WORKSHOP

ICH E8(R1)
General Considerations For Clinical Studies
Summary of the Revision (Draft)

2019.7.25

Pharmaceuticals and Medical Devices Agency

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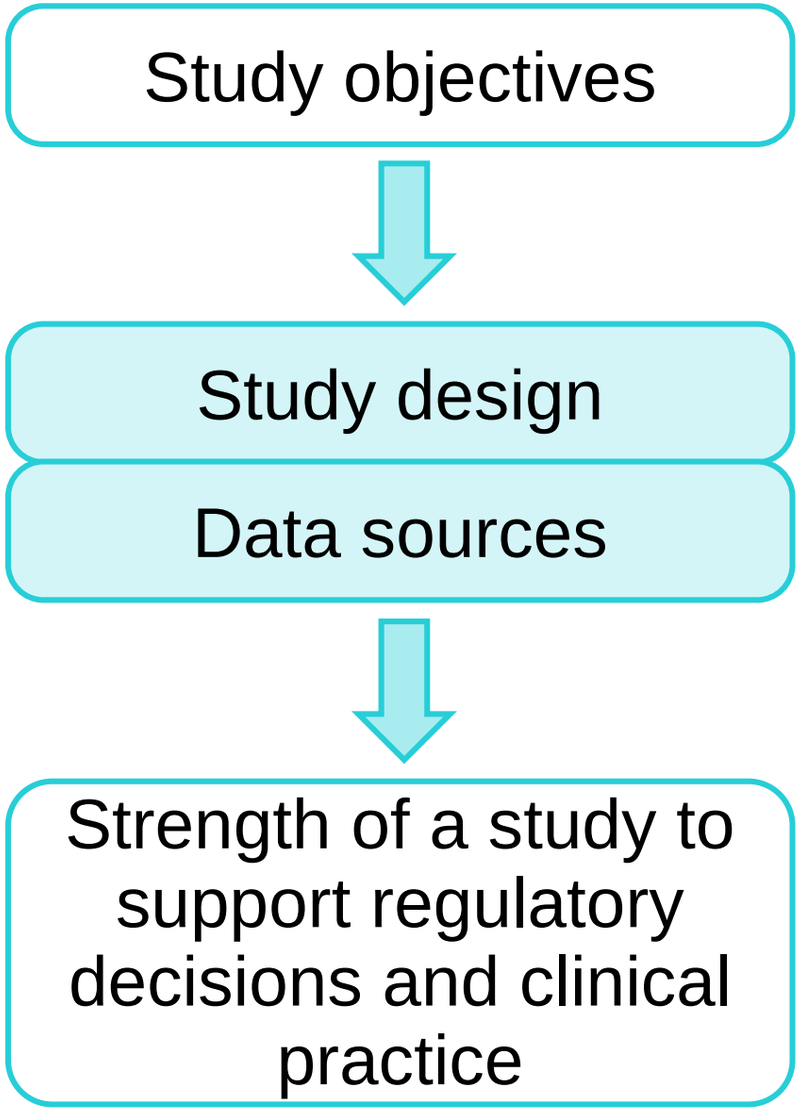
5 Design Elements for Clinical Studies



This section presents important elements that define the design of a clinical study

- Identifying the critical to quality factors
- Enabling flexibility in study design and promoting efficiency in study conduct

The elements outlined here are expected to be relevant to study types and data sources in use in clinical studies now, and that may be developed in the future.

5 Design Elements for Clinical Studies

Study objectives

Clear objectives will help to determine the study design

The process may help to further clarify the objectives

Objectives may need to be modified as practical considerations and limitations are revealed

Study design

Data sources

Strength of a study to support regulatory decisions and clinical practice

This section presents important elements that define the design of a clinical study

- Identifying the critical to quality factors
- Enabling flexibility in study design and promoting efficiency in study conduct

The elements outlined here are expected to be relevant to study types and data sources in use in clinical studies now, and that may be developed in the future.

5 Study Design

Protocol
*should be finalized before the start of the study (ICH E6)

Study objectives

Study type

Fundamental design elements
- Population
- Intervention
- Control group
- Response variable
- methods to reduce or assess bias
- Statistical analysis

Explained in this section

Data sources (5.2)

5.1.1 Study Population

Study Population

- Should be chosen to support the study objectives
- Defined through the inclusion and exclusion criteria for the study
- In practice, the study population is limited to subjects available to participate and for whom consent is available (see ICH E6)

Recruitment efforts should ensure that the study subjects reflect the planned population for the study

If objectives include obtaining information on certain subgroups, then efforts should be made to ensure adequate representation of these subgroups

5.1.1 Study Population

Selection of study population

Definition of study population

- Narrow: Maximize the sensitivity of the study for detecting a certain effect
  - In early phases, tend to be more homogeneous in study population definitions
- Broad: More closely represent the population for which the drug is intended
  - In later phases or post-approval, tend to be more heterogeneous

Recruitment for a precision medicine study

- May target the subgroup of diseased patients with a particular phenotype or genotype, either exclusively or through an enrichment study design

Choice of study population will depend on the study objectives, and the degree to which a study succeeds in recruiting and enrolling the desired population will impact the ability of the study to meet those objectives.

5.1.1 Study Population

Selection of study population

Example: study population representative of clinical practice

- May be the target of a pragmatic trial conducted within an existing healthcare system
- Recruitment procedures may differ from other types of studies, in that the inclusion and exclusion criteria may be assessed based on existing medical records

5.1.1 Study Population

Unit of study population

Because of the study objectives or because of feasibility or efficiency, there may be situations in which the population unit is not an individual but a group of subjects (known as a cluster)

- Some vaccine studies make use of cluster randomisation to measure their protective effects on communities

The use of a cluster unit has implications for multiple design elements and quality factors (e.g., intervention, analysis, consent)

5.1.1 Study Population

Size of study population (number of subjects)

The study should plan to have a sufficient number of subjects to make statistical conclusions based on the findings either by

- obtaining a certain precision
- controlling the probabilities of making false conclusions

(see ICH E9 Statistical Principles for Clinical Trials)

A larger database may be needed to establish the safety of a drug (see ICH E1)

5.1.2 Intervention

Interventional study

- the choice of the study drug and the health management of the subjects are controlled by the study (with proper regard to human subject protection and regulatory requirements)
- often have the potential to control biases better than observational studies (see Section 5.1.5)

Factors for the choice: study objectives, feasibility, data sources, and anticipated biases and uncertainty

Observational study

- The choice of the study drug and the health management of the subjects are merely observed in the study
- Usually conducted in the post-approval period

Varying overlap between interventional and observational studies

Pragmatic trial is a mix of the two types

- Intervention is controlled by the study
- Health management is controlled to a lesser degree

5.1.3 Control Group

Drug effect of interest

- Effect relative to not receiving the drug, or
- Effect relative to receiving other therapies

e.g. Comparisons with placebo, no treatment, active controls or different doses of the drug under investigation

Control group (ICH E10)

To derive the comparisons, information on a group of subjects not receiving the drug or receiving other therapies is usually needed

The choice of a control group may be influenced by the study objectives, ethical considerations, and study feasibility

5.1.3 Control Group

Source of control group data

Internal control group	• All subjects in the study are selected by the same processes • Data are acquired by the same procedures at the same time ⇨ Only differences observed among subjects in the study are due to the treatment they receive
External control group	• Subjects are selected from an external source • Subjects may be treated at an earlier time (historical control group) or during the same time but in another setting than subjects in the study • External control subjects may differ from subjects participating in the study with respect to follow-up and measurement of study outcomes and other data elements • External control subjects may differ from study subjects with respect to some demographic and background characteristics, possibly reflecting a somewhat different subject population ⇨ Should be taken into account in the design and analysis of the study

5.1.3 Control Group

Source of control group data

It may be possible for a single clinical study to use both internal and external control subjects.

Conduct of the study may be facilitated by supplementing the internal control group with additional data on an external control group

In some circumstances, rather than using a separate group of control subjects, subjects may function as their own control receiving the drug and control at different points of time.

- Crossover designs for interventional studies
- Case-crossover designs for non-interventional studies

5.1.3 Control Group

Critical to quality factors

Critical to quality factors that are associated with the choice and use of the control group, including ...

- Study objective
- Availability and quality of control data
- Feasibility of conducting the study
- Ethical considerations
- Comparability between treatment and control populations
- Comparability of outcome ascertainment

5.1.3 Control Group

Critical to quality factors

In case subject level data are not be available for external control groups

- If summary measures are available from the external source, they may be used to form the basis of comparisons with treated subjects to estimate and test hypotheses about drug effects
- However, the critical to quality factor of comparability between treatment groups is unable to be addressed through adjustment for subject-level covariates

In case control data considered adequate to support comparisons are not available

- Responses to treatment observed in the study may be compared to a relevant and justified target value for the control response rate (e.g., tumour response rate in oncology; cure rate for anti-infectives)
- Even in cases where comparable control data are available, an external target value may still be useful in evaluating the response rate observed in the study

5.1.4 Response Variables

Response variable

- Subject-level attribute of interest that may be affected by the drug
- May relate to the pharmacokinetics, pharmacodynamics, efficacy, safety, or use of the drug post-approval including compliance with risk minimisation measures
- Study endpoints = Response variables that are chosen to assess drug effects

5.1.4 Response Variables

Choice of primary endpoint

- The choice of primary endpoint is critical to the quality of the study
- The primary endpoint should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the study, taking into account feasibility considerations (ICH E9)
- Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives.
- The choice of endpoints should be meaningful for the intended population and take into account the views of patients.

5.1.4 Response Variables

Definition of study endpoint

- The definition of each study endpoint should be specific
- The specificity should include ...
  - How it is ascertained
  - At what time point in a subject's treatment course of the drug and follow-up it is ascertained
- The methods used to ascertain endpoints should be of sufficient accuracy, precision, responsiveness (sensitivity to change), reproducibility, reliability, and validity.

Pragmatic trials may make use of existing data from healthcare systems to obtain response variables rather than through study specific data collection, similar to the way healthcare data can be used to select the study population as described above (See Sec 5.1.1)

5.1.4 Response Variables

Collection of response variables

The knowledge of the drug, the clinical context, and the purpose of a given study affect what response variables should be collected.

Examples:

Proof-of-concept study	May employ short-term surrogates rather than objective clinical outcomes
Large-scale confirmatory study	Clinical outcomes would be used to confirm a clinically meaningful effect
Post-approval study	In case the safety profile of the drug is well characterised, the extent of safety data collection may be tailored to the objectives of the study

5.1.5 Methods to Reduce or Assess Bias

- The study design should address sources of bias that can undermine the reliability of results.
- This section addresses the more common sources.
- ICH E9 discusses principles for controlling and reducing bias mainly in the context of interventional studies.

5.1.5 Methods to Reduce or Assess Bias

Randomisation

- In conducting a controlled study, randomised allocation is the preferred means of assuring comparability of test groups, thereby minimising the possibility of bias in treatment assignment
- Randomisation addresses differences between the groups at the time of randomisation but does not prevent differences arising after randomisation.
    - Events after randomisation (intercurrent events) may affect the comparability of the groups (e.g. Differences between the groups because subjects in one group dropping out of the study because of adverse events or lack of efficacy)
    - Careful consideration of the potential impact of intercurrent events will help with the identification of critical to quality factors, such as preventing dropouts, retrieving data for dropouts, and definition of treatment effect in the presence of dropouts.

5.1.5 Methods to Reduce or Assess Bias

Blinding/Masking

- Concealing the treatment assignments (blinding or masking) limits the occurrence of conscious or unconscious bias in the conduct and interpretation of a clinical study that may affect the course of treatment, monitoring, endpoint ascertainment, and subject responses.
    - Single-blind study: treatment assignment is not known by the study participant
    - Double-blind study: investigator and sponsor staff are also unaware of the treatment assignments
- Maintaining confidentiality of interim study results also can help to reduce bias.
- In an open-label study (either single-arm or unblinded comparative), the consequences of the lack of blinding may be reduced through the use of pre-specified decision rules for aspects of study conduct.

5.1.5 Methods to Reduce or Assess Bias

Challenges in observational studies

- Observational studies pose unique challenges to the control of bias.
- Multiple design elements are often necessary to address these challenges, including methods to address biases associated with ...
    1. Selection of subjects
    2. Differences in prognostic factors associated with the choice of therapies (confounding)
    3. Ascertainment of response variables and other important study variables

5.1.6 Statistical Analysis

The statistical analysis of a study encompasses important elements necessary to achieving the study objectives.

Importance of pre-finalisation of analysis plan

Study protocol

- Should include a statistical methods section that is appropriate for the objectives and study design (ICH E6 and E9)
- Should be finalised before the conduct of the study

Statistical analysis plan

- May be used to provide the necessary details for implementation
- Should be finalised before the unblinding of study data, or in the case of an open-label study, before the conduct of the study

These steps will increase confidence that important aspects of analysis planning were not based on accumulating data in the study or inappropriate use of external data

Examples of negative impact

- Change of analysis methods after examining unblinded study data
- Selection of external control subjects based on outcomes to be used in comparison

5.1.6 Statistical Analysis

Analysis plan

Following contents should be described (ICH E9)

- Statistical analyses of primary and secondary endpoints to achieve study objectives with respect to both efficacy and safety
- Any interim analyses and/or planned design adaptations

Analysis plan should describe ...

- Analytical methods for the estimation and tests of hypotheses about the drug effect
- Addressing the method of treatment allocation
- Measurement methods of response variables
- Analysis population
- Other critical to quality factors relating to the planned analysis strategy appropriate for the study design.

5.1.6 Statistical Analysis

Analysis plan

The plan should address the handling of intercurrent events, such as

- Treatment discontinuations
- Use of rescue medication
- Missed visits
- Other protocol violations.

Details will be published as ICH E9(R1)

Statistical analysis plan should describe how the various sources of bias discussed above will be addressed in the context of the particular study design and data sources (see Section 5.1.5)

5.1.6 Statistical Analysis

Pre-specification for use of existing data sources

Pre-specification is particularly important for studies that make use of existing data sources rather than primary data collection (see Section 5.2)

> Not only for the statistical analysis planned for the study but also for any feasibility analysis to assess the applicability of the existing data

For example, for a single arm interventional study with an external control, the specifics of the external control should be specified prior to the conduct of the interventional aspect of the study. Assurances and procedures should be in place so that any review of the data prior to the design of the study does not threaten the study integrity.

5.1.6 Statistical Analysis

Sensitivity analyses

Sensitivity analyses should be planned to test the impact of the assumptions made for the primary analyses on the results of the study.

Examples:

- If the primary analysis relies on a particular assumption about the reasons data are missing, the impact of those assumptions on the study results should be assess
- In case of observational studies, additional confounders might be considered

Details will be published as ICH E9(R1)

5.2 Study Data

- The study data should reliably contain the necessary information to conduct, monitor, and analyse the study.
- The study data may be acquired through a variety of methods, including paper-based and electronic capture.
- Data from the use of technologies (e.g., digital health tools), EHR databases and patient registries may contribute to the development of a new investigational drug or for further evaluation of an approved drug.

5.2 Study Data

Types of study data

(1) Data generated specifically for the present study
(2) Data obtained from sources external to the present study

The distinction between the two types may not always be clear. Clinical study data may consist of data collected during scheduled study visits and information obtained from existing medical records.

Primary data collection	• Data collection for study purposes using processes that ensure a sufficient level of quality
Secondary data use	• Use of data that were collected for other purposes and are not collected just for the study • Secondary data may have had careful quality control processes implemented during their acquisition, but those processes were not designed with the objectives of the present study in mind • E.g. National death databases, disease/drug registries, claims data, medical and administrative records from routine medical practice

5.2 Study Data

Consideration on secondary data use

- Appropriateness of the available data should be considered

  For example, when using existing EHR data to ascertain the study endpoint, information in the EHR about outcomes would need to be converted to the study endpoint.

  ⇨ The sensitivity, specificity, and timing of the outcomes in the record should be considered.

  In some cases, secondary data use may need to be supplemented with primary data.

- Concealing the drug name in the measurement and recording of data is typically not present in secondary data use.
- Absence of affirmative information on a condition or event does not necessarily mean the condition is not present
- There may be a delay between events and their presence in existing data sources.

5.2 Study Data

Use of data standards

- The use of data standards for the terminology, storage, exchange, and access of study data promotes the reliability and the proper interpretation of the data.
- Data standards also facilitate the ease and correctness of the data analysis.
- International data standards exist for many sources of study data.
- Data standards should be developed for emerging sources of study data.

Protection of personal data

- For all data sources, procedures to ensure the confidentiality of personal data should be implemented.
- The study design should explicitly address the protection of personal data.
- Local regulations related to privacy of participants' data should be followed.

6 Conduct and Reporting

6.1 Study Conduct

The principles and approaches set out in this guideline, including those of quality by design, should inform the approach taken to the conduct and reporting of clinical studies and the proportionality of control measures employed to ensure the integrity of the critical to quality factors.

The study should be conducted according to

- the principles described in this guideline
- ICH E6 and other relevant ICH guidelines

See, Annex 2: ICH E family of guideline
Annex 3: Selected examples of critical to quality factors

6.1.1 Protocol Adherence

- Adherence to the study protocol is essential.
- Many aspects of adherence should be considered among the study's critical to quality factors
- If modification of the protocol becomes necessary, a clear description of the rationale for the modification should be provided in a protocol amendment (ICH E6).

6.1.2 Training

Timing and objectives

- Prior to enrolment of the first study subject
- Updated training should occur during the conduct of the study
  - To reinforce the importance of adherence to study procedures
  - To address issues related to critical to quality factors observed during the course of the study

Target of training

- sponsors
- investigators
- coordinators
- other local site staff
- site monitors
- adjudicators
- members of the data monitoring committee
- and third-party service providers (e.g., central laboratory or reading centre personnel)

6.1.3 Data Management

- Manner and timelines in which study data are collected and managed are critical contributors to overall study quality (ICH E6).
- Operational checks and statistical surveillance can identify important data quality issues at a point at which corrective action is feasible.
- Data management procedures should account for the diversity of data sources in use for clinical studies.

6.1.4 Access to Interim Data

- Inappropriate access to data during the conduct of the study may compromise study integrity.
- In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results.
- Even in studies without planned interim analyses, special attention should be paid to any ongoing monitoring of data to avoid inappropriate access.

6.2 Subject Safety

Descriptions about subject safety in this guideline

- Sec.2.1: Important standards of ethical conduct and the protection of subjects in clinical studies
- Sec.6.2 (this section): safety related considerations during the conduct of the study

6.2.1 Safety Monitoring

- Goals: To protect study subjects and to characterize the safety profile of the drug
- Procedures and systems for the identification, monitoring, and reporting of safety concerns including the timing of reporting during the study should be clearly specified
- The approach should reflect the risks to the study subjects and what is known about the drug and the study population
- Guidance is available on reporting of safety data to appropriate authorities and on the content of safety reports (ICH E2A, E2B, E2D, and ICH E6)

6.2.2 Withdrawal Criteria

- To ensure the protection of the subjects, clear criteria for stopping study treatment while
  - remaining in the study, or
  - withdrawing from the study altogether

  are necessary
- However, consideration could be given to methods that will preserve subjects' safety and rights while still minimising loss of critical data, if possible.

Critical data should be collected if possible

6.2.3 Data Monitoring Committee

- An important component of safety monitoring in many clinical studies is the use of a data monitoring committee (DMC).
- DMC monitors accumulating data while the study is being conducted to make determinations on whether to continue, modify, or terminate a study.
- During programme planning, the need for an external safety monitoring committee to monitor safety data across studies in a development programme may also be assessed.
- If a data monitoring committee is needed for either an individual study or the entire development programme, procedures governing its operation and, in particular, the review of unblinded data while preserving study integrity (ICH E9) should be established.

6.3 Study Reporting

Documentation of clinical study report

- Clinical study reports should be adequately documented following the approaches outlined in other ICH guidelines

ICH E3 and other guidelines

- ICH E3 focuses particularly on the report format for interventional clinical studies

➡ Other types of studies (e.g., observational studies) should use reporting formats appropriate for the type of study and information being reported.

6.3 Study Reporting

Transparency of clinical research

- transparency of clinical research in drug development includes,
  - registration of clinical trials on publicly accessible and recognised databases
  - public posting of clinical trial results

  Adopting such practices for observational studies also promotes transparency
- Making objective and unbiased information publicly available
  - enhancing clinical research
  - reducing unnecessary clinical studies
  - informing decisions in clinical practice

→ Can benefit public health in general, as well as individual patient populations

7 Considerations in Identifying Critical to Quality Factors

Discussion of critical to quality factors in this guideline

Sec.3: Designing Quality into Clinical Studies

The identification of critical to quality factors should be supported by proactive, cross-functional discussions and decision making at the time of study planning

Sec.4: Drug Development Planning

Sec.5: Design elements for Clinical studies

Sec.6: Conduct and Reporting

Different factors will stand out as critical for different types of studies

In designing a study, applicable aspects such as the following should be considered to support the identification of critical to quality factors, as shown in Sec.7

7 Considerations in Identifying Critical to Quality Factors

- Engagement of all relevant stakeholders, including patients, is considered during study planning and design.
- The prerequisite non-clinical studies, and where applicable, clinical studies, are complete and adequate to support the study being designed.
- The study objectives address relevant scientific questions appropriate for a given study's role in the development programme, taking into account the accumulated knowledge about the product.
- The clinical study design supports a meaningful comparison of the effects of the drug when compared to the chosen internal or external control groups.
- Adequate measures are used to protect subjects' rights, safety, and welfare (informed consent process, Institutional Review Board/Ethics Committee review, investigator and clinical study site training, pseudonymisation, etc.).
- A feasibility assessment is conducted to ensure the study is operationally viable.

7 Considerations in Identifying Critical to Quality Factors

- The number of subjects included, the duration of the study, and the frequency of study visits are sufficient to support the study objective.
- The eligibility criteria should be reflective of the study objectives and be well documented in the clinical study protocol.
- Information about study subjects that may be important to understanding the benefit/risk of the drug (e.g., age, weight, sex, co-morbidities, concomitant therapies) is specified in the protocol, captured and incorporated in the design, conduct, and analysis, as appropriate.
- The choice of response variables and the methods to assess them are well-defined and support evaluation of the effects of the drug.
- Clinical study procedures include adequate measures to minimise bias (e.g., randomisation, blinding).
- The statistical analysis plan is pre-specified and defines the analysis methods appropriate for the endpoints and the populations of interest.

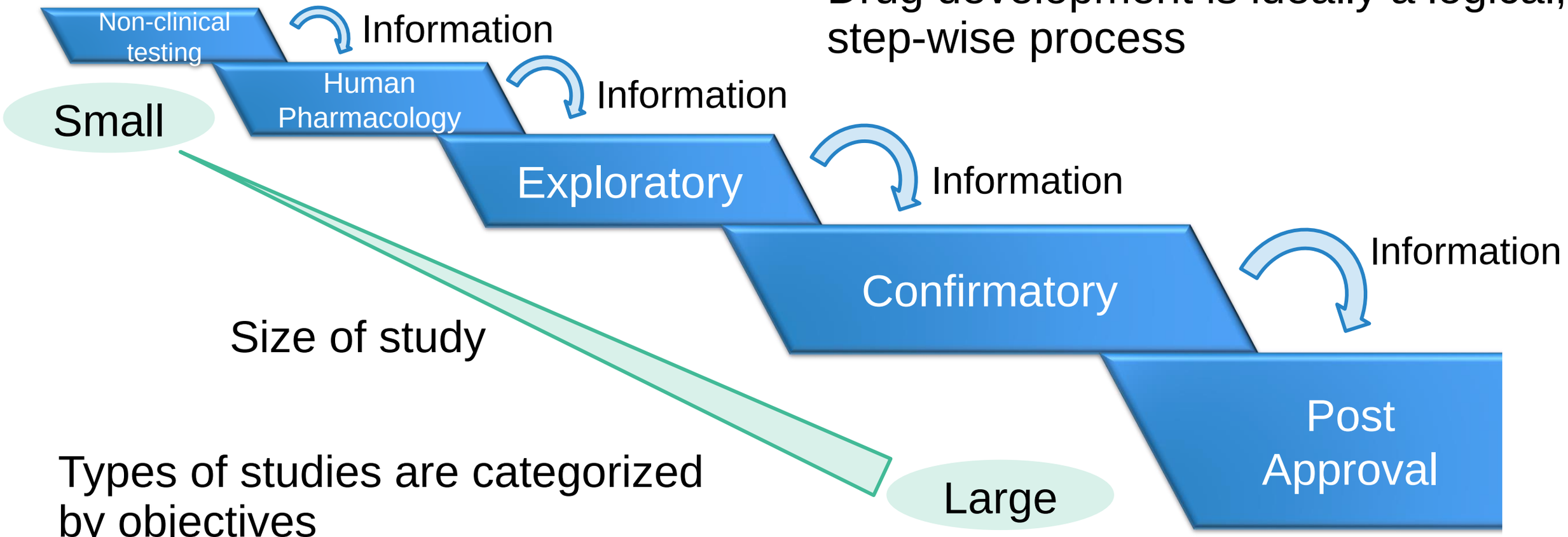
7 Considerations in Identifying Critical to Quality Factors

- Systems and processes are in place to ensure the integrity of critical study data.
- The extent and nature of study monitoring are tailored to the specific study design and objectives and the need to ensure subject safety.
- The need for a data monitoring committee is assessed.

These considerations are not exhaustive and may not apply to all studies. Other aspects may need to be considered to identify the critical to quality factors for each individual study.

Annex1: Types of Studies

Drug development is ideally a logical, step-wise process



Types of studies are categorized by objectives

Annex 1 is updated version of “Table1. An Approach to Classifying Clinical Studies According to Objective“ in the original E8

Annex1: Types of Studies

Type of Study	Objective(s) of Study	Study Examples
Non-clinical testing to support and supplement clinical investigations	• Assess non-clinical PK/PD • Assess toxicity • Assess developmental toxicity • Assess mutagenicity, carcinogenicity • Assess immunogenicity and cross-reactivity • Understand target and mechanism of action	• AMES test • ADME studies • Animal carcinogenicity • Mechanism of action investigations in animal disease models • Animal toxicology • Animal PK/PD
Human Pharmacology	• Assess tolerance and safety • Define/describe clinical PK and PD • Explore drug metabolism and drug interactions • Estimate activity, immunogenicity • Assess renal/hepatic tolerance • Assess cardiac toxicity	• BA/BE studies under fasted/fed conditions • Dose-tolerance studies • Single and multiple-rising dose PK and/or PD studies • Drug-drug interaction studies • QTc prolongation study
Exploratory	• Explore use for the targeted indication • Estimate dose/dosing regimen for subsequent studies • Explore dose-response/exposure-response relationship • Provide basis for confirmatory study design (e.g., clinical endpoints, patient reported outcome measures, effect modifiers, target population, etc.)	• Randomized controlled clinical trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose finding studies • Biomarker exploration studies • Studies to validate patient reported outcomes

Annex1: Types of Studies

Type of Study	Objective(s) of Study	Study Examples
Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile in larger, more representative patient populations • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response/exposure-response relationship • Establish safety profile and confirm efficacy in specific populations (e.g., paediatrics, elderly)	• Randomized controlled clinical trials to establish efficacy in larger, more representative patient populations, commonly employing clinical endpoints but may also use surrogate or pharmacological endpoints • Dose-response studies • Clinical safety studies • Studies of mortality/morbidity outcomes • Studies in special populations
Post-Approval	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendations	• Comparative effectiveness studies • Long-term follow-up studies • Studies of additional endpoints • Large, simple trials • Pragmatic trials • Pharmacoeconomic studies • Observational studies

Annex2: ICH E Family of Guidelines

Integrated set of guidance covering the design, conduct, analysis and reporting of clinical studies

Overall introduction to designing quality into clinical studies and focusing on those factors critical to the quality of the studies

E8 General Considerations for Clinical Trials

Design and analysis:
E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

Populations:
E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11–E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

Conduct and reporting:
E3 Clinical Study Report
E6 Good Clinical Practice

Genetics/Genomics:
E15 Definitions in Pharmacogenetics/Pharmacogenomics
E17 Qualification of Genomic Biomarkers
E18 Genomic Sampling

Safety Reporting：
E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A-E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

The ICH e family guidelines should be considered and used in an integrated, holistic way

Annex3: Selected Examples of Critical to Quality Factors

Selected Examples of Critical to Quality Factors	E1	E2A -E2F	E3	E4	E5	E6	E7	E8	E9
Protocol Design									
Eligibility Criteria						✓	✓	✓	✓
Randomisation				✓		✓		✓	✓
Blinding/Masking						✓		✓	✓
Types of Controls	✓			✓				✓	
Data Quality	✓						✓	✓	✓
Endpoints				✓	✓			✓	✓
Accrual									✓

Relationship between selected examples of critical to quality factors and each ICH e-guideline

Annex3: Selected Examples of Critical to Quality Factors

Selected Examples of Critical to Quality Factors	E1	E2A -E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Protocol Design																	
Eligibility Criteria						✓	✓	✓	✓		✓	✓	✓			✓	
Randomisation				✓		✓		✓	✓	✓		✓	✓			✓	
Blinding/Masking						✓		✓	✓	✓							
Types of Controls	✓			✓				✓		✓			✓			✓	
Data Quality	✓						✓	✓	✓								
Endpoints				✓	✓			✓	✓	✓	✓	✓				✓	
Procedures Supporting Study Endpoints and Data Integrity					✓	✓		✓	✓	✓	✓	✓				✓	
Investigational Product (IP) Handling and Administration						✓							✓				
Feasibility																	
Study and Site Feasibility																✓	✓
Accrual									✓		✓		✓				

Annex3: Selected Examples of Critical to Quality Factors

Selected Examples of Critical to Quality Factors	E1	E2A -E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Patient Safety																	
Informed Consent						✓					✓						✓
Withdrawal Criteria and Trial Participant Retention			✓			✓					✓		✓				
Signal Detection and Safety Reporting		✓ B	✓			✓						✓	✓				
Data Monitoring Committee (DMC) /Stopping Rules						✓			✓	✓			✓				
Study Conduct																	
Training						✓							✓			✓	✓
Data Recording and Reporting		✓ B,C,F	✓	✓					✓		✓		✓		✓	✓	✓
Data Monitoring and Management		✓ A,B,D	✓						✓						✓	✓	✓
Statistical Analysis			✓	✓	✓				✓				✓			✓	
Study Reporting																	
Dissemination of Study Results		✓ D,F															✓
Third-Party Engagement																	
Delegation of Sponsor Responsibilities						✓											
Collaborations						✓											

Conclusion

- This document focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions.
- The principles and approaches set out in this guideline, including those of quality by design, should inform the approach taken to the design, conduct, and reporting of clinical studies and the proportionality of control measures employed to ensure the integrity of the critical to quality factors.

This is a guideline that everyone involved in the conduct of clinical trials should be widely informed.

Future Task

E8(R1) is in the public consultation period -> will be finalized in summer 2020

パブリックコメント

- 意見募集中案件
- 意見募集終了案件
- 結果公示案件
- 全ての案件

- パブリックコメント（制度）について
- このページの見方について

パブリックコメント：意見募集中案件詳細

厚生 ／薬事

「ICH　E8（R1）　臨床試験の一般指針　ガイドライン（案）」に関する御意見の募集について

案件番号	495190053
定めようとする命令等の題名	ICH　E8（R1）　臨床試験の一般指針　ガイドライン（案）
根拠法令項	－
行政手続法に基づく手続であるか否か	任意の意見募集
問合せ先 （所管府省・部局名等）	厚生労働省医薬・生活衛生局医薬品審査管理課 電話：03-5253-1111（内線 2745）

案の公示日	2019年05月21日	意見・情報受付開始日	2019年05月21日	意見・情報受付締切日	2019年09月17日
意見提出が30日未満の場合その理由					

https://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495190053&Mode=0

The deadline of public comment is Sep 17, 2019

We are waiting for your feedback

Future Task

E6(R3)：Discussion will start this summer

Reflection Paper: GCP Renovation

Guideline effort 1:Revision of E8

Guideline effort 2: Develop new ICH E6 Overarching Principles. Appropriate subset of the elements for study quality and CTQ factors identified in the E8(R1) could be carried over and referenced.

Guideline effort 3: Develop E6 Annex 1 focused on traditional interventional trials of investigational unapproved/approved drugs in a controlled setting with prospective collection of trial data.

Guideline effort 4: Develop E6 Annex 2 focused on non-traditional interventional trials and/or data sources.

Guideline effort 5: Develop E6 Annex 3 focused on non-traditional trial designs.

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Reflection_Papers/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf