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ICH E-3 Guidelines and Clinical Study Report Writing

PALS
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Agenda

- Overview
- Key Features
- Opportunity in CSR
- Emphasis
- Exceptions
- Walk-through the ICH E3 CSR Structure

Overview

- Developed by ICH Expert Working Group
- Applicable to European Union, Japan and USA
- Aim: to develop a CSR that is complete, free from ambiguity, well organized and easy to review
- Provides guidance for structure and content of CSRs, and appendices organization
- Aligned with the requirements of Common Technical Documents (CTD), particularly electronic CTD (eCTD)
- Allows flexibility for better representation of study results
- Covers therapeutic, prophylactic or diagnostic agent (referred to herein as drug or treatment) studies conducted in humans
- Does not cover exploratory, and pharmacokinetic studies, and studies with combination products, thereby needs adjustments

Key Features of a complete CSR (1-16)

- Clinical description
- Clearly explains study design, methods, and study conduct
- Statistical description, and analyses
- Results
- Data outputs: key tables and figures into the main text of the report, and other at the end of the text, allowing replication
- Appendices:
  - Protocol and sample case report forms
  - Investigator related information
  - Information related to the test drugs/investigational products
  - Technical statistical documentation and outputs
  - Related publications
  - Patient data listings

Opportunity

- Chance to explain any differences/discrepancies
  - Explain and clarify study features that were not well described in protocol
  - Changes/differences from actual protocol: deviations and violations
- Changes or updates to planned statistical analyses such as interim analyses, post-hoc and/or exploratory analyses
- Chance to explain safety events in detail
- Chance to explain study population characteristics
- Chance to explain any advancements in techniques etc. during the study period

Data: what to emphasize

- Demographic and other potentially predictive characteristics of the study population
- Study sub-groups, and effect and impact
- Summarize overall data, add details to key findings, and safety findings
- Interpret the results in view of available data
- Add explanations for data transformation, and its impact
- Explain assumptions, and derived data sets
- Simplify complicated statistical outputs
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Exceptions

- Abbreviated reports
  - Uncontrolled studies, studies not designed to establish efficacy, seriously flawed or aborted studies
  - Include summarized efficacy results, if applicable but full safety reporting
  - Enough detail of design and results to allow the regulatory authority to determine whether a full report is needed
  - In doubt: consult the regulatory authority.
- Post-authorization Safety Studies
  - May have a slightly different format
  - Includes full safety and available efficacy data, as appropriate

A walk through CSR structure

WHAT DOES ICH E3 SUGGESTS

1. Title Page

- Study title, name of investigational product, indication studied
- Study design, study phase
- Sponsor
- Protocol identification (code or number)
- Study initiation date (first patient enrolled, or any other verifiable definition), date of early study termination, if any, and study completion date (last patient completed)
- Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer
- CSR signatory, and their complete address
- Compliance statement (ICH, GCP)
- Date of the report

Synopsis, ToC, and List of Abbreviations (2-4)

- 2. Synopsis
  - 1-3 pages
  - Brief discussion of methods
  - Include data along with p-values for key results
  - Stand-alone, and should not refer to any of other CSR sections.
  - Include investigators, number of sites, date of report
- 3. Table of Contents
  - Page numbers
  - List and locations of appendices, tabulations and CRFs
- 4. List of Abbreviations

5. Ethics

- 5.1 IRB/IEC
  - Indicate study and any amendments review by an Independent Ethics Committee or Institutional Review Board.
  - List of all IECs or IRBs in Appendix 16.1.3
- 5.2 Ethical Conduct
  - In accordance with the ethical principles that have their origins in the Declaration of Helsinki
- 5.3 Patient Information and Consent
  - Methods for the same
  - Sample consent form in Appendix 16.1.3

6. Investigators and Study Administrative Structure

- Principal and coordinating investigator (compleet
- Steering committee
- Administration, monitoring and evaluation committees
- Statistician
- Central laboratory facilities
- Contract research organization (CRO)
- Clinical trial supply management
- Appendix 16.1.4: a list of the investigators with their affiliations, their role in the study and their qualifications (curriculum vitae or equivalent), and other persons whose participation materially affected the conduct of the study
- Appendix 16.1.5: Principal Investigator/Sponsor's responsible Medical Office (multiple PIs)

Introduction and Objectives (7 and 8)

- 7. Introduction
  - Context of the development of the test drug/investigational product, relating the critical features of the study
  - Any guidelines
- 8. Objectives
  - As in protocol
  - Also add if there were additional objective (post-hoc) or explanatory that were not covered in statistical analysis plan or a protocol version

9. Investigational Plan

- 9.1 Overall Study Design and Plan
- 9.2 Discussion of Study Design, including the choice of Control Groups
- Clearly present study design in-line with the one actually used vs. originally planned
- Study visits can be omitted
- Refer to Appendix 16.1.1 (protocol and amendments), and Appendix 16.1.2 (sample CRF)
- Include
  - Population and treatments, and controls
  - Allocation, blinding, masking, assessors
  - Treatment and withdrawal periods
  - Add a flowchart
  - Interim analysis

9. Investigational Plan

- 9.3 Study Population
  - 9.3.1 Inclusion Criteria
  - 9.3.2 Exclusion Criteria
- 9.3.3 Removal of Patients from Therapy or Assessment
- 9.4 Study Treatments
  - 9.4.1 Treatments Administered
  - 9.4.2 Identity of Investigational Product(s)
  - 9.4.3 Method of Assigning Patients to Treatment Groups
  - 9.4.4 Selection of Doses in the Study
  - 9.4.5 Selection and Timing of Dose for each Patient
  - 9.4.6 Blinding
  - 9.4.7 Prior and Concomitant Therapy
  - 9.4.8 Treatment Compliance

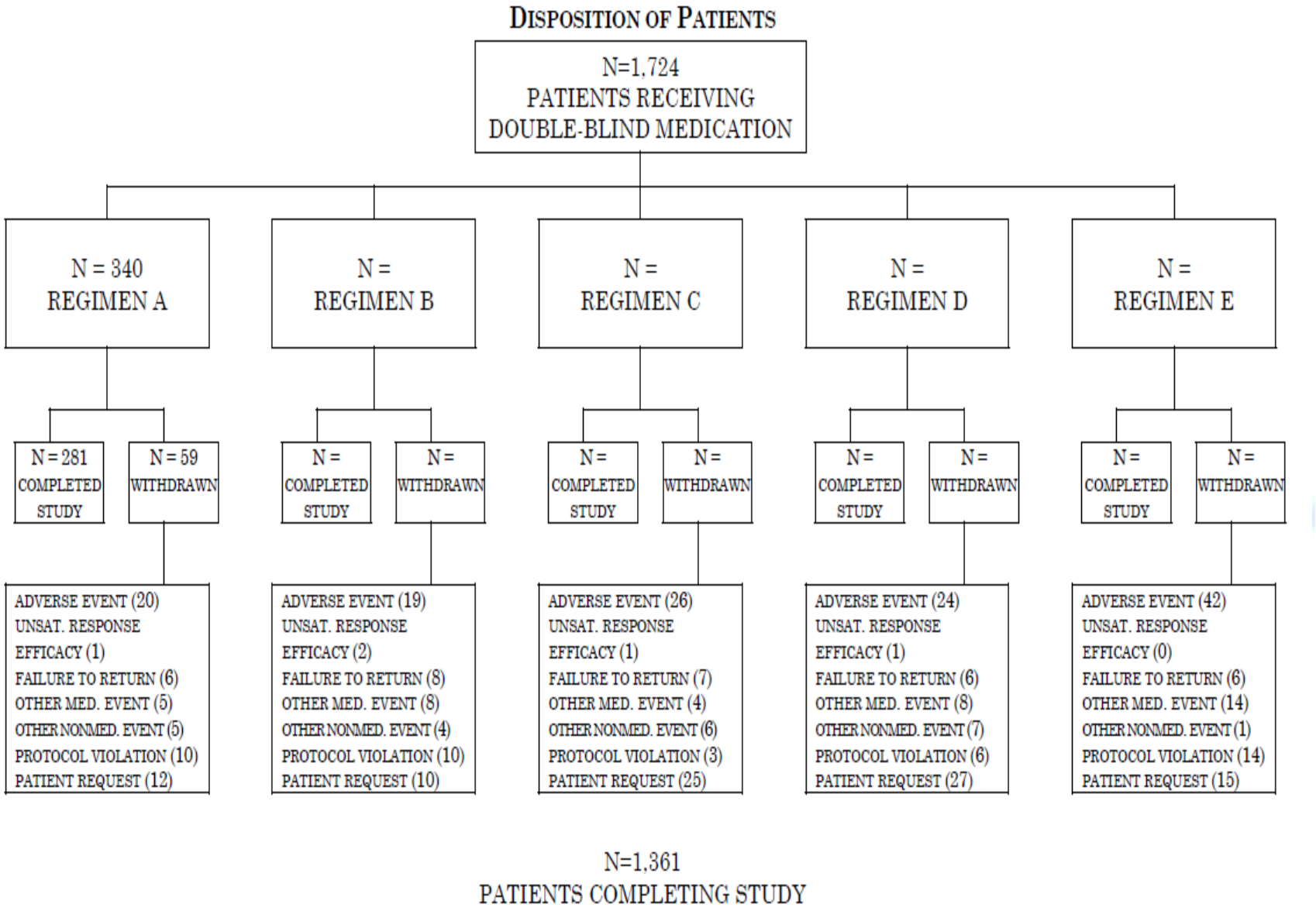
9. Investigational Plan

- 9.5 Efficacy and Safety Variables
  - 9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart
  - 9.5.2 Appropriateness of Measurements
  - 9.5.3 Primary Efficacy Variable(s)
  - 9.5.4 Drug Concentration Measurements
- 9.6 Data Quality Assurance
- 9.7 Statistical Methods Planned in the Protocol and Sample Size Determination
  - 9.7.1 Statistical and Analytical Plans
  - 9.7.2 Determination of Sample Size
- 9.8 Changes in the Conduct of the Study or Planned Analysis

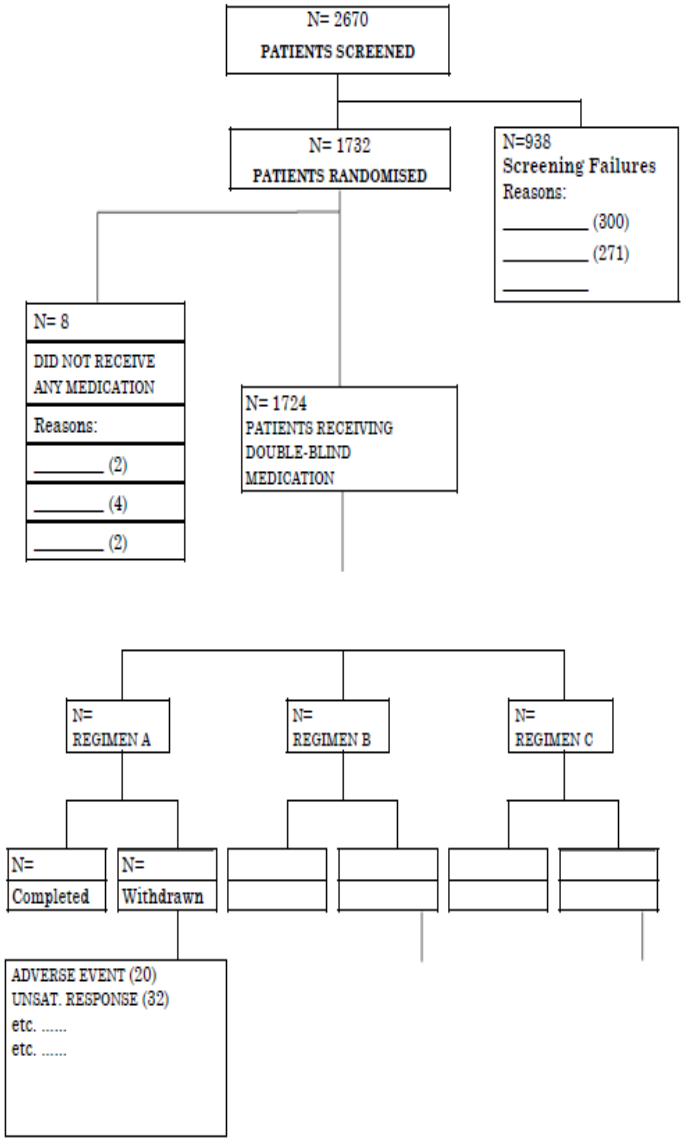
Study Subjects, Efficacy Evaluation (10 & 11)

- 10 Study Subjects
  - 10.1 Subject Disposition
  - 10.2 Protocol Deviations
- 11 Efficacy Evaluation
  - 11.1 Data Sets Analyzed
  - 11.2 Demographics and Other Baseline Characteristics
  - 11.3 Measurement of Treatment Compliance
  - 11.4 Efficacy Results and Tabulations of Individual Subject Data
    - 11.4.1 Analysis of Efficacy
    - 11.4.2 Statistical/Analytical Issues
    - 11.4.3 Tabulation of Individual Response Data
    - 11.4.4 Drug Dose, Drug Concentration, and Relationships to Response
    - 11.4.5 Drug-Drug and Drug-Disease Interactions
    - 11.4.6 By-Patient Displays
    - 11.4.7 Efficacy Conclusions

Sample Patient Disposition Chart



Sample Patient Disposition Chart: CONSORT



12. Safety Evaluation

- 12.1 Extent of Exposure
- 12.2 Adverse Events
  - 12.2.1 Brief Summary of Adverse Events
  - 12.2.2 Display of Adverse Events
  - 12.2.3 Analysis of Adverse Events
  - 12.2.4 Listing of Adverse Events by Patient
- 12.3 Deaths, Other SAEs, and Other Significant AE
  - 12.3.1 Listing of Deaths, other SAEs, and Other Significant AEs
    - 12.3.1.1 Deaths
    - 12.3.1.2 Other Serious Adverse Events
    - 12.3.1.3 Other Significant Adverse Events

12. Safety Evaluation

- 12.3.2 Narratives of Deaths, Other SAEs, and Certain Other Significant AEs
- 12.3.3 Analysis and Discussion of Deaths, Other SAEs and Other Significant AEs

- 12.4 Clinical Laboratory Evaluation
  - 12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)
  - 12.4.2 Evaluation of Each Laboratory Parameter
    - 12.4.2.1 Laboratory Values Over Time
    - 12.4.2.2 Individual Patient Changes
    - 12.4.2.3 Individual Clinically Significant Abnormalities
- 12.5 Vital Signs, Physical Findings, and Other Safety Observations
- 12.6 Safety Conclusions

13. Discussion

- The efficacy and safety results briefly summarized and discussed
- Do not introduce new results
- Identify any new or unexpected findings, comment on their significance and discuss any potential problems
- Clinical relevance and importance of the results should be discussed in the light of other existing data
- Specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies, if any

Sections 14-16

- 14 TFGs Referred to but not included in Text
  - 14.1 Demographic Data
  - 14.2 Efficacy Data
  - 14.3 Safety Data
- 15. Reference List
- 16. Appendices
  - 16.1 Study Information
  - 16.2 Patient Data Listings
  - 16.3 CRFs
  - 16.4 Individual Patient Data Listings

16.1 Study Information

- 16.1.1 Protocol and protocol amendments
- 16.1.2 Sample case report form (unique pages only)
- 16.1.3 List of IECs or IRBs, information for patient and sample consent forms
- 16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience
- 16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement
- 16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
- 16.1.7 Randomization scheme and codes
- 16.1.8 Audit certificates (if available)
- 16.1.9 Documentation of statistical methods
- 16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used
- 16.1.11 Publications based on the study
- 16.1.12 Important publications referenced in the report

16.2 Patient Data Listings

- 16.2.1 Discontinued patients
- 16.2.2 Protocol deviations
- 16.2.3 Patients excluded from the efficacy analysis
- 16.2.4 Demographic data
- 16.2.5 Compliance and/or drug concentration data (if available)
- 16.2.6 Individual efficacy response data
- 16.2.7 Adverse event listings (each patient)
- 16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities

Appendices: additional

- Appendices already available in TMF (in accordance with E6) or CTD-based regulatory submission (in accordance with M4) should be referenced accordingly
- It is acceptable to add any new appendices if needed, e.g. biomarkers, device details etc.

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Thank You!

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

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Change/Revision History

Revision Description	Slide No.	Rationale for the Change	Change type (Add/Modify/Delete)	Modified By	Date Modified (DD-Mmm-YYYY)
Initial Release	NA	NA	NA	NA	Na