Safety Data Management and Reporting

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1) Abstract

Collecting and reporting information about the safety of an experimental compound or product constitutes a significant challenge for clinical data management. This chapter reviews the wide range of factors that must be considered by the clinical research team for the successful completion of a project's safety data management and reporting responsibilities. Industry guidelines and regulations for collecting and reporting reliable, high-quality safety data are discussed. The importance of degrees of precision and descriptions of severity when capturing data about adverse events is emphasized in this chapter. The use of medical dictionaries, especially MedDRA, is reviewed with consideration for the process of encoding safety data to dictionary terms and various approaches to this task. Laboratory data and other forms of data, such as specialized tests, as potential sources of safety data. Special consideration is given to the capture of serious adverse events and their reporting to regulatory agencies. General issues to consider when reporting safety data to the FDA are also discussed.

2) Introduction

Beginning in 1938, the FDA required that drugs have proof of safety before they could be marketed. This was because of a poisonous ingredient found in Elixir Sulfanilamide. In 1962, after the Thalidomide disaster in Western Europe, the Kefauver-Harris amendment was passed, requiring that drugs must be safe and show evidence of effectiveness for the related use. The 1990s introduced post marketing surveillance, and in 1993, MedWatch was launched to make it easier doctors and consumers to report adverse events.[1]

3) Learning Objectives

After reading this chapter, the reader should understand:

- The purpose of and regulatory basis for safety surveillance and the collection and reporting of safety data.
- The categories and classification of safety related events that may occur in clinical trials.
- The importance of coding and controlled terminology in safety data.
- How AEs and SAEs (Adverse Events and Serious Adverse Events) are identified.
- Data collected about safety events.
- The reporting process for safety events for trials run under an Investigational New Drug (IND) as well as federally funded studies.
- How safety data is validated includes reconciliation of externally managed safety data.

The safety data in a clinical study are simultaneously a rich source of information and an enormous challenge. The data manager and the statistician, as part of the product team, must work closely with other team members to ensure that safety data are captured in a sensible way to facilitate proper interpretation and meaningful analysis and summary. Ensuring quality requires that the team capture, process, and report the data in a way that facilitates the drawing of reliable conclusions. When determining the balance between business and science, consideration should be made to collect only data that will support conclusions, and to ensure that data is fit for purpose.

Safety data may be displayed and reported in many ways. To ensure adequate reporting of results that pertain to product effects, judgment and scientific selection are needed to identify the trends and salient features of the data. Producing voluminous pages that are incomprehensible and clinically meaningless can dilute real effects. However, the discernment of these effects is the driving goal of the safety data processing and reporting.

4) Scope

This chapter discusses practices, procedures, and recommendations for data managers to understand and implement Safety Data collection, management, and reporting during clinical trials. This chapter will cover identification and classification of safety-related events reportable to IRBs (Institutional Review Board), DSMBs (Data Safety Management Board), regulatory authorities and clinical sites using the investigational therapeutic. The chapter focuses on safety data collection, management, validation, and reporting for investigational drugs in clinical trials run under an IND as well as federally funded studies. Safety processes for devices are only briefly discussed with reference to additional resources. Similarly post marketing surveillance is not covered in depth.

5) Minimum Standards

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Efficacy Guidelines contain passages of significant relevance to the reporting of safety data in trials:
Section 4 of the ICH(E1A), Clinical Safety for drugs used in Long-Term Treatment, states that available information suggests that most ADEs (Adverse Drug Event) first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for six months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time.

To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g. in the general range of 0.5%-5%). 300—600 patients should be adequate for observation.

Section 1.1 of the ICH(E2F), Pharmacovigilance, states that “periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subject” and impresses the need to “inform regulators and other interested parties (e.g., ethics committees) at regular intervals about the results of such analyses and the evolving safety profile of an investigational drug and apprise them of actions proposed or being taken to address safety concerns.”

Section 1.2 and 1.3 note that “A (Drug Safety Update Report) should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug,” and that “The DSUR should concentrate primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects.”

The ICH E2 offers further guidance on data collection related to pharmacovigilance.

Section IIIA (ICH E2) states that all ADRs (Adverse Drug Reactions) that are both serious and unexpected are subject to expedited reporting, and that other ADRs should be considered on a case-by-case basis. Most notably, expedited reporting is needed for an "expected", serious ADR, an increase in the rate of occurrence, which is judged to be clinically significant, for a significant hazard to the patient population, such as lack of efficacy with a medicinal product using in treating life-threatening disease, or for a major safety finding from a newly completed animal study (such as carcinogenicity).

The role of statistics in clinical trial design and analysis is essential according to ICH guidelines. **ICH E9, Statistical Principles for Clinical Trials,** is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of

clinical trials of an investigational product in the context of its overall clinical development.

Section 3.6 describes the data capture and processing requirements:

> "Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. 'Missing values' should be distinguishable from the 'value zero' or 'characteristic absent'…Specifically, timely and reliable processes for recording data and rectifying errors and omissions are necessary to ensure delivery of a quality database and the achievement of the trial objectives through the implementation of the planned analysis."

Section 6.2 indicates several factors considered to evaluate the safety and tolerability of a drug.

> "In any clinical trial the methods and measurements chosen to evaluate the safety and tolerability of a drug will depend on a number of factors, including knowledge of the adverse effects of closely related drugs, information from non-clinical and earlier clinical trials and possible consequences of the pharmacodynamic/pharmacokinetic properties of the particular drug, the mode of administration, the type of subjects to be studied, and the duration of the trial. Tests such as clinical chemistry and haematology, vital signs, and clinical adverse events (diseases, signs and symptoms) usually form the main body of the safety and tolerability data. The occurrence of serious adverse events and treatment discontinuations due to adverse events are particularly important to register (see ICH E2A and ICH E3)."

Section 6.2 also shares recommendations while summarizing the data from different trials:

> "Furthermore, it is recommended that a consistent methodology be used for the data collection and evaluation throughout a clinical trial program to facilitate the combining of data from different trials. The use of a common adverse event dictionary is particularly important. This dictionary has a structure which gives the possibility to summarize the adverse event data on three different levels; system-organ class, preferred term or included term…The preferred term is the level on which adverse events usually are summarized, and preferred terms belonging to the same system-organ class could then be brought together in the descriptive presentation of data (see ICH M1)."

Section 6.3 shares information about the specific set of subjects to be evaluated for the overall safety and tolerability assessment: "The set of subjects to be summarized is usually defined as those subjects who received at least one dose of the investigational drug. Safety and tolerability variables should be collected as comprehensively as possible from these subjects, including type of adverse event, severity, onset, and duration."

Section 7.2, summarizing the Clinical Database, reiterates the need for consistent data collection and recording, which will facilitate subsequent interpretation of the series of trials.

> "An overall summary and synthesis of the evidence on safety and efficacy from all the reported clinical trials is required for a marketing application. During the design of a clinical programme careful attention should be paid to the uniform definition and collection of measurements which will facilitate subsequent interpretation of the series of trials, particularly if they are likely to be combined across trials. A common dictionary for recording the details of medication, medical history and adverse events should be selected and used."

The ICH General Principles for Planning and Design of *Multi-Regional Clinical Trials (MRCTs*) (E17) has the aim of increasing the acceptability of MRCTs global regulatory submissions. The guideline addresses "strategic programme issues as well as issues that are specific to the planning and design of confirmatory MRCTs, and it should be used together with other ICH guidelines, including E5, E6, E8, E9, E10, and E18."

ICH E17 Section 2.1.2*:*

> "All sites participating in MRCTs should meet applicable quality, ethical and regulatory standards. Specifically, MRCTs should be conducted in compliance with ICH E6 GCP standards in all regions and sites, including making sites available for GCP inspections by regulatory authorities. Monitoring plans and other quality checks should be pre-specified and implemented to address potential risks to subject rights, safety, and well-being, and to the reliability of study results. Centralized and risk-based monitoring may be particularly useful for MRCTs to monitor and mitigate the impact of emerging regional differences in, for example, trial subject retention or adverse event reporting (ICH E6)."

Section 2.2.4 offers guidance on the selection of clinical endpoints.

> "An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment. For MRCTs, the primary endpoint, whether efficacy or safety, should satisfy these criteria as well as being acceptable to all concerned regulatory authorities, to ensure that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities…In addition to endpoint selection and definition, regulatory agreement should also be obtained on the timing and methods of the primary endpoint assessment…Although endpoints may not require formal validation, some endpoints may be subject to subtle differences in understanding, when used in different cultural settings. For example, certain types of adverse events may be more sensitively reported (e.g., more or less frequently) in some regions than others, resulting in differences in reporting patterns due to cultural variation, rather than true differences in incidence. Use of these variables as endpoints in MRCTs will require careful planning. Approaches to minimize the impact of this variation in data collection and interpretation of the trial results should be described and justified in the study protocol."

Section 2.2.6*:*

> "Methods of collecting and handling efficacy and safety information should be standardized across participating regions. It is also important to provide standardized training for investigators and study personnel in each region before initiating the trial in that region to ensure that the trial objectives are met through standardised implementation of the study protocol."
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> "Safety reporting should be conducted in accordance with ICH E2. When local regulations specify different requirements, such as timelines and criteria for expedited reporting, these should also be adhered to locally. The specific period for safety reporting should be provided in the protocol, and the investigators should receive sufficient training in accordance with ICH E6 and other relevant guidelines. In the case of MRCTs, important safety information should be managed both with adherence to any local regulations and in adherence to ICH E2A. Important safety information should always be provided to the relevant stakeholders (e.g., investigators, ethics committees) in a timely manner."
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> "In MRCTs of long duration, where special concerns (e.g., serious adverse events) have been identified, and/or where operational regions are quite large (usually Phase III confirmatory studies), the use of a central independent data monitoring committee (with representation from participating regions to adequately assess

the context of the trial) should be considered, in order to monitor the accumulating efficacy and/or safety information from the MRCT while maintaining integrity of the ongoing trial. If adjudication of endpoints and/or events is planned, a centralised assessment by a single adjudication committee should be considered…Coordinated site initiation is particularly important in MRCTs to ensure proper conduct, completion, and reporting of results without any delays among regions. To comply with the quality management described in ICH E6, the sponsor should implement a system to manage quality in design, conduct, oversight, recording, evaluation, reporting and archiving of MRCTs. In this aspect, centralised and risk-based monitoring may be particularly useful for MRCTs to identify variability across regions and sites in protocol compliance (e.g., differences in follow-up, compliance with study medications, adverse event reporting and/or extent of missing data). Mitigation approaches should take regional variations into consideration."

ICH E19-Safety Data Collection expands on issues related to collection of safety data for reporting purposes once the medicinal product has received marketing authorization from a regulatory authority for the indication under investigation.

Section 2.2 addresses the factors that contribute to a determination that selective safety data would be appropriate and includes:

- Availability of post-approval safety data and findings.
- The dose, dosing regimen, dosage form, route of administration, and treatment duration used in the previously conducted studies are comparable to the planned use of the drug in the proposed study.
- The patient population from previously conducted studies is representative of subjects in the planned study regarding demographic characteristics, underlying medical conditions, concomitant drugs, and other key factors.
- In previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e. number exposure to drug, treatment duration.
- Consistency of the safety profile across previous studies.
- Characteristics of previous studies, e.g. study design, study conduct, adequacy of safety monitoring/safety data collection availability of protocols statistical analysis plan, and/or access to data.
- Knowledge of the mechanism of action of the medicinal product under study.
- Knowledge of the safety profile of approved drugs in the same pharmacologic class.

TITLE 21 CFR 312.32 requires IND holders to notify the FDA and all participating investigators of any event suspected to be related to the serious and unexpected treatment. A serious and unexpected adverse event or unexpected suspected adverse reaction is defined as follows:

> "An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended."

This guidance also identifies review of safety information by the sponsor and specifies potential sources of safety data as follows:

> "The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States."

The criteria for these IND safety reports are follows:

> "The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

With the review of regulatory requirements and guidance in mind, we recommend the following Minimum Standards for Safety Data Reporting:

Table 1

#	Minimum Standard	Reference	Evidence level	Sections referred
1	Appropriately collect, review, analyze and report events (including AEs, DSUR, ADR's, Suspected Events, etc.) to authorities on a consistent and timely manner, and according to the requirements for submission (including technical requirements).	1. ICH E6 2. ICH E8 3. ICH E9	I (Regulatory Guidance)	1. Sections 6.8 2. Section 6 3. Sections 3.6, 6.2
2	All adverse data should be reported regardless of causality. The incidence of AE's should be analyzed with an appropriate method defined in the protocol.	1. FDA 21CFR 2. ICH E6(R1) 3. ICH E3	I (Regulatory Guidance)	1. Section 312.32 2. Section 7.3.6 b 3. Section 12.2.2
3	Clinical data should be collected based on protocol requirements and chosen specifically to assess the treatment under study. Laboratory, vital sign and adverse event data constructs most safety data,	1. ICH E9 2. ICH E19 3. ICH E3	I (Regulatory Guidance)	1. Sections 6.2 2. Sections 2.4, 2.5, 2.6 3. Section 12
4	Develop standard operating procedures (SOPs) for data capture, data validation, statistical analysis, and reporting of data. The SOPs should include appropriate detail and resources for this team approach	1. ICH E6 2. ICH E9 3. ICH E19	I (Regulatory Guidance)	1. 1. Sections 1.6. 1.38, 1.55 2. 2. Section 5.8
5	Ensure adequate sample size and duration of dosing is collected to characterize possible adverse events.	1. ICH E9	I (Regulatory Guidance)	1. Section 3.6
6	Multi-Regional Trials should follow all the principles of GCP and regulations across regions and satisfy the primary end point. Standard training and Monitoring of MRCT's differences across regions should occur to maintain consistency, as reporting of adverse events can differ.	ICH E17	I (Regulatory Guidance)	Sections 2.1.2, 2.2.4, 2.2.5, 2.2.6 & 2.2.

6) Best Practices

Best practices are those identified through the literature or by the chapter writing group that do not have a strong requirement based in regulation or recommended approach based in guidance, but which do have supporting evidence either from the literature or consensus of the writing group. As such best practices like all assertions in GCDMP chapters have a literature citation where available and are tagged with a Roman numeral indicating the strength of evidence supporting the recommendation (see Table 1).

1. Develop CRFs with teams of individuals from the monitoring, data management, statistics, regulatory affairs, and medical departments, thereby ensuring adequate attention to the collection of safety data. When working on a program of studies for a specific product, ensure the collection is consistent enough to support reporting. (CDASH IG Version 2.1, Page 24).
2. Define clear reporting instructions (CDASH IG Version 2.1, Page 11).
3. Consider the level of precision that can be attained in the study and select the CRF format for collecting AEs appropriate for that level. Also, consider the level of precision in the analysis.
4. Define severity, with an understanding of its uses and limitations. (CDASH IG Version 2.1, Page 168).
5. Examine laboratory data from the perspectives of categorical shifts, changes in magnitude for the group, individual significant values or changes, and listings. Consider related parameters for compounds with potential toxicity in specific body systems.
6. Consider laboratory normalization techniques when combining data across studies or centers where varying normal ranges are used and that robust lab cleaning occurs, especially for studies utilizing local laboratories, as incorrect laboratory ranges can cause incorrect reporting of the above. (Consensus).
7. Include the study team when considering computerization, management, reporting, and analysis of safety data. These tasks are highly integrated and require joint considerations of individual team constituents. (Consensus).
8. Ensure that scope of adverse events collection is consistent with the protocol requirements. Sponsor should define appropriate data collection requirements (e.g., therapeutic area specific requirements, special populations, data collection period etc.), which may vary based on the requirements for characterizing and reporting product safety and is usually defined in the protocol. (CDASH IG).
9. Identify and define common SAE data fields for SAE data collection (CDASH Serious Adverse Event Supplement, Version 2. 2021).
10. Apply standards commensurate with the utilization of the results residing in the databases when using databases for safety reporting (e.g., expedited reporting, ongoing review by monitoring boards, or routine reporting). If important decisions are made based on the information in the database, know the data's appropriateness and level of quality. (Consensus).
11. Use MedDRA for coding Adverse events, to facilitate consistent data retrieval, medically meaningful groupings for review, analysis and/or summary of safety data. Always output the data utilizing the most recent version of MedDRA. (MedDRA Best Practices, Maintenance and Support Services Organization's (MSSO) Recommendations for Implementation and Use of MedDRA 2018.

Table 2 GCDMP Evidence Grading Criteria

Evidence Level	Criteria
I	Large, controlled experiments, meta, or pooled analysis of controlled experiments, regulation, or regulatory guidance
II	Small, controlled experiments with unclear results
III	Reviews or synthesis of the empirical literature

IV	Observational studies with a comparison group
V	Observational studies including demonstration projects and case studies with no control
VI	Consensus of the writing group including GCDMP Executive Committee and public comment process
VII	Opinion papers

7) Safety Data Terminologies, Categorization & Definitions

Below is a non-exhaustive list of definitions that are used throughout the following sections, and with which anyone working on or overseeing a clinical trial should be familiar. While company-specific terminology is often present, for this chapter's purposes, the terms defined below will be used in this chapter.

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 R2).

Adverse Drug Reactions: In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (ICH E6 R2).

Unexpected Adverse Drug Reaction: An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. (FDA – Safety Reporting Requirements for INDs and BA/BE studies, 2012).

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies less certainty about causality than adverse reaction, which means any adverse event caused by a drug. (FDA 21 CFR 312.32(a).

Suspected Unexpected Serious Adverse Reaction (SUSAR): A suspected adverse reaction (see definition above) that is considered both serious and unexpected. (FDA 21 CFR 312.32(a).

Treatment Emergent Adverse Event: An event that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state. (ICH E9).

A *Serious Adverse Event*: This (experience or reaction) is any untoward medical occurrence that at any dose results in death, and/or is life-threatening. Note that the term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. (ICH E2A).

Adverse Events of Special Interest: A noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (e.g. hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor. (CIOMS Cumulative Glossary 2023).

Reporting an Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) to *IRB*s: Any problem or event which, in the opinion of the local investigator, was unanticipated, places subjects or others at a greater risk of harm than was previously known or recognized and was possibly related to the research procedures.[2]

Investigator Brochure (IB): A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. (E6R2).

Development Safety Update Report (DSUR): presents a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether it is marketed (ICH E2F). A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. (ICH E2F).

Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board (DSMB), Safety Review Committee (SRC)): An independent data monitoring committee that may be established by the sponsor to assess at predefined intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. (E6R2).

Investigational New Drug (IND*) Annual Report*: A sponsor is required, within 60 days of the anniversary date that the IND went into effect (i.e. the date the FDA permitted the study to begin), to submit a brief report of the progress of the investigation. Some of the topics include: the status of each study and each study completed during the previous year, description of the investigational plan for the upcoming year, any revisions to the IB and significant protocol updates. To promote global harmonization, the FDA will accept the DSUR (see definition above) to meet an IND application annual report requirement. (21 CFR part 11 312.33.).

8) Safety Data Management

The management of all data collected during a clinical trial is important, however in many aspects the safety data may be the most critical given that the data will lead to conclusions about the efficacy, efficiency, and welfare of the patient population. Various tools and standardized dictionaries are available for use during a clinical trial, and it is the responsibility of the Sponsor to select the most appropriate and the role of the data manager to ensure consistent usage throughout the study.

I. Identification of Adverse Events

Adverse events can be reported by subjects via physical examinations, electronic patient reported outcomes (ePRO), or paper questionnaires and open-ended discussions with the PI. Adverse events can also be identified through other clinical trial evaluations, such as laboratory results, neurological exams, and ECGs. It is important not to question participants about specific, expected events to avoid collection bias.

ePRO tools exist to aid in the subject reported collection of adverse events in real time, such as the PRO-*CTCAE*™.[3, 4] A number of ePRO tools are available for mobile devices, such as Android and iOS, and can seamlessly transfer the data for consumption. These tools often have a library of adverse event terms/symptoms to choose from, along with severity, frequency, and other pertinent adverse event specific information.

When implementing ePRO for the collection of adverse events, ensure the questions are easy and timely for patients to complete, provide education and step-by-step workflows and perform robust testing of the tool and reconciliations as needed, as well as describe the appropriate process and timing of data transfers.

II. Data Collection

a. CRF/Database design requirements

The accuracy of safety evaluation depends on the quality of the data reporting. The quality of an SAE case report depends on the accuracy and completeness of specific information obtained about AE. This issue of completeness or accuracy in SAE case reports has been identified as a crucial factor hampering the usefulness of SAE case reports.[5]

The process of detecting and reporting of safety data must be established in collaboration with Sponsor and oversight committees.[6]

To ensure uniform Good Clinical Practice standards in the collection of safety data, it is important to harmonize the way to gather data and act on important safety information arising. Clean safety data is promoted through the careful design of data collection forms in accordance with the study protocol, regulatory requirements with proper planning from the monitoring, data management, statistics, regulatory affairs, and medical departments, an extensive training for the study team including site staff, followed by user feedback mechanism that could be built into the CRF design and the maintenance process of the reporting tool. (ICH E6R2).

While the Clinical Data Management operation may be first to be aware of an adverse event, the responsibility of submitting a Suspected Unexpected Serious Adverse Reactions (SUSAR) to competent authorities, ethic committees and investigators typically lies within drug safety.

The data management safety role starts with the data collection and clinical database preparation before safety reconciliation. Safety data management includes monitoring and tracking of all adverse events, serious adverse events, serious and medically significant adverse drug reactions (ADRs) and other medical-related product information, coding of all reported events. Reporting of such information in accordance with the sponsor and regulatory reporting timelines should either be done electronically by the system or as an aggregated report.

Clinical Data Management and Safety organizations may run independently and may use separate databases designed to comply with different data standards. Sponsors can utilize separate reporting databases to meet independent reporting requirements although some data are common. The Clinical Data Interchange Consortium (CDISC) has set the standards for clinical trial data, while the International Conference of Harmonization (ICH) dictate drug safety ones.[7]

Without question, electronic case report form (eCRF) design and the ultimate completion of the forms by the clinical investigators or clinical research coordinators is one of the most critical steps in a successful clinical trial. The quality of the data collected relies primarily on the quality of the eCRFs designed and implemented. No matter how the time and effort into conducting the trial, if the correct data points were not collected, a meaningful analysis may not be possible. It is reasonable to state that the design, development, and quality assurance of such an instrument must be given the utmost attention. The quality of the information originally reported directly impacts the quality of data output.[6]

b. Key data points

The list of variables provided in Table 3 is not exhaustive nor will be applicable to all studies; this is to guide the decision-making process for the Sponsor, and to allow the data manager to have a list of variables that can be referred to and aid in ensuring the most relevant data is collected. Code lists may differ, but CDISC Terms should be considered.

Table 3 Key Data Points. (CDASH)

DATA COLLECTED ON THE ADVERSE EVENT FORM	
Adverse Event – Preferred and reported term	
Start Date and End Date	
Severity OR Toxicity Grade	
Severity – • Mild • Moderate • Severe **Toxicity Grade –** • Grade 1–5	*Either AESEV or AETOXGE must appear on the CRF. Some studies may mandate the collection of both. Refer to ICH E3 guidelines for CSR Section 12.2.4. CTCAE grade is commonly used in oncology studies although it can be used elsewhere.*
Serious	
• Congenital Anomaly or Birth Defect • Persistent or significant disability/incapacity • Death • Hospitalization or prolongation of existing hospitalization • Life threatening • Other medically important event	*Assess if an adverse event should be classified as serious based on the "serious" criteria defined in the protocol.*
Relationship to Study Treatment(s)	
• Not Related • Unlikely Related • Possibly Related • Related	
Action Taken with Study Treatment	
• Dose Increased • Dose Not Changed • Dose Reduced • Drug Interrupted • Drug Withdrawn • Not Applicable • Unknown	
Outcome	
• Fatal • Not Recovered/Not Resolved • Recovered/Resolved • Recovered/Resolved with Sequelae • Recovering/Resolving • Unknown	
Timing	
• Start/End Dates • Optional Timing	
DATA COLLECTED ON OTHER CRF FORMS	
Patient Identifier Demography Details	

Study Treatment at the time of AE
Test drug/investigational product dose
Duration of test drug/investigational product treatment
Concomitant treatment during study
Diagnostic/lab testing

c. Recommendations and standards

Fundamental eCRF design principles should be followed based on Clinical Data Acquisition Standards Harmonization (CDASH) and internal standards. From an eCRF design perspective, the CDASH represent a global, consensus-based standards development process with commons from organizations in all the ICH regions (US, Europe, and Japan). It describes recommended data collection sets for sixteen domains, including demographic, adverse events and other safety domains that are common to all therapeutic areas and types of clinical research. The document also includes recommendations and best practice guidelines, regulatory references, and other information on the CDASH project. The CDASH Core Team recommendations would encourage consistent implementation and the most optimal use of the CDASH standard. Find these useful publications outlined in the

III. Reporting

a. Precision, specificity, & accuracy

As the regulated biopharmaceutical industry strives for greater harmonization of safety reporting regulations and standards, there is an increasing emphasis on safety surveillance and data quality. In addition to supporting patient/subject safety, increased data quality facilitates communication of complete and accurate information to those involved in clinical research and post-marketing processes (including regulatory bodies, sponsoring companies, study site personnel, and marketing authorization holders). Collection of high-quality data can also result in greater time and cost efficiency during product development and marketing (e.g. less querying of incomplete data, a decrease in site monitoring costs and reduction of the risk of delayed regulatory approval). The quality of adverse event data is central to safety monitoring in clinical trials, to the risk assessment of marketing applications and in the evaluation of safety signals within post marketing data. (Meddra PTC).

The data quality recorded by investigators directly impacts the quality of MedDRA coding.
Inaccurate coding of safety events results in distortion of safety information. Investigators need to improve their verbatim reporting and to understand the high sensitivity and granularity of MedDRA and their impact on the final coding. Toneatti et al. found that difficulties in coding with MedDRA were due to both the lack of precision in the investigator verbatim and the high specificity and sensitivity of MedDRA. For example, investigators should distinguish between true medical diagnosis and biological qualitative results to avoid as much as possible the lack of multi-axial linkages between the “Investigations” System Organ Class (SOC, the highest level of MedDRA) and any other SOC.[5, 8]

Clear initial data can be collected through careful design of data collection forms, and training of individuals in data collection and follow-up. To promote consistency, organizations should document term selection methods and quality assurance procedures in coding guidelines consistent with MedDRA Term Selection: Points to Consider document. CRF Completion Guidelines Chapter in GCDMP covers the general instructions and guidance to be shared to the sites.

Below are examples of specific scenarios for adverse event reporting, to ensure quality data capture that enable accurate coding:

- Avoid abbreviations: Some abbreviations are universally accepted, but most are subject to interpretation. For example, GU Pain can be interpreted as Genito Urinary Pain or Gastric Ulcer Pain.
- Avoid ambiguous/incomplete terms: Report the specific term with location wherever applicable. e.g. Congestion could be Pulmonary congestion or nasal congestion.
- Avoid reporting multiple diagnosis/combination terms: e.g., vomiting and diarrhea, require a query to site to split and report each event separately or to report a single confirmed diagnosis.
- Avoid reporting extraneous information that does not contribute to the medical diagnosis or concept: e.g., "patient had headache," "headache," "headache at 2 a.m.," etc. can be reported as headache without extraneous information which enables auto-encoding.
- Avoid reporting laboratory values or investigations without qualifiers. AE should include a qualifier or a diagnosis. If referencing significant Lab or investigation values, the AE must indicate if the result is increased, decreased, high, low etc. or a diagnosed condition that would explain such a value. For example, "Hemoglobin 6.0" will not be appropriate to capture as AE. Instead, use a term such as "decreased hemoglobin" or "anemia." If using CTCAE criteria, the grade will be entered and will indicate severity.

The precision with which AE data are captured relates directly to how the data can be analyzed and reported. There are three basic types of precision in a clinical trial.

High Precision: Investigation in a Phase One sequestered environment (i.e. a phase one) often incorporates medical monitoring that is continuous and high precision. With a few subjects in a sequestered environment, a nurse or physician is by the bedside continuously. In such an environment, clock time may be recorded so that precise data can be collected for onset and offset of an AE. Hence, duration of the AE and elapsed time since initiation of treatment can be calculated in a meaningful way. Clock time is meaningful in such an environment for some events, although it may be difficult to assess the precise minute that sleepiness begins, or a rash is cleared.

Moderate Precision: Investigation in a hospital often incorporates medical monitoring that is daily, frequent (but not continuous), and of moderate precision. Hospitalization offers a controlled and sequestered environment such that a nurse or physician can assess the subject daily. In such an environment, clock time may not make sense for all events, but date can be precisely recorded. Onset and offset of an AE can be recorded in terms of days but not hours. Duration (in days) and elapsed days since initiation of treatment of the AE can be calculated.

Low Precision: Investigation in an outpatient study where subjects return to the facility after days, weeks, or months incorporates low precision. In such an environment, clock-time and date may not be meaningful. Use of subject diaries may assist with the determination of the duration of the AE or elapsed time since treatment. However, subject diaries are frequently inaccurate. In such studies, it is recommended to capture frequency (e.g. single episode, intermittent, continuous), maximal severity, most-harsh relationship, and other such information rather than to attempt to record each event with time of onset and offset. When an investigation is of low precision, but attempts have been made to record data as if it were moderate or high precision, the result is a database with dates (or times) that are rough guesses and that may be far from accurate.

The precision with which AE data were collected has an important impact on how the data can be analyzed in a meaningful way. In an outpatient study, dates cannot be interpreted with the same reliance as in a sequestered study. When dates are present in the database, it may be tempting for the statistician to employ survival-analysis techniques to analyze time-to-event. However, if these data are inaccurate, the resulting analysis can lead to incorrect or unreliable conclusions.

When considering the capture of severity of adverse events, it is tempting to make the assessment in terms of its impact on activities. This method of assessment may be meaningful for some events, such as "pain," but not meaningful for others, such as "alopecia." Severity is not assessable at all. For example, "mild suicide" is not meaningful. Some events are episodic rather than graduated by severity, such as "hair-line fracture." For example, an assessment of diarrhea as "severe" is often made because of duration or frequency of episodes (which are different parameters). However, diarrhea is episodic.[9]

The concept of severity is only meaningful within a particular event. When one considers severity of AEs for an organ class (e.g. CNS), ranking among mild, moderate, and severe AEs is not meaningful. If one considers "mild stroke" and "severe flush" (both CNS events), these rankings are not sensible compared to rankings such as "mild headache" and "severe headache" for which a relative ranking does make sense.

A common data display encouraged by the ICH and the FDA is a breakdown by severity. In this context, it is easy to confuse severity with seriousness or to misinterpret severity altogether. A breakdown that ignores the particular events and counts mild AEs separately from moderate AEs will give a distorted assessment when the same study includes reports of "mild stroke" or "mild MI" and also reports of "severe rash" or "severe sleepiness." A more meaningful display breaks down severity within a particular event.

b. Time period, multiple occurrences

Baseline AEs: A baseline AE is defined as any adverse event that happens prior to the administration of the investigational product but after the patient has been deemed eligible and consented to the trial. If randomization is part of the study methodology, the Study PI and/or Sponsor if the participant will continue if a baseline AE is identified before Randomization. After Randomization but prior to the start of the study protocol, the AE should be documented but the participant would, depending on the AE, need to remain in the study. Examples of baseline AEs include, but are not limited to, surgery (either emergency or planned), exacerbation of a pre-existing condition, or contracting a temporary condition such as influenza. Baseline AEs need to be documented as carefully as intra- or post-protocol AEs as there may be confounding factors that are introduced.

Persistent/ Recurring AEs: Persistent and recurring AEs are those that start during the course of the trial and are long-term (e.g., hypertension) or repeated (e.g., migraines); regardless, they should be detected fairly early as they may have long-term effects for the health and well-being of the patient, not the least of which may be introduction of concomitant medication(s) or other therapies that may be contraindications to the study intervention.

On the AE form it is strongly recommended that "Ongoing" is a binary field that indicates that the AE is continuous (for persistent) or that the event is a potential for repetition (for recurring). Recurring AEs should each be documented separately. Worsening or other changes to the AE (for example, the migraine symptoms now include auditory and visual auras) should be documented and as appropriate communicated to the Sponsor as soon as a pattern is confirmed. Analysis and data quality checks need to take the repetitive nature into account to ensure that any dates do not overlap, or if there is overlapping that it makes sense (for example, if "numbness in the extremities" is the AE, and the subsequent event starts before the previous event ends, verification of dates should include confirmation that the affected body areas are separate and distinct).

c. Workflow supporting AE/SAE data collection

Paper-to-paper workflow: Clinical data are recorded on paper case report forms (CRF) and safety data (AEs/SAEs) are reported on paper SAE report form that is usually faxed to the CRO/sponsor. Within the CRF, the Investigator documents all AEs (non-serious AEs and SAEs) on the provided AE pages which are entered into the clinical database. The DM

validates this AE/SAE information (e.g. check for completeness, duplicates, events of special interest) and send queries to sites.

eCRF-to-paper workflow: Clinical data, including safety data (AEs/SAEs) information, are collected electronically in EDC however SAEs must additionally be reported via paper forms and sent to the CRO/sponsor. The DM validate this SAE information (e.g. check for completeness, duplicates, events of special interest etc.) and send queries to site. Non-serious AEs and SAEs are entered into the eCRF and are available to generate aggregate reports at any time as soon as the site enters that data.

eCRF-to-electronic workflow for SAEs: Clinical data along with safety data are entered into the eCRF. The SAE may then be sent to the Safety database through a graphical user interface, E2B messaging or a data integration HUB. The timing of the transfer process may vary by the method used. There is a back-up process in case the EDC system would be down when an SAE needed to be reported. The benefit of this is that the SAE reconciliation will be minimal. With this method, the responsibility for data cleaning may or may not be split between Data management and Safety. Companies considering this type of process should consult their EDC provider to see what their system may have in place. It would also be beneficial to read the CDISC SAE Supplement version 2 document.

d. Medical devices

Medical Device serious adverse event reporting is similar yet different in from reporting for Biologics and Drugs. There are sections in the reporting form FDA 3500A that are filled out by distinct roles users, distributors, manufacturers, or importers. The reporting requirements for medical devices are specified in 21CFR Part 803.50. The types of data that are different includes device manufacturer, the city and state where this occurred, the product name/brand name and code or serial number. Dates of device implantation or explanation should be recorded. The report needs to include whether the device was operated by a medical professional or a lay person. If the device has an expiration date, this needs to be reported. If the device was removed, it should be noted if the device was returned to the manufacturer. Consideration should also be taken into environmental factors that could have influenced the event.

The reporting period is 10 days from the awareness for the user facility, and 30 days from awareness for the manufacturer and the importer. A five-day reporting period is required if the event could necessitate remedial action to prevent substantial harm to public health or if the FDA had required a five-day reporting period.

The types of issues that can occur with medical devices include mislabeling, device failure or malfunction, user error, or inadequate/improper design.

The reporting standard is to report if the device may have caused or contributed to serious injury or death, or that the device may have malfunctioned in a way that in the future it could cause serious injury or death.

What is similar with biologics and drugs are the other details reported including subject identifier, subject date of birth or age at time of event, gender, weight, date of event, date of report, outcome of the event, past medical history, and description of relevant tests to include date and result. Concomitant medications and procedures are to be included; however, there is no need to report products used to treat the event.

9) Data Validation

I. Edit Checks

Edit checks should be created to help ensure any deviations from key safety parameters are noted and managed. Ensure that edit checks are defined for all safety parameters in CRF and all checks are programmed, validated, and documented in accordance with standard operating procedures.

The most used types of programmed edit checks include missing values and inconsistencies across CRF modules. For complete information on edit checks, see the GCMDP chapter entitled Edit Check Design.

In addition to ensuring the database is complete, correct, allowable, valid, and consistent, other types of data quality checks may be applied. Once these checks have been identified, appropriate and verified programs are created to help identify discrepancies. Data quality checks and any manual review specifications, and medical review requirements should be defined and described. All derivation and validation procedures may be fully tested and documented in the Data Management Plan or a referenced validation document.

A comprehensive safety data review will help identify trends and alert investigators immediately of patient safety issues during the study. In addition to SAEs, non-serious adverse events and other pertinent patient information should be reviewed early in the study, ensuring that the Data and Safety Monitoring Board (DSMB) has a current, complete picture of the patient safety profile. Interim efficacy and safety data reviews can also be performed at earlier points in the study in an EDC-based study using the most current, near real-time patient information.

II. Serious Adverse Event Data Management and Reconciliation

Because serious adverse event (SAE) data may be stored in a safety database separate from the clinical trial data, a reconciliation of the two datasets must be conducted to ensure consistency. This procedure applies to all projects where both a clinical database and a drug or device safety SAE database are maintained as two separate databases.

In instances where data is integrated directly into the safety database, reconciliation is often still required. When there is unexpected system downtime or site staff has incorrectly followed the process, there are instances when the safety database may not match the clinical database, even when the databases are integrated. The processes and procedures around integrating the safety and clinical databases should be thoroughly reviewed to ensure reconciliation is completed.

Serious adverse event (SAE) data reconciliation involves the comparison of key safety data variables between two databases. Reconciliation is performed to ensure consistency between events residing in the SAE database and those residing in the clinical database. It is an iterative process that occurs multiple times during the study. When to reconcile is determined by the frequency of data receipt, scheduling of safety updates, and timing of interim and final reports and should be documented.

Standardize the capture of SAE data elements in both the clinical database and the safety database.
Conduct the reconciliation of SAE event to ensure that data in safety and clinical databases are consistent.

Establish the time intervals in the project where reconciliation will be performed and the mechanisms to cover interim analyses or safety data reporting. Often, SAEs continue to be reported after a clinical trial has concluded. It is important to establish a cutoff point after which no SAEs will be added to the clinical database, even if the safety data or safety database is updated. Data items commonly reconciled or used in additional data cleaning can be found in Table 4.

Table 4 Data items commonly used in Serious Adverse Event (SAE) Data Reconciliation

Items collected on AE form:

- Protocol
- Investigator
- Subject Identification
    - Randomization or Enrollment Number
    - Date of Birth (full date of birth not collected)
    - Gender
    - Race
- Event Number
- Diagnosis/Verbatim
- Coded or preferred term
- Onset date
- Resolution date
- Date of death
- Outcome
- Severity
- Causality assessment
- Action taken with study drug

Sometimes items are used from other modules for further reconciliation, clarification, or cleaning.

From the discontinuation module, items may include but not be limited to:

- Subject identification
- Primary reason for discontinuation being an event
- Hospitalization
- Cause of death listed on the death certificate
- Autopsy result

From the concomitant medication modules, items used for data cleaning outside of reconciliation may include but not limited to:

- Subject Identification
- Medication name
- Start date
- Stop date or ongoing
- Indication

From the dosing modules, items used for data cleaning outside of reconciliation may include but not be limited to:

- Start/End dates, including interruptions

Clinical data management, safety leads, and clinical operations should establish a mutually agreeable turnaround time for researching, retrieving, and correcting any discrepancies found during or since the last reconciliation period.

Listings are obtained from either the safety database or the clinical database, and the two databases are manually or programmatically reconciled through direct comparison of these listings. Either way, the differences will require manual review by trained staff. Ancillary documents can be used for clarification or corroboration, such as hospitalization discharge summaries, death certificates, or autopsy reports. Even programmatic reconciliation of fewer than one hundred events can be cost effective in both time and quality. The company can validate the process once and run as frequently as data and time allow.

Verify that all SAEs from the clinical database also reside in the drug safety database. Note that SAEs from the safety database may not be in the clinical database until all data entry has been completed. Depending on the reporting requirements, SAEs in the safety database may span to cover more than one SAE in the clinical database. Some Ss may not be reported in the clinical database due to differing reporting requirements. Thus, there may not be a 1:1 match in

the number of events. The documentation of what is expected and acceptable should be defined prior to the reconciliation.

Document all SAEs included in the clinical database but not included in the safety database. These are potentially unreported events. Include copies of the appropriate CRFs to the safety contact person, if applicable if allowed by company SOPs.

Research and resolve or document all differences between SAEs that are present in both databases. There may be some acceptable differences. Examples of these differences include but are not limited to:
a) possible coding differences if different dictionaries are used for coding;
b) date of birth differences if systems and regulations require reporting of DOB as partial in one system; and
c) outcomes and causalities may be defined differently between systems, etc.

A list of acceptable differences should be provided to the reconciler. For example, slight variations in AE terminology used in describing events may be of no consequence, though at the preferred term level, the terms should match. There may also be a difference in start dates as the event may have started prior to progressing to a serious event.

Documentation of the reconciliation should include the entirety of the issue. If multiple rounds of reconciliation occur prior to the issue being resolved, previous comments and responses should remain.

Depending on the nature of discrepancies, it may be necessary to seek input from the medical monitor or designee before deciding on a course of action.

Prior to data lock, verify that all queries have been answered correctly and integrated into the database(s). Ensure that all expected SAE information has been received and reconciliation has been performed on all events. Written notification should be made when reconciliation has been successfully completed. This helps avoid confusion should the safety database be held open for updates after the study ends.

Any final inconsistencies that cannot be resolved should be documented.

Adverse events of special interest: Based on ***CIOMS*** ICH Glossary:

> "An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

Although not required as part of a protocol, if a definition or criteria has been provided for the AESI, then this may warrant collection of additional information across the entire study population to better characterise these events. These events may fall into any number of categories, and care should be taken to standardize these prior to data collection. Examples of events include laboratory results, vital signs, risk factors, concomitant therapies, and/or concomitant illnesses. For example, if gastrointestinal haemorrhage was an adverse event of special interest, one might want to proactively collect concomitant antithrombotic therapy across the entire study population (see E19 – Optimization of Safety Data Collection). (ICH).

As indicated in ICH Topic E2F Development Safety Update Report regarding adverse event of special interest (AESI): “If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained.”

AESI has been an important part in presenting the safety profile for a compound in clinical trials. With the use of MedDRA system organ class (SOC), preferred term (PT), along with Standardized MedDRA Queries (SMQs) and even Customized MedDRA Queries (CMQs), AESI reporting becomes more specific and detailed.

Safety monitoring during clinical trials is a crucial component for drug development. Before a drug can receive regulatory approval for marketing, rigorous safety monitoring and reporting from preclinical to all phases of clinical trials are required. With the reference of guidance on safety reporting and availability of Medical Dictionary for Regulatory Activities (MedDRA), collecting and reporting adverse events are now more of a standardized process.

III. Data Coding and Dictionary Management

Medical Dictionary of Regulatory Affairs (MedDRA): A clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process developed by the International Conference on Harmonization (ICH).

MedDRA was developed by an ICH Expert Working Group to address many of the limitations of older adverse event terminologies. The intent of ICH, in developing MedDRA, was to have a standard, medically rigorous, and well-maintained terminology to facilitate communication. MedDRA's structure allows for aggregation of reported terms in medically meaningful groupings to facilitate analysis of safety data. Specifically, some of the applications for MedDRA are:

To aggregate reported terms in medically meaningful groupings for review, analysis and/or summary of safety data (CDAS SAE Supplement version 2.0

To facilitate identification of common data sets for evaluation of clinical and safety information, To facilitate consistent retrieval of specific cases or medical conditions from a database,

To improve consistency in comparing and understanding safety signals and aggregated clinical data,

To facilitate electronic data interchange of clinical safety information.

Organisations are encouraged to document their term selection methods and quality assurance procedures in specific coding guidelines which should be consistent with the MedDRA Term Selection: Points to Consider (MTS: PTC). The quality of the original reported information directly impacts the quality of data output. Clarification should be obtained for data that are ambiguous, confusing, or unintelligible. Clear initial data can be promoted through careful design of data collection forms, and training of individuals in data collection and follow-up (e.g. investigators). To promote consistency, organizations should document their term selection methods and quality assurance procedures in coding guidelines consistent with this MTS: PTC document. MedDRA is a standardized terminology with a pre-defined term hierarchy that should not be altered.

It is recommended that trial data is coded using the most recent version of MedDRA as it is continuously maintained with the latest terminologies, advances and addresses any errors from previous versions. Trials coded with the same version of MedDRA supports consistency of coding and analysis with related trials. Each organization should have a versioning strategy that should be documented and would to have similar versioning strategy for safety and clinical databases.

Identifying and reporting Adverse Events of Special Interest (AESIs) are important in clinical trial safety data management with the use of MedDRA terminologies, *system organ class (SOC*), *preferred term (PT*), along with *Standardized MedDRA Queries (SMQs*) and even *Customized MedDRA Queries (CMQs).* A specific SMQ or a selection of SMQs may be used to retrieve relevant cases for subsequent medical review. SMQs may be used to create a "watch list" (e.g. an automated notification system) to alert the user of incoming cases needing urgent review.

Cumulative Summary Tabulation: Although not directly relevant to a Clinical Data Manager's role, it is important to understand the potential impacts downstream of data issues. One such area is the Cumulative Summary Tabulation, which is an overview of the adverse events and other critical occurrences during a trial. Having lower quality data means that this potentially important summary will be incomplete or inaccurate, possibly leading to erroneous and/or life-threatening decisions.

The ICH E2CR2 Section 3.6.2 outlines some characteristics that a Cumulative Summary Tabulation should have; although none of these are flagged as mandatory, they are important to consider when designing the Safety Data CRFs and collecting/managing that data. From the ICH Guideline:

System Organ Class (SOC) should organize the tabulation(s), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development program. Although it may appear to be an analytical tool, this section should not serve to provide analyses or conclusions based on the SAEs. In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious, which is one of the reasons having clearly defined terms prior to starting the study is key. MedDRA terminologies, Preferred Term (PT) and SOC, should be in the summary tabulations. The tabulations should include blinded and unblinded clinical trial data and caution should be taken to not unblind data for the specific purpose of preparing the tabulations.
Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report (for example, those that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population.)

The summary tabulations should include all SAEs for the investigational drug, active controls, and placebo.

IV. Safety Signals

According to the WHO (World Health Organization). A signal is "information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment." Signal detection is a critical component of pharmacovigilance. While it is not an area that data management is commonly involved in, it is essential to understand the need to provide data for this effort. "Signal detection is information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" according to CIOMS Working Group 8

(CIOMS 2010). The WHO definition adds that "a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information."

These signals may be identified by data visualization tools, by statistical analysis or by both methods. Signal detection is usually done on a periodic basis during clinical trials. Any potential signals identified should be further explored to validate the signal via statistical methods.

V. Post Market Safety Surveillance

Pre-marketing clinical trials often have limitations in obtaining adequate safety information, with limited population, short duration and narrow indications studied. Post marketing monitoring offers the benefits of comprehensive safety evaluation with its ability to study high risk populations, low frequency reactions (not identified in clinical trials), long term effects, drug-drug/ food interactions, increased severity and/or reporting frequency of known reactions.[10]

When a treatment is being approved by a regulatory agency, the manufacturer may be required to make a post marketing commitment as a condition of approval. If required, the regulatory agency tracks the progress of these studies via regular communications with the company. These studies may target specific populations such as pediatrics or they may be conducted to further explore known risks or to assess potential signals of serious risk.

The first system to track adverse events post approval was the Yellow Card scheme in the UK in 1964.[11] This was followed by WHO starting the VigiBase, which collects adverse event reports now from around the world and is managed by the Uppsala Monitoring Center. The FDA's Adverse Event Reporting System (FAERS) started in 1969 and the Vaccine Adverse Reporting System (VAERS) in 1990, which is jointly managed by the FDA and the CDC. (Sonawane, 2018). Most Regulatory agencies around the world either have their own reporting or work with the VigiBase System managed by the Uppsala Monitoring Center (UMC) and the World Health Organization. These systems rely on manufacturers, health professionals, and consumers to report events to detect unusual or unexpected events to the agencies.[12, 13]

Recommended Standard Operating Procedures

- Design of Data Collection Instruments
- Coding of Adverse Events
- Maintenance of Coding Dictionaries
- Reconciliation of Serious AEs in SAE Database with Clinical Trial Database
- Management of AE Analysis File
- Management of Laboratory Data and Normal Ranges
- Preparing Integrated Summaries of Safety Data

10) Regulations Guidance and Standards

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12) Chapter Revision History

Date	Revision description
September 2000	Initial publication.
May 2007	Revised for style, grammar, and clarity. Substance of chapter content unchanged.
January 2022	Content updated and organization of material revised. Revised for style, clarity, and format.
August 2023	Content refreshed updated to latest information. New information about the DSUR, signal detection and AEs of special interest. Removed some text that was covered in other chapters Added some information about SAE differences with medical device studies.