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A Selective Approach to Safety Data Collection in Specific Late-stage Pre-approval or Post-approval Clinical Trials E19

Step 4 document – to be implemented

12 October 2022

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

Legal Notice

2

Background

- **This document has been signed off as *Step 4* document (27 September 2022) to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper (12 July 2017) and Business Plan (12 July 2017)**

Key Principles

- **Selective safety data collection refers to the reduced collection of certain types of data in specific late-stage clinical trials that may be pre-approval or post-approval**
- **When appropriately justified, selective safety data collection in certain clinical trials can facilitate the conduct of large-scale efficacy and safety trials to answer important scientific questions about a drug without compromise to patient care or safety**
- **Implementing selective safety data collection in a clinical trial requires early consultation with regulatory authorities and careful planning of the trial design and methods for data collection and analyses**

Guideline Objectives 1/2

- **Scope: The Guideline applies to collection of safety data from interventional clinical trials primarily in post-approval settings and in certain pre-approval settings.**
- **Out of Scope: This Guideline is not applicable to gene therapy or rare/orphan disease clinical trials.**
- **Objectives:**
  - **This Guideline describes factors that can justify selective safety data collection while ensuring that patient care and safety are not compromised**
  - **This Guideline describes types of data that may be appropriate for selective safety data collection and data that should generally be collected to ensure patient safety**

Guideline Objectives 2/2

- **Objectives (continued):**
  - **This Guideline provides some examples of how selective safety data collection can be implemented in a drug development program**
  - **This Guideline describes practical considerations in the design and conduct of clinical trials implementing selective safety data collection and complexities for data analyses of such trials**
- **When appropriately justified and adequately designed, certain clinical trials utilising selective safety data collection approved by multiple regulatory authorities may facilitate the conduct of large clinical efficacy and safety trials to answer important scientific questions. Selective collection of safety data following the principles of this Guideline does not alter local/regional safety reporting requirements**

Table of Contents

Table of Contents (2)

Summary of Guideline Content (1/13)

Section 1. Introduction

- Defines what selective safety data collection is
- Limits application of guideline primarily to interventional post-approval trials and in certain circumstances, pre-approval trials
- Emphasises the importance of having a robust safety database to ensure that the safety profile of a drug is well-characterised before considering selective safety data collection

Summary of Guideline Content (2/13)

Section 2. General Principles

Subsection 2.1 Emphasises that ensuring safety of trial participants is paramount. Selective safety data collection does not affect:

- the responsibilities of investigators and health care professionals to monitor trial participants and provide appropriate standards of care
- the reporting obligations of health care professionals, such as safety reporting in accordance with local/regional requirements, should be followed
- the documentation of adverse events by health care professionals in the patient's medical records

Summary of Guideline Content (3/13)

Section 2. General Principles (continued)

Subsection 2.2 describes the factors that can contribute to the conclusion that the safety profile of a drug is sufficiently characterised to justify selective safety data collection. The list is not exhaustive and the absence or presence of any of the factors is not determinative; however, the greater the number of applicable factors, the stronger support for selective safety data collection

Summary of Guideline Content (4/13)

General Principles Subsection 2.2 continued

Contributing factors include:

- **The drug has gained marketing authorisation by any regulatory agency**
- **A thorough understanding of the drug's mechanism of action, including off-target effects**
- **The existence of an extensive clinical safety database**
- **Similarity of the proposed trial and study population to prior trials**
- **A thorough understanding of the drug's clinical pharmacology**
- **A thorough understanding of the non-clinical data**
- **Presence of extensive high quality post-approval safety data**

Summary of Guideline Content (5/13)

Section 2. General Principles (continued)

Subsection 2.3 emphasises that approaches for collection of baseline data are not impacted by adopting a selective safety data approach because baseline data are essential to ensure enrolled trial participants meet study eligibility criteria and to enable assessment of efficacy and safety by baseline patient characteristics

Summary of Guideline Content (6/13)

Section 2. General Principles (continued)

Subsection 2.4 lists data elements that should generally be collected to ensure adequate safety evaluation in a trial

- Serious adverse events (see ICH E2A; ICH E6)
- Important medical events (see ICH E2A)
- Medication error/overdose (intentional or unintentional)
- Adverse event that led to study drug discontinuation
- Pregnancy and lactation exposure and outcomes
- Adverse events of special interest, including laboratory abnormalities, identified in the protocol as critical to safety evaluations (see ICH E6; ICH E2F: Development Safety Update Report; CIOMS VI).

Summary of Guideline Content (7/13)

Section 2. General Principles (continued)

Subsection 2.5 lists data that may be appropriate for selective collection (i.e., not collected or reduced frequency of collection)

- **Non-serious adverse events**
- **Various types of laboratory monitoring (e.g., serum chemistries, haematology) electrocardiograms, and imaging trials**
- **Physical examinations and vital sign data**
- **Once concomitant medication use is documented at baseline, changes in concomitant therapies (e.g., changes in dose, added therapies, discontinuation of therapies) may not need to be collected.**

Summary of Guideline Content (8/13)

Section 2. General Principles (continued)

Subsection 2.6 acknowledges that the contribution of non-serious adverse events (AEs) to the benefit-risk profile of a drug may differ depending on the indication and patients enrolled such that selective safety data collection may not be applicable in some trials even if the safety of the drug is sufficiently characterised in other settings.

Subsection 2.7 emphasises importance of early consultation with regulatory authorities. Multiple regional trials implementing selective safety data collection should consider ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials

Summary of Guideline Content (9/13)

Section 2. General Principles (continued)

Subsection 2.8 provides examples of where selective safety data collection can be considered for a drug with a well-characterised safety profile

- Clinical trial to support use in a new population with an approved drug where the new population is similar to or was well-represented in the prior trial(s) supporting approval
- Clinical trial to expand the labeled indication of an approved drug with additional endpoints in the same population
- Clinical trial with objective to evaluate a specific safety parameter
- Clinical trial designed to provide additional evidence of efficacy

Summary of Guideline Content (10/13)

Section 3. Implementation of Selective Safety Data Collection

This section provides examples of how selective safety data collection can be implemented including:

- **Selective safety data collection in all patients in the trial**
- **Comprehensive safety data collection for a specific subset of patients in the trial population and selective safety data collection in the rest of the trial population**
- **Comprehensive safety data collection for the initial period of the trial with selective data collection thereafter**
- **Comprehensive safety data collection from randomly selected sites or patients across all sites; selective safety data collection in remaining sites or patients**

Summary of Guideline Content (11/13)

Section 4. Practical Considerations for Selective Safety Data Collection

- This section discusses the importance of planning and discussion with regulatory authorities in advance of study implementation to gain agreement on study design and protocol
- Efficiency of trial conduct may also have disadvantages (e.g., data never collected can present challenges if unexpected findings emerge during trial conduct).
- Complexities in data analyses, presentation, and summarisation need to be considered, especially if safety data collection is not applied uniformly throughout trial conduct

Summary of Guideline Content (12/13)

Section 5. Relationship with Other Guidelines/Regulations

This Guideline should be considered with the following ICH Guidelines

Area of Interest	ICH Guideline
Conduct of Clinical Trials and Clinical Safety Data Management	ICH E2A, ICH E2F, ICH E1, ICH E3, ICH E6, ICH E8, ICH E17
Evaluation of Information Generated Through Post-approval Pharmacovigilance Activities	ICH E2E, ICH E2D, ICH E2C,

Summary of Guideline Content (13/13)

Section 5. Relationship with Other Guidelines/Regulations (continued)

The following non-ICH scientific guidance documents were referenced in ICH E19:

- FDA, United States. Guidance for Clinical Trial Sponsors-Establishment and Operation of Clinical Trial Data Monitoring Committees. March 2006;
- EC, Europe. Guideline on Data Monitoring Committees. 2005. EMEA/CHMP/EWP/5872/03;
- FDA, United States. Guidance for Industry on "Determining the Extent of Safety Data Collection Needed in Late-stage Premarket and Post-approval Clinical Investigations". February 2016. And further relevant guidelines from the various ICH contributor countries/regions;
- EC, Europe. Risk Proportionate Approaches in Clinical Trials; Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation. 25 April 2017. (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use.

Considerations

- **The following should be considered before applying the principles of ICH E19 into the design and conduct of a clinical trial**
  - **Is the safety profile of the drug well-characterised?**
  - **Do the study objectives and design of the clinical trial (e.g., indication, patient population, dosing regimen, duration of use) support the use of selective safety data collection?**
  - **Has the plan to implement selective safety data collection for the clinical trial been discussed with regulatory authorities and has agreement been reached on the final protocol?**

Conclusions

- **ICH E19 Guideline will have a significant impact on the feasibility and efficiency of clinical trials designed to yield important new medical knowledge and advance public health (e.g., on long-term efficacy and safety of a drug)**
- **The principles in ICH E19 should be presented at multiple public meetings to promote awareness of this important Guideline**

Contact

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

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