Seven Steps for Statistical Success in Clinical Trials Good Clinical Practice Guidelines (Part 1)

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Course Objective

- Statisticians around the world, working on the planning, conduct and analysis of clinical trials, need to be aware of the many guidance documents to ensure they are providing high quality work to international standards
- The objective of this training is to introduce, refresh or update your knowledge of ICH and other International Guidance

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Agenda

Introduction

ICH Framework

1. ICH E6 (R2) GCP
2. ICH E9 Biostatistics
3. ICH E9 (R1) Estimands
4. ICH E10 Control Groups
5. ICH E17 Multi-Regional Trials
6. Additional Guidance
7. Adaptive Trials Guidance

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International Council for Harmonization

ICH
harmonisation for better health

Inception in 1990

ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.

www.ich.org

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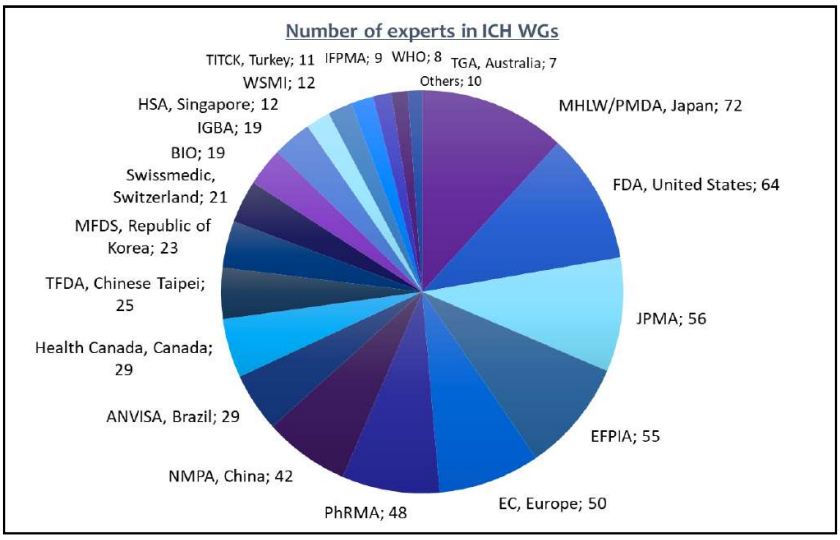
ICH Experts – May 2019



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ICH Guidelines

Quality Guidelines

Efficacy Guidelines

Safety Guidelines

Multidisciplinary Guidelines

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Development Steps for ICH Guidelines

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ICH "E"-Family Guidelines

E1	Clinical Safety in Long Term Treatment	1994	E11	Clinical Trials in Pediatric Populations	2017R
E2	Pharmacovigilance	1994R	E12	Clinical Evaluations by Therapeutic Category	2000
E3	Clinical Study Report	2012	E13		
E4	Dose Response Studies	1994	E14	Clinical Evaluation of QT	2015
E5	Ethnic Factors	2006	E15	Definitions in Pharmacogenetics /Pharmacogenomics	2007
E6	Good Clinical Practice	2016	E16	Qualification of Genomic Biomarkers	2010
E7	Clinical Trials in Geriatric Populations	2010	E17	Multiregional Clinical Trials	2017
E8	General Considerations for Clinical Trials	1997	E18	Genomic Sampling	2017
E9	Statistical Principles for Clinical Trials	2019	E19	Safety Data Collection	2019
E10	Choice of Control Group in CT	2000	E20	Adaptive Clinical Trials	2023

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E6 Good Clinical Practice

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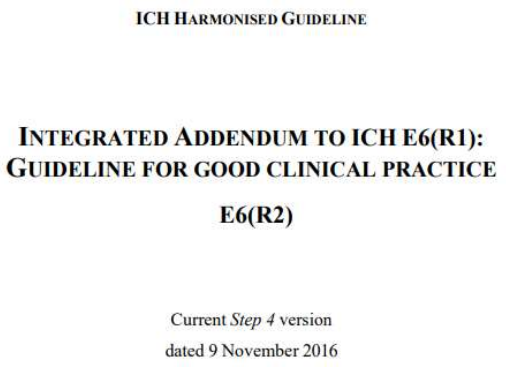
Structure of E6(R2) Document



ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version
dated 9 November 2016

Sections

Glossary
Principles
IRB/IEC
Investigator
Sponsor
Protocols and Amendments
Investigators Brochure
Essential Documents

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E6 Principles

1. Clinical trials should be conducted in accordance with the **ethical principles** that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).	6. A trial should be conducted in compliance with the protocol that has received **prior institutional review board (IRB)/independent ethics committee (IEC) approval**/favourable opinion.
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the **anticipated benefits justify the risks**.	7. The medical care given to, and medical decisions made on behalf of, subjects should always be the **responsibility of a qualified physician** or, when appropriate, of a qualified dentist.
3. The **rights, safety, and well-being of the trial subjects** are the most important considerations and should prevail over interests of science and society.	8. Each individual involved in conducting a trial should be **qualified by education, training, and experience** to perform his or her respective task(s).
4. Clinical trials should be **scientifically sound, and described in a clear, detailed protocol**.	9. **Freely given informed consent** should be obtained from every subject prior to clinical trial participation.
5. The available nonclinical and clinical information on an investigational product should be adequate to **support the proposed clinical trial**.	10. All clinical trial **information should be recorded, handled, and stored** in a way that allows its accurate reporting, interpretation and verification.

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E6 Principles (Addendum)

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification…
…**irrespective of the type of media** used.

11. The **confidentiality of records** that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable **good manufacturing practice** (GMP). They should be used in accordance with the approved protocol.

13. **Systems with procedures** that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

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E6 Sponsors

5.0 Quality Management
5.1 QA/QC
5.2 CRO
5.3 Medical Expertise
5.4 Trial Design
5.5 Trial Management, Data handling and Record Keeping
5.6 Investigator Selection
5.7 Allocation of Responsibilities
5.8 Compensation to Subject and Investigators
5.9 Financing
5.10 Notification to Regulatory Authorities
5.11 Conformation of Review by IRB/IEC
5.12 Information on IP
5.13 Manufacturing, Packaging, Labelling and Coding IP
5.14 Supply and Handling if IP
5.15 Record Access
5.16 Safety Information
5.17 ADR Reporting
5.18 Monitoring
5.19 Audit
5.20 Non-Compliance
5.21 Premature termination or Suspension of Trials
5.22 Clinical Trial Reports
5.23 Multicentre Trials

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E6 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

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E6 Trial Management, Data Handling and Record Keeping

Electronic Data Handling

System validated for completeness, accuracy and reliability

Maintain SOPs

Audit trail data changes

Prevents unauthorized access

List of staff authorized to make data changes

Backup system

Safeguard of Blinding

Comparisons to source

Record Keeping

Subject ID Codes

Keep Essential Documents

Record Retention

Notification to regulatory bodies

Transfer of data ownership

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E6 Clinical Trial Protocols and Amendments

6.1 General Information
6.2 Background Information
6.3 Trial Objective and Purpose
6.4 Trial Design
6.5 Selection/Withdrawal of Subjects
6.6 Treatment of Subjects
6.7 Assessment of Efficacy
6.8 Assessment of Safety
6.9 Statistics
6.10 Direct Access to Source Data/Documents
6.11 QC and QA
6.12 Ethics
6.13 Data Handling and Record keeping
6.14 Financing and Insurance
6.15 Publication Policy
6.16 Supplements

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E6 Protocol: Trial Design

6.41. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.	6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.	6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any
6.4.3 A description of the measures taken to minimize/avoid bias, including: (a) Randomization. (b) Blinding.	6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.
6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).	6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.
6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.	www.spirit-statement.org www.transceleratebiopharmainc.com

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E6 Protocol: Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).	6.9.5 Procedure for accounting for missing, unused, and spurious data.
6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.	6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
6.9.3 The level of significance to be used.	6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).
6.9.4 Criteria for the termination of the trial.	

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E9 Biostatistics

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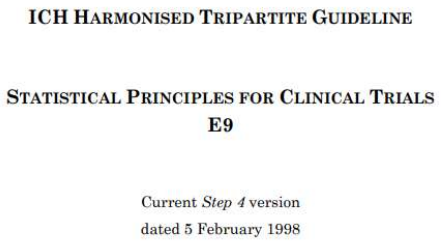
Structure of E9 Document



ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998

Section

1. Introduction
2. Overall Clinical Development
3. Trial Design
4. Trial Conduct
5. Data Analysis
6. Evaluation of Safety and Tolerability
7. Reporting
8. Glossary

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E9 Overall Clinical Development

Primary and Secondary Variables

- Primary variable
- Secondary variables
- Composite variables
- Global assessment variables
- Multiple primary variables
  - using more than 1 primary variable
  - identify if all variables are required to be significant, or just one
  - address type I error, if required
- Surrogate variables
- Categorised variables

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E9 Overall Clinical Development

Design Techniques to Avoid Bias

Blinding
- double blind is the standard
- if some sponsor staff must know, SOPs should guard against inappropriate dissemination of treatment codes

Breaking the blind for an individual
- only needed if the knowledge of the treatment code will alter further rescue treatment

Unblinding a study

Randomization
- randomisation schedule should be reproducible and secure
- using > 2 or 3 stratification factors is rarely necessary
- stratification factors should be taken account of in analysis
- allocation of treatment to patient can be complicated
- emergency access to treatment code must be provided
- dynamic allocation is possible, but must not be deterministic

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E9 Trial Design

Multicentre Trials

Enables large trials and improves generalisation

Strong protocol defined standards and assessments

Design
- mostly defined by investigator, not location
- stratify randomisation by centre if not many small centres
- primary analysis reflects randomisation
- combination rules must be pre-specified

Analysis
- check for heterogeneity among centres (graphical methods, treatment x centre interaction test)
- if real heterogeneity exists, interpreting main treatment effect is difficult

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E9 Trial Design

Types of Comparison

Superiority
- trials to show treatments differ (i.e. are better)
- comparison against placebo or active control

Equivalence or Non-Inferiority
- trials to show similarity between treatments, (equivalence) or that treatment is "at least as good as" another (non-inferiority)
- comparison against active control, may need additional placebo control

Dose Response
- investigates the shape and location of dose-response curve
- starting dose, strategies for dose adjustment, maximal dose
- include zero dose
- CIs and graphical methods are as important as testing

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E9 Trial Design

Sample Size

Aim
- to be large enough to provide a reliable answer to the questions addressed by the primary objective

In the protocol, specify
- primary variable, test statistic, null and alternative hypothesis, type I error, power, method for dealing with withdrawals and protocol violations
- estimates of other quantities needed (e.g. variance, control group response rate)
- difference to be detected, or equivalence/non-inferiority margin

Investigate sensitivity of sample size to assumptions

Sample size re-estimation is possible

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E9 Trial Conduct

Interim Analysis and Early Stopping

Interim analyses
- Planned: specified in the protocol
- Unplanned: protocol amendment before interim analysis

Reasons
- stop for efficacy, futility, or safety

Protocol
- schedule of analyses, stopping guidelines and properties
- protection of type I error

Process
- completely confidential, possibly with an independent DMC

Unplanned interim analyses should be avoided

E9 Trial Conduct

Independent DMCs

Written procedures (DMC Charter)
- to include control of dissemination of results

Maintain records of meetings
- interim results
- meeting minutes
- available for review after trial completion

Membership
- clinical trial scientists, statisticians

E9 Data Analysis

Pre-specification of Analysis

Principle features described in the protocol

- proposed confirmatory analysis of primary variable
- how anticipated analysis problems will be handled

Statistical analysis plan

- written after finalising protocol
- detailed procedures for analysis of primary, secondary and other data

Blinded review

- SAP reviewed and possibly updated in blinded review
- should be finalised before breaking the blind (and prove it)
- only results envisaged in the protocol (+ amendments) can be regarded as confirmatory.

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E9 Data Analysis

Analysis Sets

Full Analysis Set (FAS)

Per Protocol Set (PPS)

Roles of different analysis sets

- advantageous to show lack of sensitivity of principal results to choice of analysis set
- the need to exclude a large proportion of patients from the PPS may throw doubt on overall validity of the trial
- in superiority trials FAS is used as the primary set
- in equivalence or non-inferiority trials, the FAS is not conservative and its role should be considered carefully

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E9 Data Analysis

Estimation, CIs and Testing

The protocol should specify

- hypotheses to be tested
- treatment effects to be estimated (with confidence intervals)
- the methods to accomplish this and the underlying statistical model should be made clear
- any adjustment for baseline data should be detailed

The primary analysis should be clearly identified

All effects to be fitted in the analysis should be fully specified

Two-sided testing is preferred

- one-sided testing using type I error at half the usual two-sided error is allowed

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E9 Data Analysis

Adjusting Significance and Confidence Levels

Multiplicity may arise from multiple

- primary endpoints
- comparisons
- time points

Avoiding or reducing multiplicity is preferred

- specifying a primary endpoint
- specifying a primary comparison
- use of summary measures over time

Adjustment should always be considered or an explanation of why it is not necessary

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E9 Data Analysis

Data Integrity and Software Validation

Credibility of results depends on the quality and validity of the methods and software used for data management and processing the data

- data entry
- storage
- verification
- correction
- retrieval

Data management should be based on thorough and effective SOPs

Computer software should be reliable and testing procedures should be documented

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E9 R1 Estimands

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Structure of E9(R1) Document

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

Section

1. Purpose and scope
2. Framework
3. Estimands
4. Impact on Trial Design and Conduct
5. Impact on Trial Analysis
6. Documenting estimands and sensitivity analyses
7. Glossary

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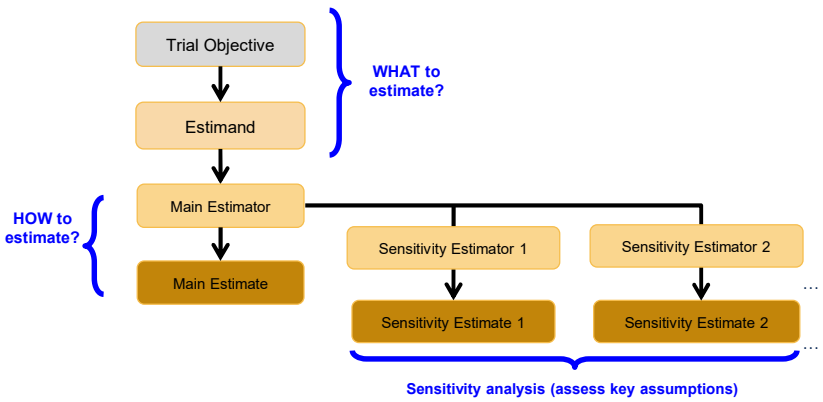
E9(R1) Framework

Estimand Framework



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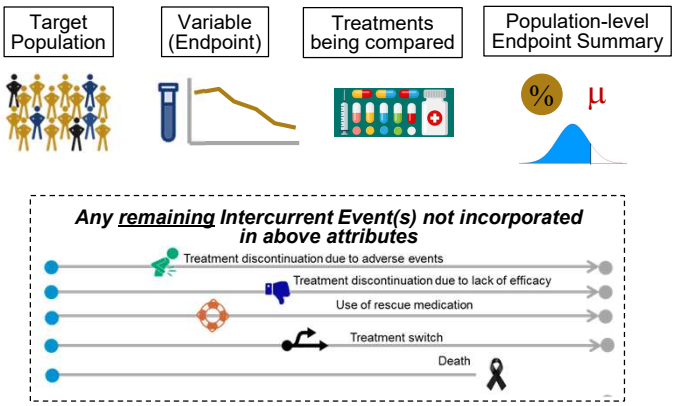
E9(R1) Estimands

Estimand - Definition



Estimand A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

Intercurrent event Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

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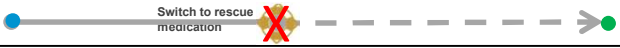
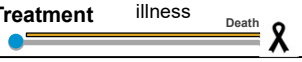
E9(R1) Estimands

Strategies for Addressing Intercurrent Events

Strategy	*Example of Endpoint or Treatment Effect of Interest*
Treatment Policy	Overall survival regardless of whether or when **treatment switching** happens 
Composite	Heart attack **or treatment discontinuation due to AE** 
Hypothetical	Change in HbA1c if **rescue medication** is not used 
Principal Stratum	Infection severity in subpopulation that will **become infected** despite preventive treatment 
While on Treatment	QoL under palliative treatment until **death** in terminal illness 

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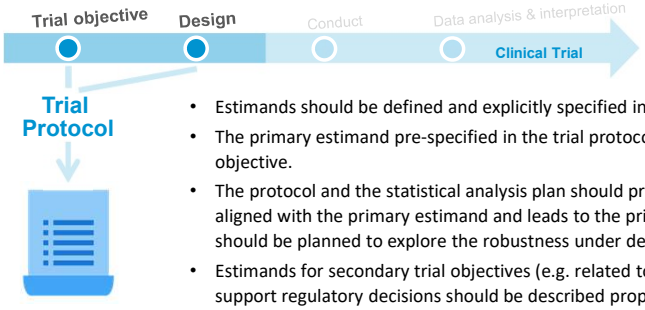
E9(R1) Documenting estimands and sensitivity analysis

Incorporating Estimands in Protocol Writing



- Estimands should be defined and explicitly specified in the clinical trial protocol.
- The primary estimand pre-specified in the trial protocol should correspond to the primary trial objective.
- The protocol and the statistical analysis plan should pre-specify the main estimator that is aligned with the primary estimand and leads to the primary analysis. Suitable sensitivity analysis should be planned to explore the robustness under deviations from its assumptions.
- Estimands for secondary trial objectives (e.g. related to secondary variables) that are likely to support regulatory decisions should be described properly, each with a corresponding main estimator. Suitable sensitivity analysis should be planned.
- Additional trial objectives may be considered for exploratory purposes, leading to additional estimands.
- It is not a regulatory requirement to document in detail an estimand for each exploratory question.

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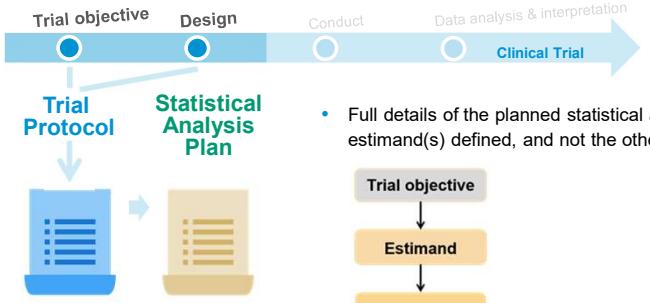
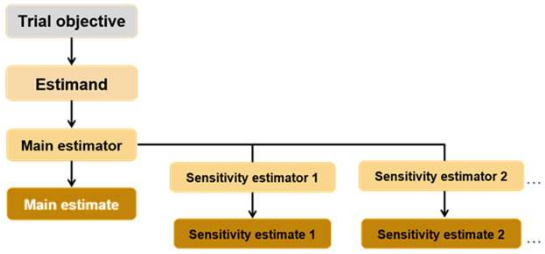
E9(R1) Documenting estimands and sensitivity analysis

Incorporating Estimands in the SAP



- Full details of the planned statistical analyses should align with the estimand(s) defined, and not the other way around!



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E9 (R1) Thinking Process

1	Therapeutic setting and intent of treatment determining a trial objective
2	Identify intercurrent events
3	Discuss strategies to address intercurrent events
4	Construct the estimand(s)
5	Align choices on trial design, data collection and method of estimation
6	Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7	Document the chosen estimands

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E10 Control Groups

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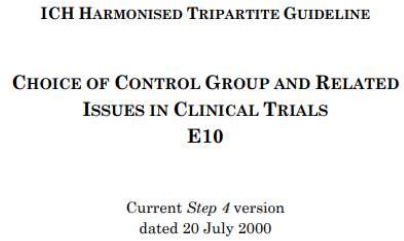
Structure of E10 Document



ICH HARMONISED TRIPARTITE GUIDELINE

CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS
E10

Current *Step 4* version
dated 20 July 2000

Section

1. Introduction
2. Detailed Considerations of Types of Control
3. Choosing the Control Group

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E10 Types of Control

- Placebo concurrent control
- No-treatment concurrent control
- Dose-response concurrent control
- Active concurrent control
- External control (including historical control)
- Multiple control groups

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E10 Choosing the Control Group

Usefulness of Specific Concurrent Control Types in Various Situations

Trial Objective	Type of Control: Placebo	Active Non-Inferiority	Active Superiority	Dose Response (DR)	Placebo + Active	Placebo + DR	Active + DR	Active + Placebo + DR
Measure Absolute Effect Size	Y	N	N	N	Y	Y	N	Y
Show Existence of Effect	Y	P	Y	Y	Y	Y	Y	Y
Show Dose Response Relationship	N	N	N	Y	N	Y	Y	Y
Compare Therapies	N	P	Y	N	Y	N	P	Y

Y= Yes, N=No, P=Possible - depending on historical evidence of sensitivity to drug effects.

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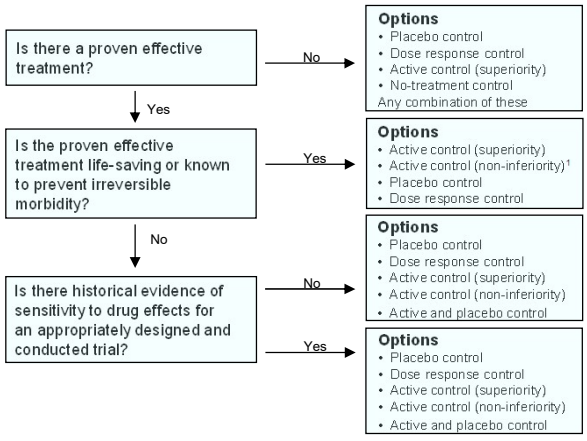
E10 Choosing the Control Group

Choosing the Concurrent Control for Demonstrating Efficacy



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Structure of E17 Document

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

E17

Final version
Adopted on 16 November 2017

Section

1. Introduction
2. General Recommendations
   - Strategy
   - Design and Analysis
3. Glossary

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E17 Principles

- Increases efficiency of drug development
- Identify intrinsic and extrinsic factors early
- Assumption that treatment effect applies to each region
- Prespecification of pooling or subpopulation
- Plan a single primary analysis approach
- Ensure high quality design and conduct to ICH E6
- Gain prior acceptance of approach

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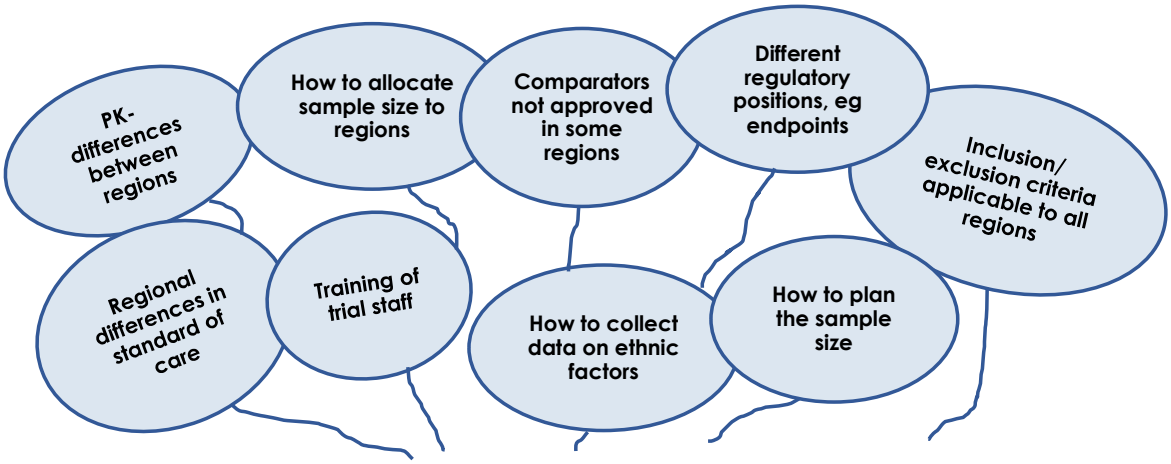
E17 Consideration of Regional Variability



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E17 Sample Size Allocations to Regions

1. **Proportional Allocation** Allocation of subjects to regions in proportion to size of region and disease prevalence.
2. **Equal Allocation** Allocation of equal numbers of subjects to each region.
3. **Preservation of Effect** Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.
4. **Local Significance** Allocation of a sufficient number of subjects to be able to achieve significant results within each region.
5. **Fixed Minimum Number** Allocation of a fixed minimum number of subjects to a region.

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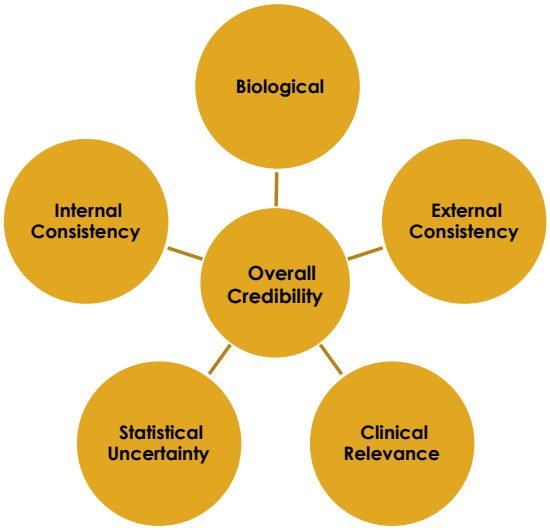
E17 Examination of regional consistency



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E17 Examination of regional consistency

Evaluation of regional consistency is NOT hypothesis testing, but a supportive and/or descriptive investigation, whether prior assumptions hold true.

- Descriptive summaries
- Graphical displays (e.g., forest plots)
- Model-based estimation (including covariate-adjusted analysis)
- Test of treatment-by-region interaction as a method for signal generation

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Agenda

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Seven Steps for Statistical Success in Clinical Trials Good Clinical Practice Guidelines (Part 1)

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Shaping the Future of Drug Development

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