ISCTM | 22nd Annual Scientific meeting

Session 1: Methodological Opportunities and Challenges with Long-term Post-marketing Data

Regulatory Perspective

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Disclaimer

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

Examples of Source(s) of Safety Concern

- Biological plausibility, theoretical concern
- Animal data
- Clinical trials
- Pharmacovigilance, spontaneous reports, e.g., FDA Adverse Event Reporting System (FAERS)
- Medical literature
- Similar drugs on the market
- Others

Types of Epidemiologic Studies

- Experimental studies (interventional studies), e.g., clinical trials
- Observational studies (non-interventional)
  - Study design
    - Cohort design, case-control design, self-controlled designs
  - Data sources
    - Electronic healthcare data, e.g., electronic health records (EHRs), administrative claims data
    - Lab, radiology, biobank, vital statistics (e.g., birth registries, death registries)
    - Primary data collection, e.g., drug registries, disease registries, surveys and interviews
    - Others, e.g., social media

General Approaches for Postmarket Safety Assessment

- Routine pharmacovigilance*
  - Spontaneous reports, case reports or case series from medical literature, etc.

- Non-interventional (observational) studies
  - Registry-based studies
    - Prospective cohort studies with primary data collection
    - Could be supplemented by EHR or other data sources
  - Healthcare database studies
    - Electronic healthcare data, such as EHR and claims data
    - Could be supplemented by linkage to other data sources and primary data collection

*Draft Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff
Available at: https://www.fda.gov/media/130216/download

Non-interventional Studies – Key Considerations

- Predefined study question
- Required level of evidence based on regulatory objective of study
- Fit-for-use data
  - Data relevance and reliability
- Appropriate study design and methods
  - Study period, population, inclusion/exclusion criteria, exposure/comparator, outcome, covariates, follow-up, analysis, bias and confounding (impact on study results and how to mitigate)

Study Question

Consider: what is the fundamental concept to measure?

- Does data allow for direct measure of the concept?
- If not, can the concept be measured indirectly (e.g., surrogate endpoint)?
- Does the indirect measure of concept change the study question?

Regulatory Objective of Study

Determines the required level of certainty

When high level of certainty is typically required:

- ❑ To evaluate effectiveness for a new indication of an approved drug.
- ❑ To evaluate a comparative safety claim.
- ❑ To quantify a known risk with substantial existing information.

When less stringent requirement may be allowed:

- ❑ To improve current knowledge on safety when little is known.

Using Real-World Data To Generate Evidence – General Principles

- In general, data should be sufficiently accurate and complete to address the regulatory question
- Data alone are not evidence. Relevant and reliable data must be used in conjunction with appropriate study design and analysis
- The study question of interest should be established first, and then the data source and study design most appropriate for addressing the question 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
- 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 real-world data source, including applicable validation studies

Importance of Understanding Mechanism of Action in Causal Inference Assessment

- Mechanism determines the biological time scale of causation, which drives nearly every major study design decision. Understanding the mechanism helps ensure that study design reflects underlying biology rather than statistical association alone.

For example:

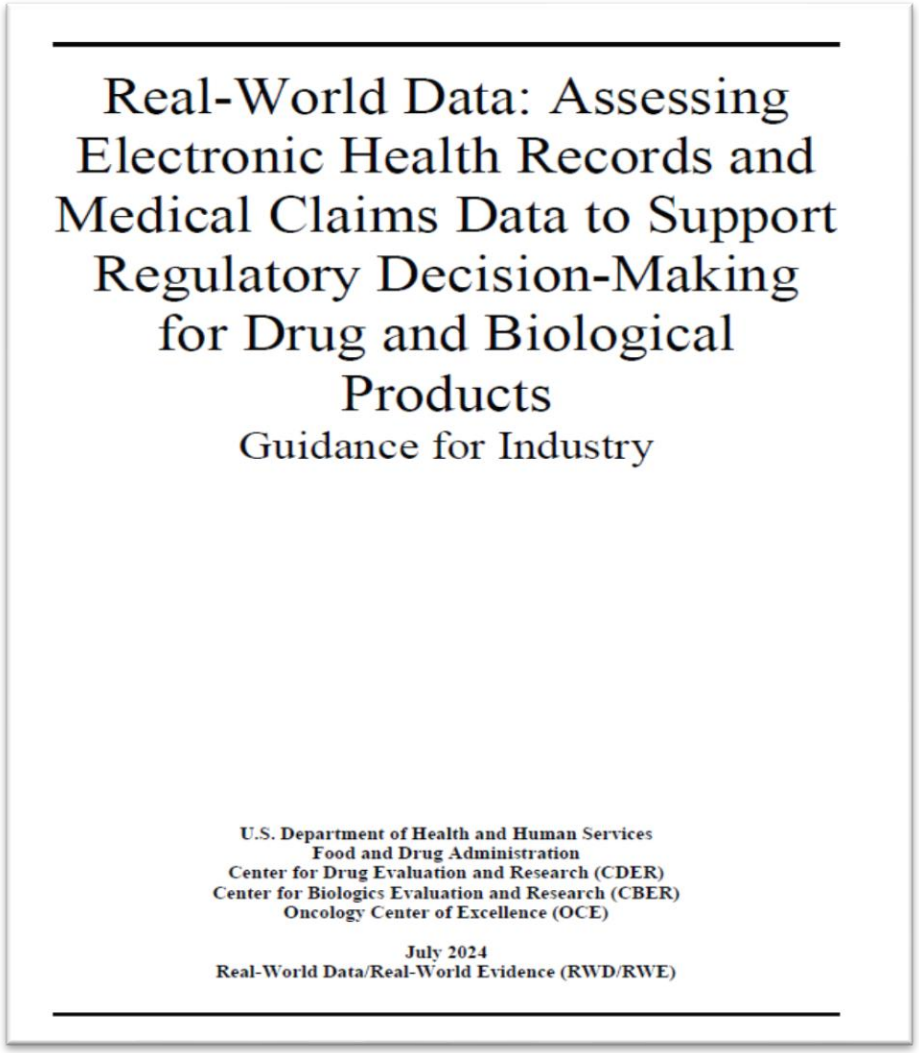
- For outcomes with progressive biological change, consider cumulative exposure/dose in exposure definition; “current use yes/no” only may be inadequate
- Consider induction time, carryover effect, and latency time in follow-up specification (e.g., time 0, lagging strategy, length of follow-up)
- Consider factors that drive confounding in the context of exposure-outcome relationship (e.g., treatment indication, disease severity, comorbidities)

Examples of Current Guidelines That Provide General Principles for Data Source Selection, Study Design, and Reporting

- FDA Guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making (July 2024)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory
- International Council for Harmonisation (ICH) Harmonized Guideline (M14): General Principles on Planning, Designing, Analyzing, and Reporting of Non-Interventional Studies (Sep 2025) https://database.ich.org/sites/default/files/ICH_M14_Step4_Final_Guideline_2025_0905.pdf
- HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE-ISPOR Task Force (June 2022) https://pubmed.ncbi.nlm.nih.gov/36215113/

ISPE: The International Society for Pharmacoepidemiology
ISPOR: The Professional Society for Health Economics and Outcomes Research

FDA Guidance on Real-World Data (July 2024)



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

Guidance for Industry

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)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

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FDA RWD Guidance (July 2024): Key Concepts to Highlight

- Data relevance and reliability
- Study design elements: Definition, ascertainment, and validation
  - Distinguish conceptual and operational definitions

Conceptual	Current medical and scientific thinking regarding the variable of interest; Intended to minimize the effect of variability in practice by different physicians and over time
Operational	Developed based on the conceptual definition to extract the most complete and accurate data from the data source, such as code-based data, lab/imaging, physician's notes, patient survey

  - Consider the complexity and impact of misclassification
  - How to determine the extent of validation
- Data quality

ICH M14: General Principles on Planning, Designing, Analyzing, and Reporting of Non-Interventional Studies (Sep 2025)

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

General Principles on Planning, Designing, Analysing, and Reporting of Non-interventional Studies That Utilise Real-World Data for Safety Assessment of Medicines

M14

Final Version

Adopted on 04 September 2025

ICH M14 Outlines High-level Best Practice for Non-Interventional Pharmacoepidemiology Studies

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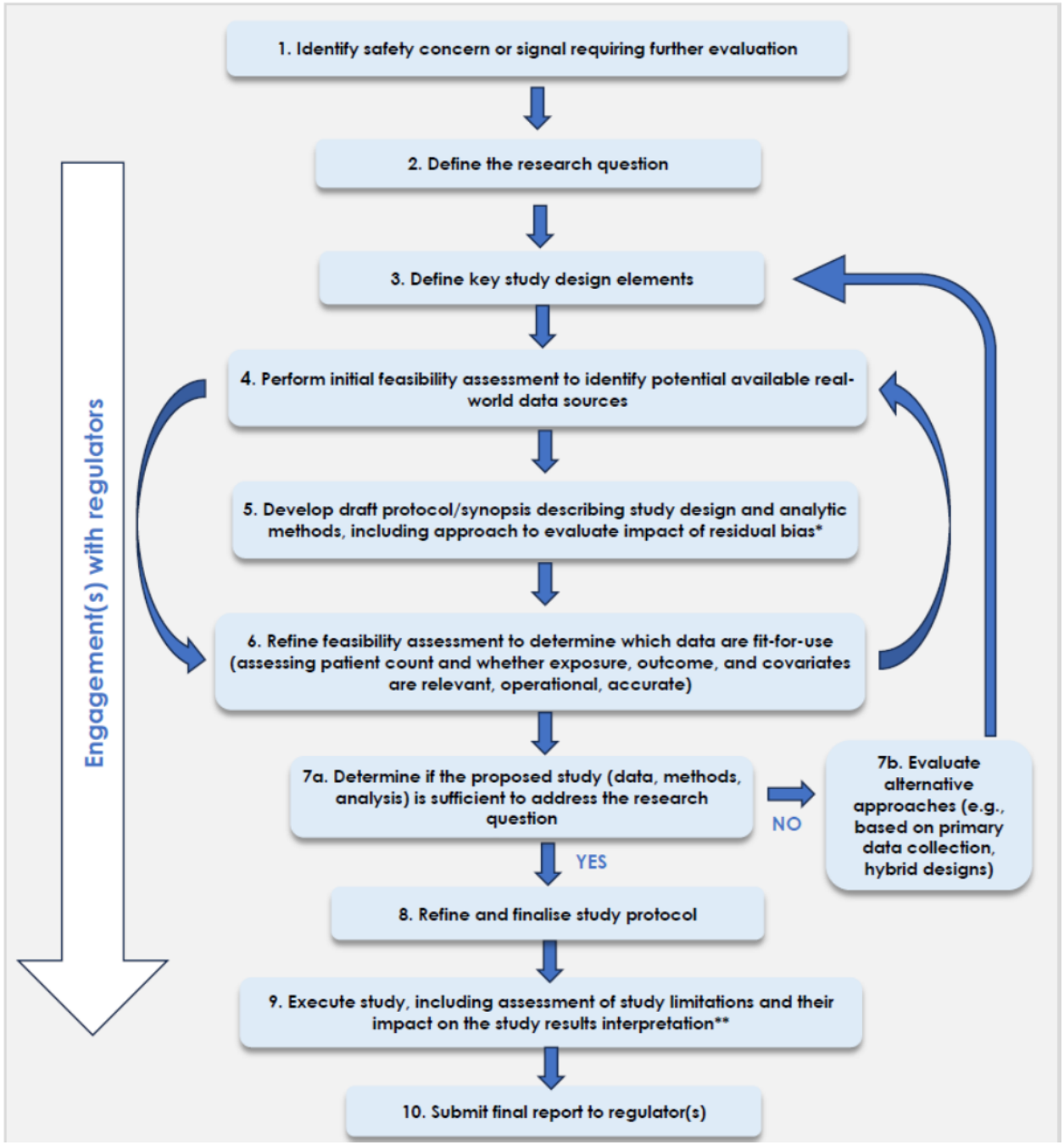
ICH M14: Conceptual Framework for generating adequate evidence using real-world data



- Define research question
- Integrated, iterative assessment of three components
  - Data fitness-for-purpose
  - Appropriateness of study design and methods
  - Robust qualitative/quantitative assessment of study limitations and their impact on study validity and interpretation of findings
- All three components considered jointly can enable a decision on whether the proposed study, if executed according to the protocol, can generate adequate evidence to address research question

ICH M14: Objectives and Expected Benefits

- Provide recommendations and high-level best practices for the conduct of non-interventional studies, to streamline the development and regulatory assessment of study protocols and reports

Therefore,

- Improve efficiency and transparency in study development, reporting, submission, and review, and resultant regulatory actions
- Improve the ability of the study protocol and report to be accepted across regulatory authorities

❖ The principles presented in this guideline may apply to both safety and effectiveness studies when real-world data are included.

ISPE/ISPOR Joint Task Force: HARPER

HARPER: A standard protocol template with embedded instructions which harmonized across existing guidance and templates

Received: 7 February 2022 | Revised: 17 June 2022 | Accepted: 28 June 2022
DOI: 10.1002/pds.5507

ORIGINAL ARTICLE

WILEY

HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force

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HARPER: Aiming for Transparency and Efficiency

- Help researchers thoroughly consider, then document their decisions and rationale regarding key study parameters that define causal question
- Facilitate decision-making by enabling reviewers to readily assess potential for biases related to the researcher's choices and rationale
- Facilitate reproducibility of results

Takeaway Messages

- Methodological challenges vary by study question of interest
- FDA does not endorse any type of data source or study methodology
- Researchers should identify the data-design combination best suited to address the study question
- To facilitate FDA review, the protocol should provide a detailed description and justification of study design and data source(s)
- Discussion with the relevant FDA review division early in the application process is strongly encouraged (case-by-case)


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