Selective Safety Data Collection in Clinical Trials

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Learning Objectives

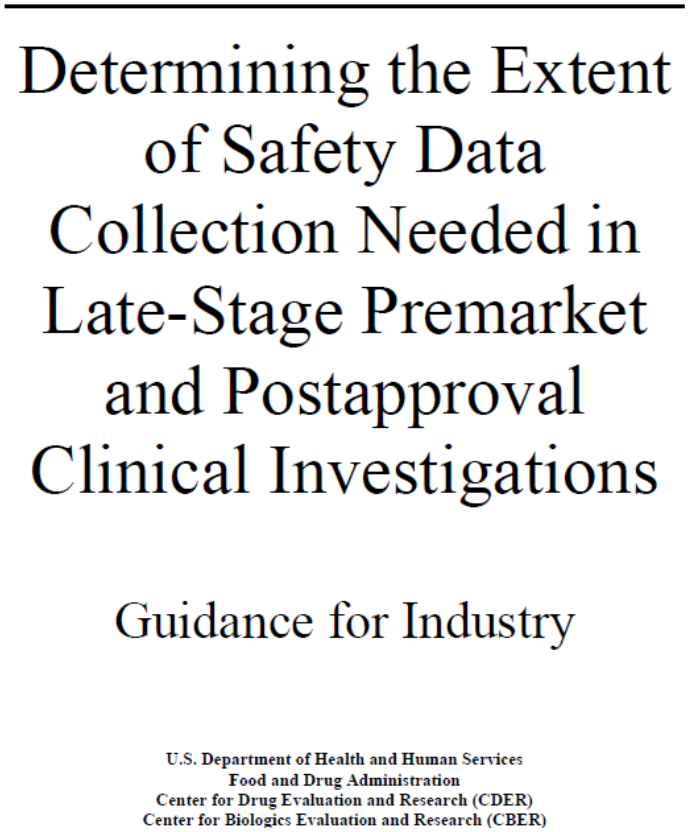
- Understand what is Selective Safety Data Collection (SSDC)
- Understand the importance of ICH E19 guideline to SSDC and global drug development
- Describe situations where and how SSDC can be implemented in drug development

Outline

- Defining Selective Safety Data Collection
- Background for development E19
- Scope of E19
- Purpose of safety monitoring in clinical trials
- Factors contributing to establishing safety profile
- Data reduction and data collection
- Possible trial scenarios and methodologies for implementing E19
- Concluding remarks and next steps

What is Selective Safety Data Collection (SSDC)

SSDC refers to the prospectively planned reduction in collection of certain types of data in a clinical trial for drugs with a well-characterized safety profile where continued collection of comprehensive safety data may provide only limited additional knowledge of clinical importance.



Why was E19 proposed for development as an ICH Guideline?

- Drug development is a global endeavor
- Alignment between regulators and industry essential to advance principles laid out in previously published guidance on this topic

Objectives of E19

- Provides recommendations regarding appropriate use of a selective approach to safety data collection in some late-stage pre- or post-marketing studies of drugs where the safety profile, with respect to commonly occurring adverse events, is well-understood and documented
- Tailoring the method of safety data collection may enable greater efficiency in the conduct of clinical trials. This may facilitate the conduct of large-scale efficacy and safety clinical trials with large numbers of participants and long-term follow-up

- **ICH E19 Guideline published 27 September 2022**
  https://database.ich.org/sites/default/files/ICH_E19_Guideline_Step4_2022_0826_0.pdf
- **FDA E19 Final Guidance issued 5 December 2022**
  https://www.fda.gov/media/163670/download

Scope of E19

- Interventional clinical trials
- More often, post-approval trials
- In some circumstances, may be considered for pre-approval trials
- Not applicable to gene therapy or rare/orphan disease clinical trials
- Selective safety data collection (SSDC) following the principles of this guidance does not alter local/regional safety reporting requirements

Ensuring Safety of Trial Participants

Safety monitoring in a clinical trial serves two purposes:

- **To protect the safety and well-being of individual trial participants**
- **To obtain safety information to be used in the assessment of the risk profile of the investigational medicinal product**

When is the safety profile of a drug well-understood and documented?

Guidance lists several factors for consideration BUT not considered to be an exhaustive list or determinative

- **Regulatory status of drug (e.g., marketing status of drug)**
- **Mechanistic Factors (e.g., MOA including untoward effects, one of many in class or first-in-class)**
- **Clinical Safety Database (number and duration of exposure, dose, intensity of safety monitoring)**
- **Similarity of Planned Clinical Trial to Previous Trials (e.g., dosing regimen, patient population)**
- **Clinical Pharmacology (e.g., DDIs, ADME)**
- **Non-clinical Data (e.g., safety and pharmacologic effect well-characterized from animal studies)**
- **Post-authorization Data (extent and quality of post-marketing safety data)**

Data Reduction/Collection

When it has been determined and agreed to with regulatory authorities that SSDC may be appropriate for a clinical trial, collection of certain information may be limited or reduced in frequency of collection (need to be specified in protocol):

- Non serious AEs
- Some laboratory monitoring*
- Physical examination and vital sign data*
- Concomitant meds*

Should generally expect that the following will be collected:

- Serious adverse events (SAEs)
- Important medical events
- Medication error/overdose (intentional or unintentional)
- AEs leading to study drug discontinuation
- Pregnancy and lactation exposures and outcomes
- AESI, including laboratory abnormalities, identified in the protocol

*If an SAE, AESI, important medical event, or an AE resulting in study drug or trial discontinuation occurs, sponsor may need to collect above information for the individual patient to characterize the particular event

Situations Where SSDC May be Considered

- Approved drug seeking new indication in similar population to the one that is already approved
- Approved drug seeking to expand label to include additional endpoints in the same patient population
- Safety trial with objective to investigate specific safety concern
- Trial designed to provide additional evidence of efficacy when current available data support a well-characterized safety profile

Possible Approaches to Implementing SSDC in a Clinical Trial

- SSDC in everyone
- Comprehensive collection for a specific subset, SSDC in the rest
- Comprehensive collection in everyone initially, SSDC thereafter
- Comprehensive collection in a representative subset, SSDC for remainder of patients

SSDC prior to ICH E19

How Many Clinical Trials Exist that Have Adopted Selective Safety Data Collection? NEJM Literature Search Results: The Possibility of Harmonizing the ICH E19 Guideline

Yuki Yamatani[1,2] · Hiroyuki Saeki, Ph.D.[1,3] · Risa Tanaka[1,4] · Takuji Komeda[1,5] · Yukiko Watabe, MSc[6,7] · Hironori Sakai, Ph.D.[1,8]

Therapeutic Innovation & Regulatory Science (2022) 56:677-684

- Literature search of trials published in NEJM from 1Feb 2016-31Dec 2019 and reviewed texts, protocols and SAPs to identify trials adopting SSDC
- SSDC defined as trials not collecting some of the AE data commonly collected in clinical trials (i.e., deaths, SAEs, AEs leading to discontinuation, and non-serious AEs)
- 459 papers reported results of clinical trials of which 44 (9.6%) identified as adopting SSDC

Key Considerations Before Implementing SSDC

- Is the safety profile of the drug well-characterized?
- Do the study objectives and design of the trial support SSDC?
- Has agreement been reached with regulatory agency on the protocol implementing SSDC?

E19 Implementation

Currently at Step 5 of the ICH process

- Harmonized ICH guidelines are implemented by ICH regulatory members and observers within their respective country/region

Members/Regions where ICH E19 has been implemented:

- EC (Europe)
- EDA (Egypt)
- FDA (U.S.)
- HAS (Singapore)
- HC (Canada)
- MHLW/PMDA (Japan)
- SFDA (Saudi Arabia)
- Swissmedic (Switzerland)
- TFDA (Chinese Taipei)

Selective Safety Data Collection (SSDC) Demonstration Project

- The E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials Guidance was published in late 2022.
- The podcast and Guidance Snapshot are now available.
  - Guidance Snapshot
  - FDA podcast (and transcript)
- The guidance provides internationally harmonized guidance on applying SSDC in specific pre-approval or post-approval late-stage clinical trials.
- With its SSDC demonstration project, C3TI is aiming to promote the adoption of SSDC principles into appropriate drug development programs.
- For the demonstration project, the trial must be a late-stage pre- or post-marketing trial for a drug where the safety profile, with respect to commonly occurring adverse events, is well-understood and documented.

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Guidance Snapshot

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

Guidance for Industry

What is Recommended in This Guidance?

This guidance is intended to provide internationally harmonized guidance on the use of selective safety data collection, SSDC, that may be applied in specific pre-approval or post-approval late-stage clinical trials.

Why Is This Guidance Important?

By tailoring the method and streamlining the approach to safety data collection, it may be possible to carry out clinical trials with greater efficiency. This may facilitate the conduct of large-scale efficacy and safety clinical trials with large numbers of participants and long-term follow-up. In all circumstances in which the use of SSDC is considered, it is important that the welfare of every trial participant is safeguarded. This document describes circumstances in which it may be appropriate to reduce the collection of safety data in late-stage pre-approval and post-approval clinical trials, e.g., long term outcome trials, when appropriate and with agreement from regulatory authorities.

What is SSDC?

SSDC refers to the reduced collection of certain types of data in a clinical trial after thorough consideration of factors that would justify such an approach. Throughout the course of medicinal product development sponsors collect extensive safety-related data that may include vital signs and other physical examination data, laboratory data, and all adverse events. In specific phase 3 or post-approval clinical trials, if the safety profile of a drug is well-understood and documented, collection of comprehensive safety data may provide only limited additional knowledge of clinical importance. In such circumstances, a more selective approach to safety data collection may be adequate.

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Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about selective safety data collection, read the guidance. To see additional Guidance Snapshots, check out the pilot program.

Conclusion

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

Challenge Question #1

Selective Safety Data Collections refers to

A. eliminating safety data collection entirely in a trial with a drug that has a well-established safety profile

B. prospectively planned reduction in collection of certain types of data in a clinical trial for drugs with a well-characterized safety profile

C. Only collecting safety information in patients who experience and adverse event

Challenge Question #2

Which scenario would NOT be appropriate for SSDC?

A. An already approved drug for reduction of CVD risk in T2D is being studied for reduction in peripheral vascular disease in T2D

B. A Phase 2 dose-response study of a 1st in class immunomodulator being developed for the treatment of pediatric dermatoses

C. A post-approval safety trial evaluating the risk of renal failure where the only safety signal of concern pre-approval was imbalances in serum creatinine elevation