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Overview of ICH Guidelines

PALS
Pharma Academy of Learning and Sharing

Agenda

- ICH E2B
- ICH E3
- ICH E9
- ICH M2
- ICH M4

ICH E2B (R2)

MAINTENANCE OF THE ICH GUIDELINE ON CLINICAL SAFETY DATA MANAGEMENT : DATA ELEMENTS FOR TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS

ICH - E2B

Objectives

- Standardize the data elements for transmission of individual case safety reports
- Identify and define the data elements for the transmission of all types of individual case safety reports, regardless of source and destination

ICH - E2B

- Includes case safety reports for
  - ✓ pre and post approval periods
  - ✓ adverse drug reaction and adverse event reports.
- Not used for cases in the integrated safety summary of a marketing license application dossier.
- For adverse reactions, used only for subject expedited reporting

ICH - E2B

Individual case safety reports need to be transmitted

- from identified reporting sources to regulatory authorities and pharmaceutical companies
- between regulatory authorities
- between pharmaceutical companies and regulatory authorities
- within authorities or pharmaceutical companies
- from clinical investigators, via the sponsor, to ethics committees
- from authorities to the World Health Organization (WHO) Collaborating Center for International Drug Monitoring.

ICH - E2B

- Currently in paper-based formats (e.g., yellow cards, CIOMS forms, MedWatch, …) or electronic media (e.g. within pharmaceutical companies, or with WHO), usually by on-line access, tape or file transfer
- Structured data are strongly recommended in electronic transmission
- Electronic transmission implemented with MedDRA, where applicable.
- When MedDRA terms are used, the version number should be provided.

ICH - E2B

- The format includes provisions for transmitting all the relevant data elements useful to assess an individual adverse drug reaction or adverse event report.
- The data elements are sufficiently comprehensive to cover complex reports from most sources, different data sets, and transmission situations or requirements.
- Unknown data elements are not included in the transmission.

ICH - E2B

Minimum information for transmission of a report includes

- ✓ at least one identifiable patient (Section B.1)
  -e.g., initials, age, sex

- ✓ one identifiable reporter (Section A.2)
  -e.g., initials, address, qualification
  -patient and reporter can be the same individual

- ✓ one reaction/event (Section B.2)

- ✓ one suspect drug (Section B.4)

ICH - E2B

Administrative information includes:

- ✓ the sender's (case) safety report unique identifier (A.1.0.1)
- ✓ the date of receipt of the most recent information (A.1.7)
- ✓ the worldwide unique case identification number (A.1.10)
- ✓ the sender identifier (A.3.1.2).

Content of the Data Elements

A: Administrative and Identification Information

- A.1 - Identification of the case safety report
- A.2 - Primary source(s) of information
- A.3 - Information on sender and receiver of case safety report

ICH - E2B

Content of the Data Elements Continued

B: Information on the Case:

- B.1 - Patient characteristics
- B.2 - Reaction(s)/event(s)
- B.3 - Results of tests and procedures relevant to the investigation of the patient
- B.4 - Drug(s) information
- B.5 - Narrative case summary and further information

ICH E3

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

ICH – E3

Definition

The clinical study report is an "integrated" full report of an individual study of any therapeutic, prophylactic or diagnostic agent (referred to herein as drug or treatment) conducted in patients, in which the clinical and statistical description, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output etc.

ICH – E3

In brief the CSR is the final deliverable from a clinical trial. It is:

- A comprehensive, integrated summary of the study procedures and results

Objectives

- to allow the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions

- to assist sponsors in the development of a report that is complete, free from ambiguity, well organised, and easy to review

ICH – E3

Structure and Content

- Synopsis – summary of the report
- Introduction, rationale and discussion of study design
- Description of all assessments and any changes from protocol
- Description of statistical methods
- Presentation of all results in tables and text
- Discussion and conclusions
- Patient narratives
- Tables and figures
- Appendices (administrative information/documents /listings of all patient data)

ICH – E3

- The CSR Model Report contains:
  - Non-data (protocol/statistical analysis plan) dependent sections
  - Outline of data dependent sections
- Is prepared prior to database lock
- Appendices of the CSR consist of:
  - Informational appendices (list of investigators, list of IRB approvals, copy of the protocol, etc)
  - Data appendices (statistical tables and listings)

ICH – E3

The report should provide

- a clear explanation of how the critical design features of the study were chosen and enough information on the plan, methods and conduct of the study so that there is no ambiguity in how the study was carried out

- enough individual patient data, including the demographic and baseline data, and details of analytical methods, to allow replication of the critical analyses when authorities wish to do so

- all analyses, tables, and figures carry, in text or as part of the table, clear identification of the set of patients from which they were generated

ICH – E3

- The full integrated report should include the most detailed discussion of individual adverse events or laboratory abnormalities.
- Depending on the nature and importance of studies, a less detailed report might be appropriate.
- Data listings that are part of the report should be readily usable by the reviewer.
- Data should be presented in the report at different levels of detail.

ICH – E3

- Detailed explanations should be provided as to how such values were estimated or derived and what underlying assumptions were made.
- Some data in the appendices are specific requirements of individual regulatory authorities and should be submitted as appropriate.
- The numbering should then be adapted accordingly.

ICH – E3

List of Appendices

- ✓ Appendix 16.1.1 Protocol and protocol amendments
- ✓ Appendix 16.1.2 Sample case report form
- ✓ Appendix 16.1.3 List of IECs/IRBs and sample informed consent forms
- ✓ Appendix 16.1.4 List of Investigators and CVs
- ✓ Appendix 16.1.5 Signature of principal investigator or sponsor's responsible medical officer
- ✓ Appendix 16.1.6 Study drug batch information
- ✓ Appendix 16.1.7 Randomization schedule
- ✓ Appendix 16.1.8 Audit certificates (if applicable)

ICH – E3

List of Appendices Continued

- ✓ Appendix 16.1.9 Statistical Analysis Plan
- ✓ Appendix 16.1.10 Laboratory certifications and lab normal ranges
- ✓ Appendix 16.1.11 Publications based on the study (if applicable)
- ✓ Appendix 16.1.12 Important publications referenced in the report (if applicable)

Narratives

- Patient narratives included in the CSR are for patients who experienced a serious adverse event (SAE), which includes deaths, and/or patients who discontinued from the study due to an adverse event
- Patient narratives are different from SAE narratives prepared by Drug Safety (Pharmacovigilance)

ICH E9

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH – E9

Objectives

- to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

- to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product

- to assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development

ICH – E9

- Describes essential considerations on the design and analysis of clinical trials, especially the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness.

- The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial.

ICH – E9

Considerations for Clinical Development

- Trial Context

  - development plan , confirmatory trial , exploratory trial

- Scope of Trials

  - population , primary and secondary variables , composite variables , global assessment variables , multiple primary variables, surrogate variables, categorised variables

- Design Techniques to Avoid Bias

  - blinding, randomisation

ICH – E9

Trial Design Considerations

- Design Configuration

  - parallel group design, crossover design, factorial designs, multicentre trials

- Type of Comparison

  - trials to show superiority , trials to show equivalence or non-inferiority, trials to show dose-response relationship

- Group Sequential Designs

- Sample Size

- Data Capture and Processing

ICH – E9

- **Trial Conduct Considerations**
  - Trial Monitoring and Interim Analysis
  - Changes in Inclusion and Exclusion Criteria
  - Accrual Rates
  - Sample Size Adjustment
  - Interim Analysis and Early Stopping
  - Role of Independent Data Monitoring Committee (IDMC)

ICH – E9

- **Data Analysis Considerations**
  - Prespecification of the Analysis
  - Analysis Sets
    - full analysis set, per protocol set, roles of the different analysis sets
  - Missing Values and Outliers
    - data transformation
  - Estimation, Confidence Intervals and Hypothesis Testing

ICH – E9

- **Data Analysis Considerations Continued**

  - Adjustment of Significance and Confidence Levels
  - Subgroups, Interactions and Covariates
  - Integrity of Data and Computer Software Validity

ICH – E9

- **Evaluation of Safety and Tolerability**
  - Scope of Evaluation
  - Choice of Variables and Data Collection
  - Set of Subjects to be Evaluated and Presentation of Data
  - Statistical Evaluation
  - Integrated Summary

ICH – E9

REPORTING

- Evaluation and Reporting
- Summarising the Clinical Database
  - efficacy data, safety data

ICH M2 (R2)

ELECTRONIC TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS MESSAGE SPECIFICATION (ICH ICSR DTD VERSION 2.1)

ICH – M2

Objective

- To facilitate the standardisation of the data elements for the transmission of ICSRs for both pre-approval and post-approval reporting periods

ICH – M2

- Need for an electronic format capable of accommodating the electronic transmission of the Safety Reports that can be directly generated and processed by a database application

- Successful electronic transmission of ICSRs relies on the agreement of common data elements and on the syntactical definition of the electronic message

ICH – M2

- **This document describes the specification of the message definition for the electronic transmission of ICSRs agreed by ICH M2.**
- **Refer to ICH E2B**

ICH M4

Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use

ICH – M4

OBJECTIVE

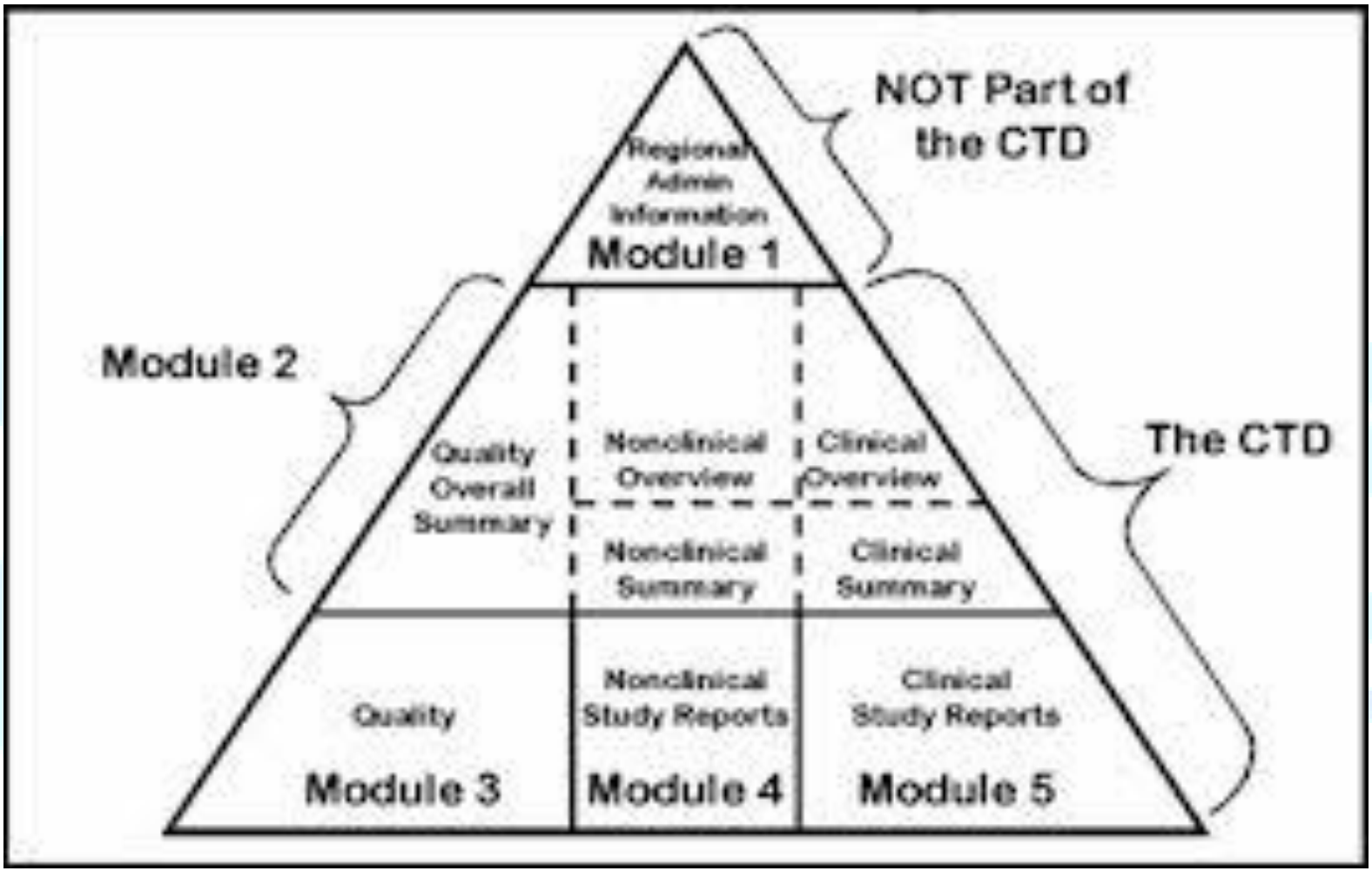
- Common format for preparation of a well-structured Common Technical Document (CTD) for applications submitted to regulatory authorities
- Reduces time and resources needed to compile applications and eases preparation of electronic submissions
- Regulatory reviews and communication with the applicant facilitated by a standard document of common elements
- Simplifies exchange of regulatory information

ICH – M4

- This guideline primarily addresses the organisation of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products).

- The display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.

ICH – M4


NOT Part of the CTD
Regional Admin Information
Module 1
Module 2
Quality Overall Summary
Nonclinical Overview
Clinical Overview
Nonclinical Summary
Clinical Summary
The CTD
Quality
Nonclinical Study Reports
Clinical Study Reports
Module 3
Module 4
Module 5

ICH – M4

ORGANISATION OF THE COMMON TECHNICAL DOCUMENT

- ✓ Module 1 is region specific
- ✓ Modules 2, 3, 4, and 5 are intended to be common for all regions

- ➢ **Module 1: Administrative Information and Prescribing Information**
  - Table of Contents of the submission including Module 1
  - Documents specific to each region (e.g., application forms, prescribing information)

ICH – M4

Module 2: Common Technical Document Summaries

- Common Technical Document Table of Contents (Modules 2-5)
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
  - Pharmacology
  - Pharmacokinetics
  - Toxicology

ICH – M4

Module 2: Common Technical Document Summaries Continued

- Clinical Summary
  - Biopharmaceutic Studies and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Literature References
  - Synopses of Individual Studies

ICH – M4

- **Module 3: Quality**
  - Table of Contents of Module 3
  - Body of Data
  - Literature References
- **Module 4: Nonclinical Study Reports**
  - Table of Contents of Module 4
  - Study Reports
  - Literature References

ICH – M4

- **Module 5: Clinical Study Reports**
  - Table of Contents of Module 5
  - Tabular Listing of All Clinical Studies
  - Clinical Study Reports
  - Literature References

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Thank You!

For any feedback/comment/clarification please contact us at PALS@tcs.com

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