) is necessary

Considerations of Operational Definitions

- Assess the performance of the variable's operational definition in an adequately large sample of the study population as part of the proposed study

- When proposing to use an operational definition that has been assessed in a prior study:
  - Ideally select those assessed in the same data source and in a similar study population
  - Secular trends in disease, diagnosis, and coding may necessitate assessment using more recent data
  - The quality of prior studies to establish sensitivity, specificity, and predictive values should always be evaluated

How to Determine the Extent of Validation?

- Overall, the extent of validation should be determined by the necessary level of certainty and the implication of potential misclassification on study inference

- Discuss the attributes of a particular study with the relevant review division (case-by-case basis)

Considerations for Misclassification

- Trade-off between false-positive and false-negative cases when selecting an operational definition
- Extent of false-positive cases and false-negative cases when determining if an operational definition with high positive predictive value might be adequate
- Complex interplay of differences in sensitivity, specificity, and disease prevalence between the exposure groups when evaluating the degree and direction of bias

Considerations for Misclassification

- Differential outcome misclassification might be minimized in studies in which the exposure status is blinded. However, even when data collection methods seem to preclude the likelihood of differential misclassification, non-differential misclassification is not guaranteed in the actual data of a particular study, therefore, the direction of bias might remain unpredictable
- When more than one misclassification exists in a study, consider how they might be related to each other
- FDA recommends consideration of quantitative bias analysis to demonstrate whether and how potential bias might affect study results

Considerations for Time-Related Data

- Clear definition of various time periods pertinent to the study design
- Time scale (e.g., calendar time, time since exposure) with adequate detail on data availability of the time unit (e.g., month, day, hour)
- Justification of proposed time periods and the potential impact on study validity, for example:
  - Appropriateness of time period before exposure to capture study variables
  - Potential temporal changes in the standard of care, the availability of other treatments, diagnosis criteria, and other relevant factors
  - Timing of disease onset (e.g., early symptoms) versus a confirmed diagnosis
  - Biologically plausible time frame when the outcome, if associated with the exposure, might be expected to occur

Additional Comments and Conclusions

- In general, data should be sufficiently accurate and complete to address the regulatory question. This guidance focuses on EHR and claims data, including considerations for potential biases that are directly related to the accuracy and completeness of study design elements.

- To facilitate FDA review, the protocol should provide a detailed description and justification of the selection of data source(s) and ascertainment and validation of study design elements. Discussion with the relevant FDA review division early in the application process is strongly encouraged.

- This guidance is about data considerations; data alone are not evidence. Relevant and reliable data must be used in conjunction with appropriate study design and analysis.

Acknowledgments

FDA Center for Drug Evaluation and Research

- Office of Medical Policy
- Office of New Drugs
- Office of Regulatory Policy
- Office of Strategic Programs
- Office of Surveillance and Epidemiology
- Office of Translational Science

FDA Center for Biologics Evaluation and Research

FDA Oncology Center of Excellence

FDA Center for Devices and Radiological Health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Question and Answer

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Moderated by

Susan C. Winckler, RPh, Esq.

Panelists

John Concato, MD, MS, MPH

Michael Blum, MD, MPH

Wei Hua, MD, PhD, MHS, MS

Natasha Pratt, PhD

Next Steps

- Submit either electronic or written comments on the draft guidance by November 29, 2021 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance
- Docket No. FDA-2020-D-2307

Next Steps

- Please join us for the second in our webinar series on FDA-issued draft guidance on Real-World Evidence. Friday, December 3 at 1:00 pm, when we'll be discussing Data Standards for Drug and Biological Product Submissions Containing Real World Data.
- Docket No. FDA-2021-D-0548
- Registration for that event is now open on the FDA Foundation website, www.reaganudall.org

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Thank you!