ICH
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ICH M14 General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines

Step 2

Step 2 document – to be released for comments

21 May 2024

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

2

Background

- **This document has been signed off as a *Step 2* document (21 May 2024) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (endorsed 5 April 2022) and a Business Plan (endorsed 5 April 2022)**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: May 2025**

Key Principles

- **This guideline provides recommendations on the plan, design and analysis of observational (non-interventional) pharmacoepidemiological studies that utilize fit-for-purpose data for safety assessment of medicines (drugs, vaccines, and other biological products)**
- **Outlines an iterative approach to develop high-quality evidence regarding the safety of a medicine that is able to address the regulatory question (acknowledging data and study limitations) and is suitable for submission**
- **Generation of robust evidence to be used for regulatory purposes relies on the reliability and relevance of the data and the application of sound pharmacoepidemiological methods**

Guideline Objectives

- **Many regions have published guidelines on the regulatory use of pharmacoepidemiological studies utilizing real-world data (RWD), but a lack of harmonisation in this area can cause challenges for sponsors and regulators**
- **Development of this guideline will promote harmonisation in the design and use of these studies, minimize the need to conduct multiple studies on the same safety concern for submission to multiple regulators, result in improved efficiency and transparency in the development, submission and review of pharmacoepidemiological studies and resultant regulatory actions**
- **Provides recommendations and high-level best practices for the conduct of these studies, with a goal of streamlining the development and regulatory assessment of study protocols and reports**

Table of Contents

Introduction

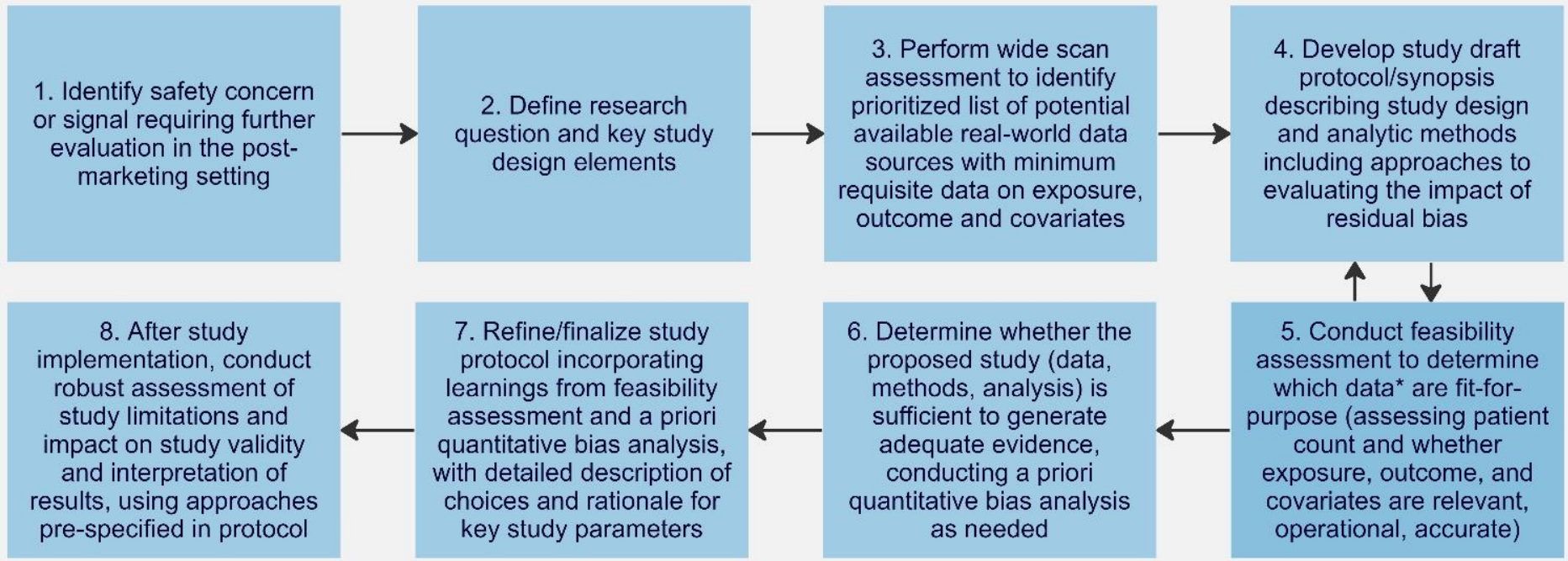
- **Provides general principles on the plan, design and analysis of pharmacoepidemiological studies that utilize fit-for-purpose data for safety assessment of medicines**
- **Outlines best practices for these studies at a high-level**
- **Aims to help streamline the sponsor development and regulatory assessment of study protocols and reports, and to increase transportability across regulators**
- **Seeks to improve the ability of the study protocol and/or results to be accepted across health authorities and support regulatory decision-making**
- **The following are considered out of scope**
  - Whether a clinical trial or a pharmacoepidemiological study is the most appropriate approach
  - Pharmacovigilance using spontaneous reports
  - Studies involving treatment assignment
  - Studies collecting and analyzing patient experience data

GENERAL PRINCIPLES

- **The guideline describes a stepwise iterative process that includes the following**
  - Clearly defining a research question that concisely summarizes the study purpose and hypotheses to be tested
  - Defining the population, exposure, outcome and required covariates
  - Identifying minimal data requirements, conducting feasibility assessments, assessing representativeness of the intended study population, consideration of sources of bias and confounding
  - Selecting an appropriate data source
  - Developing and refining the study protocol
  - Conducting the study, reporting and communicating the results, and documenting of all relevant study materials

FRAMEWORK FOR GENERATING ADEQUATE EVIDENCE USING REAL-WORLD DATA

The Guideline presents an overall framework for generating adequate evidence using fit-for-purpose real-world data to address regulatory questions on the safety of medicines, summarized in this diagram



*Single or in combination using EHR/claims data, primary data collection, or other types of RWD

INITIAL DESIGN AND FEASIBILITY

- **Studies are initiated by development of a concise statement of the study purpose and the prespecified hypotheses to be tested**
- **This research question frames the basic requirements of the study and the unknowns that will need to be addressed by feasibility assessments**
- **Feasibility assessments are used to systematically identify fit-for-purpose data and to obtain information on the statistical precision of a potential study**
  - Initial scans determine data availability, sufficiency, and to narrow the number of options. These consider whether the appropriate population are likely to be captured with adequate follow-up, in sufficient numbers, and with the needed data characteristics
  - Detailed assessments inform final database selection by demonstrating that the key data needed are available, adequately complete, with sufficient evidence of validity
  - If appropriate secondary data are not available, primary data collection may be considered
- **Feasibility assessments inform further design decisions, in an iterative process**
- **Final approach should comply with applicable regulatory requirements, and the selection of the chosen database(s) justified**

Protocol Development

- **Protocol development is undertaken by a multidisciplinary study team with the appropriate expertise. Basic steps in protocol development include**
  - Selection of a study design (e.g. cohort, case control)
  - Identifying the appropriate comparator population
  - Final selection of an appropriate data source
  - Defining a study population representative of the target population
  - Defining conceptual definitions for exposures, outcomes and covariates and then translating this to an operational definition that extracts the most complete and accurate data
  - Consideration of potential sources of study bias.
  - Development of approaches to adequately address or control for bias, with a plan for analyses to evaluate whether the chosen approaches were successful. The guideline provides an overview of common biases
  - Validation of operational definitions using applicable literature or through conduct of a separate study

Data Management

- **Approaches for data management and data quality depend on the data sources and the planned use of the study results**
- **Plans for data management, curation, quality assurance, and quality control should be developed prior to study initiation**
  - Management plans establish processes, policies, and procedures to account for potential risks to data quality and to obtain, verify, promote and document the integrity of the analytic dataset
  - Data holders are responsible for processes that ensure underlying data quality
  - Researchers* align with data holders to ensure transparency, understanding of data strengths/limitations, and meeting the standards of quality criteria required by the regulatory authorities. Further, the researcher is responsible for the management and quality assurance of all data cleaning, processing, and analytic datasets

*Those responsible for designing and executing the study such as a regulatory agency, sponsor, contract research organization, academic group, or others

Analysis

- **The analytic strategy includes descriptive and inferential analyses to address the study objectives**
  - Should be prespecified and reflect the information gained from feasibility assessments
  - Should account for and include an empirical evaluation of unmeasured or mismeasured confounding and other sources of bias
  - Distinguish between pre-specified data-driven analyses and those that are post-hoc
- **The analysis plan should describe and provide justification for the chosen statistical approaches, including the assumptions and conditions**
- **The following may be considered for inclusion**
  - Descriptive analyses, subgroup analyses, methods of estimation and associated assumptions, estimate of study size/power/statistical precision, plans to control for confounding and bias, assessment of population comparability, sensitivity analyses, type I error control, assessment of representativeness and plans for handling missing data.
  - Sensitivity analysis plans with a rationale for each analysis and the strengths and limitations
  - Prespecify plans for quantitative bias analysis used to facilitate interpretation of study results

Reporting and Submission

- **Adverse events, drug reactions, and product quality complaints may require reporting to relevant regulatory authorities and requirements may vary by region. Researchers are referred to ICH E2D applicable laws, regulations and pharmacovigilance guidelines**
- **Sponsors should discuss with regulators the required study documents and timetables for submission**
- **In the absence of specific formatting and content required by regulators, sponsors may utilize frameworks developed by the scientific community as a guide for document development, such as ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER)**

Communication of Study Protocol, Materials and Findings

- **Researchers are encouraged to make study materials publicly available**
  - Anticipated benefits include increased transparency, scientific exchange, and increased ability to reproduce the research
  - The protocol and statistical analysis plan may be made available in appropriate public registers before study initiation, and study reports upon completion
  - Research publications should be consistent with the report submitted to regulators
  - To avoid publication bias, it is recommended that the results be published even if negative or inconclusive study results are obtained
- **Results of the research should be communicated to the study participants as appropriate (for example, when primary data collection is used), the public, and patients, so that they may be aware of and understand the study results and their implications**
- **Communications to participants should include a factual summary of the overall study results in an objective, balanced and nonpromotional manner, including relevant safety information and any limitations of the study**

Study Documentation and Record Retention

- **Key documents and records related to the planning, conduct and results of a study should be kept in compliance with applicable standards and jurisdictional requirements**
- **Key principles for studies utilizing RWD in post-marketing safety studies are similar to those for ICH E6(R2) Good Clinical Practice (especially for primary data) and the International Society for Pharmacoepidemiology's Good Pharmacoepidemiological Practice (especially for secondary use of data)**

Considerations in Specific Populations

- **Specific (special) populations are often not enrolled in pre-approval clinical studies and include pregnant and lactating people, infants, children, adolescents/young adults, older adults, immunocompromised patients, and people with disabilities and/or rare disorders**
  - Studies in these populations may require unique considerations when defining the study population
- **The guideline includes considerations for pregnancy studies**
  - Among the unique considerations in these studies are the identification of pregnancies, the complexity of outcomes, and need for validated algorithms to identify gestational age or date of conception, and maternal and infant outcomes, and varying risks by trimester

Considerations

- **This guideline is not intended to be a comprehensive resource for pharmacoepidemiological methods. Researchers are referred to other resources (for example, the** ENCePP Guide on Methodological Standards in Pharmacoepidemiology)
- **This guideline references other ICH guidelines for guidance on other essential aspects of pharmacoepidemiological safety studies**
  - ICH E2D Post-Approval Safety Data Management
  - ICH E8(R1) General Considerations for Clinical Studies
  - ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the guideline on statistical principles for clinical trials
  - ICH E6(R2) Guideline for Good Clinical Practice

Conclusions

- **This harmonized guideline provides high level guidance on pharmacoepidemiological safety studies conducted for regulatory purposes with a goal of increasing quality, transportability and to streamline development, and regulatory assessment**
- **It is beyond the scope of this guideline to provide guidance on whether an interventional or pharmacoepidemiological (non-interventional) study is most appropriate**
- **This guideline is not intended as a comprehensive methods resource. Refer to other guidelines and other resources when considering appropriate study methods**

Contact

- **For any questions please contact the ICH Secretariat:**

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