WORKSHOP

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

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E8 Revision History

1997 E6 (Good Clinical Practice/GCP) was published.
E8 was published; implemented in Japan 1998.

2016.11 Osaka Meeting: proposal of ***'GCP renovation'*** by FDA

ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6 (2017)

2017.11 Geneva Meeting: E8(R1) Expert Working Group starts

2018. 6 Kobe Meeting

2018.11 Charlotte Meeting

2019. 5 E8(R1) Step 3 （starting **Public Consultation**）

2019. 6 Amsterdam Meeting（published 'Step 2 presentation'）

2020. 6 Step 4 is expected

Public Consultation (at MHLW site) **5/21～9/17**

* Each region has its own scheduling (see ICH site)

Background of E8 Revision

- Since adoption of **ICH E8 General Considerations for Clinical Trials** in 1997, clinical study design and conduct have become more complex, impacting the time and cost required to develop drugs.
- A wider range of both study designs and data sources now play a role in drug development and were not addressed in the original E8 guideline.
- Approaches for **optimizing study quality** which promote the reliability, efficiency, and patient focus of clinical trials are needed,
  - Identifying the factors that are **critical to the quality** of a clinical study at the design stage.
  - Planning the study conduct proportionate to the risks to these quality factors, thereby protecting human subjects and ensuring the reliability of study results.

Overview of Step 2 Document

General Considerations for Clinical Studies

E8(R1)

Table of Contents

1 Objectives of this Document

- Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to safe and effective drugs with **meaningful impact on patients**, while protecting those participating in the studies.
- 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**.

Subject Protection

Clinical Meaning

Diversity of Design and Resources

Designing Quality

1 Objectives of this Document (continued)

1. Describe internationally accepted principles and practices in the design and conduct of clinical studies that will facilitate acceptance of data and results by regulatory authorities
2. Provide guidance on the consideration of **quality in the design** and **conduct of clinical studies** across the product lifecycle, including the identification during study planning of factors that are **critical to the quality** of the study, and the **management of risks** to those factors during study conduct
3. Provide an overview of the types of clinical studies performed during the product lifecycle, and describe the aspects of those studies that support the **determination of** which **quality factors are critica**l to ensuring the protection of study subjects, the integrity of the data, the reliability of results, and the ability of the studies to meet their objectives
4. Provide a **guide to the ICH efficacy documents** to facilitate user's access.

2 General Principles
2.1 Protection of Clinical Study Subjects

- These (protection of study subjects) principles have their origins in the Declaration of Helsinki and should be observed in the conduct of all human clinical investigations.
- The investigator and sponsor share responsibility for the protection of study subjects together with the Institutional Review Board/Independent Ethics Committee.

Protect Study Subjects

Confidentiality of Information

- The confidentiality of information that could identify subjects should be protected in accordance with the applicable regulatory and legal requirement(s).

2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- Clinical studies should be designed, conducted, and analysed **according to sound scientific principles** to achieve their objectives, and should be reported appropriately.
- The essence of clinical research is to **ask important questions and answer** them with appropriate studies.
- The primary objective of any study should be clear and explicitly stated.

2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- Quality of a clinical study is considered in this document as fitness for purpose.

Quality = Fitness for purpose

- The purpose of a clinical study is to generate reliable information to answer key questions and support decision making while protecting study subjects.
- The quality of the information generated should therefore be sufficient to support good decision making.

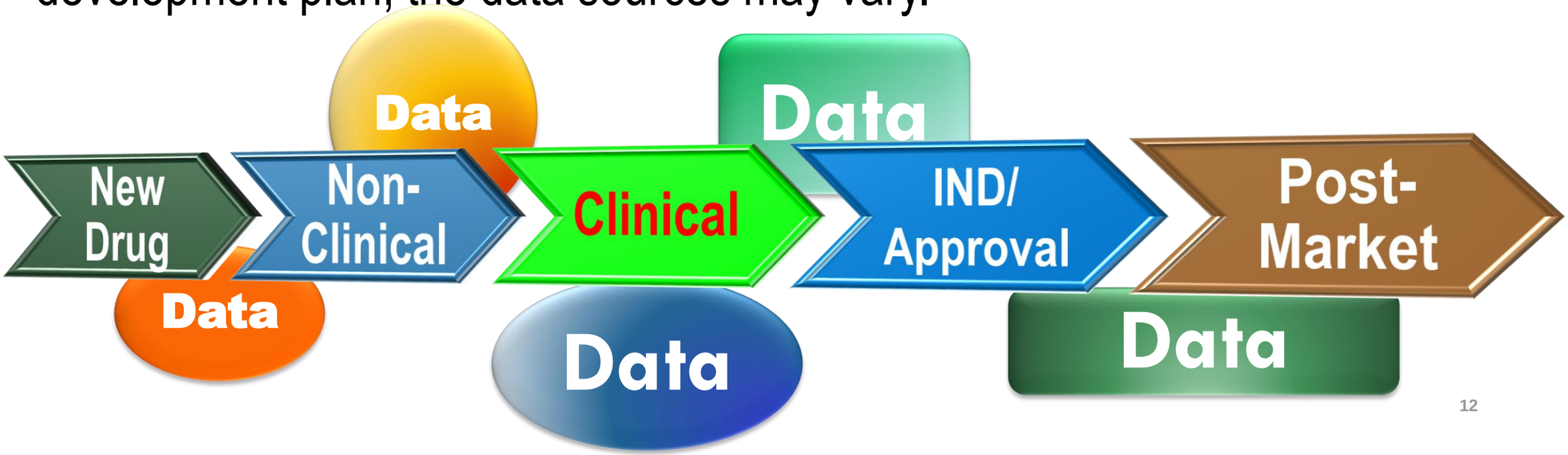
2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- **Quality by design in clinical research** sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes.

- This involves the use of a **prospective, multidisciplinary approach** to promote the quality of protocol and process design, and **clear communication** of how this will be achieved.

2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis

- Across the product lifecycle, different types of studies will be conducted with different objectives and designs.
- Depending on the study objectives and the position of the study in the overall development plan, the data sources may vary.

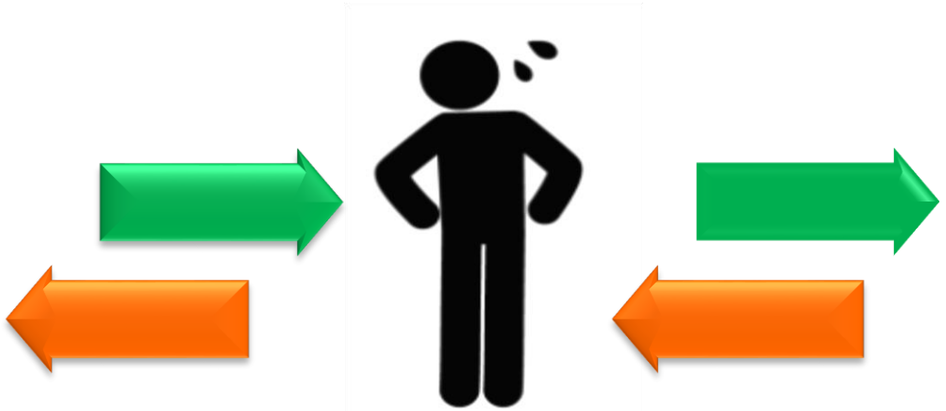


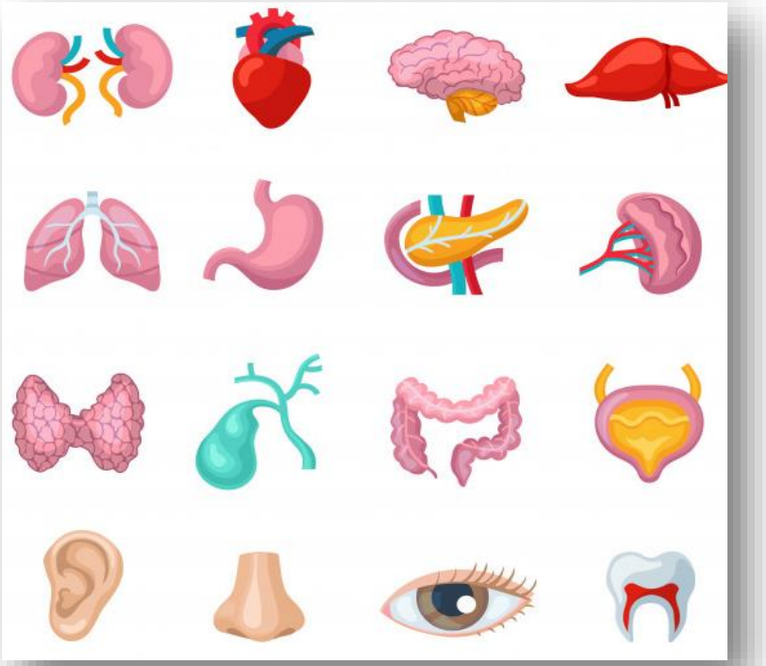
2.3 Patient Input into Study Design

- Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured.
- Patients' views can be requested on all phases of drug development.
- Involving patients at the early stage of study design is likely to increase trust in the study, facilitate recruitment, and promote adherence, which should continue throughout the duration of the study.

2.3 Patient Input into Study Design

- Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators.
- This ultimately supports the development of medicines that are better tailored to patients' needs.





3 Designing Quality into Clinical Studies

- The **quality by design approach to clinical research** involves focusing on **critical to quality factors** to ensure the protection of study subjects, the generation of reliable and meaningful results, and the **management of risks** to those factors.

3.1 Quality by Design of Clinical Studies

- Quality is a primary consideration in the design, planning, conduct and analysis of clinical studies and a necessary component of clinical development programmes.
- The likelihood that a clinical study will answer the research questions posed in a reliable manner, meaningful for decision makers and patients, while preventing important errors, can be dramatically improved through **prospective attention to the design** of all components of the study protocol, procedures and associated operational plans.
- **Quality** should **rely on good design** and its **execution** rather than overreliance on retrospective document checking, monitoring, auditing or inspection.

3.1 Quality by Design of Clinical Studies

- the need for **clear** pre-defined study **objectives** that address the primary scientific question(s);
- selection of **appropriate subjects** that have the disease, condition, or molecular/genetic profile that is being studied;
- use of approaches to **minimize bias**, such as randomisation, blinding or masking, and/or control of confounding;
- endpoints that are **well-defined and measurable**, and methods of assessment of those endpoints that are **accurate** and able to be implemented with minimal reporting or measurement bias.

Clear Objectives

Appropriate Subjects

Minimize Bias

Well-defined Endpoints

Minimal Reporting /Measurement Bias

3.2 Critical to Quality (CtQ) Factors

- A basic set of factors relevant to ensuring study quality should be identified **for each study**.
- **Emphasis** should be given to those factors that stand out as critical to study quality.
- These C-t-Q factors are **attributes of a study** whose **integrity** is fundamental to the protection of study subjects, the reliability and interpretability of the study results, and the decisions made based on the study results.
- These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making would also be undermined.

Identify for Each Study

Emphasis should be given

Attributes of a Study

Integrity is Fundamental

3.2 Critical to Quality Factors

- The design of a clinical study should **reflect the state of knowledge and experience** with the drug; the condition to be treated, diagnosed or prevented; the underlying biological mechanism (of both the condition and the treatment); and the population for which the drug is intended.
- As research progresses, knowledge increases and **uncertainties** about the safety and efficacy of a drug **decrease**.
- This state of knowledge has a clear influence on the regulatory and ethical controls that apply to the authorisation, supervision, and conduct of clinical studies.

3.2 Critical to Quality Factors

- The sponsor and other parties designing quality into a clinical study should identify the critical to quality factors.
- Having identified those factors, it is important to determine the risks that threaten their integrity, the probability and impact of those risks and to decide whether they can be accepted or should be mitigated.
- Where it is decided that risks should be mitigated, the necessary control processes should be put in place and communicated, and the necessary action taken to mitigate the risks.

The term risk is used here in the context of general risk management methodology to all factors of a study.

3.2 Critical to Quality Factors

- **Proactive communication** of the critical to quality factors and **risk mitigation activities** will support understanding of priorities and resource allocation by the sponsor and investigator sites.
- The quality factors **should be prioritized** to identify those that are critical to the study, at the time of the study design, and study procedures should be **proportionate to the risks** inherent in the study and the importance of the information collected.
- The critical to quality factors should be **clear** and should not be cluttered with minor issues.

Proactive Communication

Risk Mitigation Activity

Resource Proportionate to Benefit

Procedure Proportionate to Risks

3.3 Approach to Identifying the Critical to Quality Factors

Key Aspect

- the objectives being addressed by the study are **clearly** articulated
- the study is designed to **meet the need** it sets out to address
- these needs are **meaningful to patients**
- the study hypotheses are **specific**, **timely** and **scientifically valid**.

The approach should consider whether those objectives can be met, well and most efficiently, by the chosen design and data sources.

3.3 Approach to Identifying the Critical to Quality Factors

Feasibility

- Study designs should be **operationally feasible** and **avoid unnecessary complexity and unnecessary data collection**.

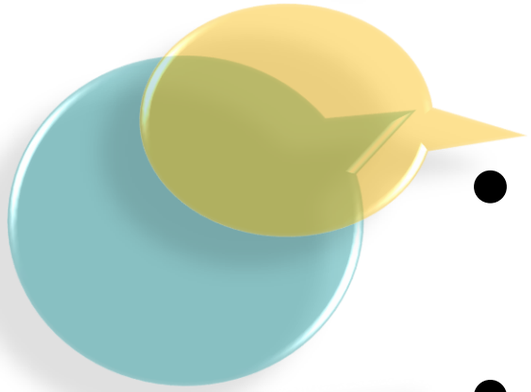
- **Patient consultation early** in the study design process contributes to these factors and would be likely to result in fewer protocol amendments.
- Protocols and case report forms/data collection methods should enable the study to be conducted as designed.

Patients Involvement

Clear Protocol and Data Collection Plan

3.3.1 Establishing a Culture that Supports Open Dialogue

Identification of C-t-Q factors will be enhanced by:



- Create a culture that values and rewards **critical thinking** and **open dialogue**.
- Choose quality measures and performance indicators that are aligned with a proactive approach to design.
- Encourage **proactive dialogue** about what is C-t-Q for a particular study or development programme.
- Discourage inflexible “one size fits all” approaches.
- Gather and synthesise evidence in a transparent manner, acknowledge gaps in data and conflicting data.

3.3.2 Focusing on Activities Essential to the Study

- **Focus effort on activities that are essential** to the reliability and meaningfulness of study outcomes for patients, and the safe, ethical conduct of the study for study subjects.
- Consider whether **nonessential activities may be eliminated** from the study to simplify conduct, improve study efficiency, and target resources to critical areas.
- **Rigorously evaluate the study design** to verify that planned activities and choice of data to be collected are essential.
- **Deploy resources to identify and prevent** or control errors that matter.

3.3.3 Engaging Stakeholders in Study Design

- Clinical study design is best informed by input from a **broad range of stakeholders**, including patients and treating physicians.
- Clinical investigators and potential study subjects have valuable insights into the **feasibility.**
- It should be open to challenge by subject matter experts and **stakeholders from outside**, as well as within, the sponsor organisation.
- The process of building quality into the study may be informed by participation of those **directly involved in successful completion of the study** such as clinical investigators, study coordinators and other site staff, and patients/patient organisations.
- When a study has novel elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints), early engagement with regulatory authorities should also be considered.

3.3.4 Reviewing Critical to Quality Factors

- Build on accumulated experience and knowledge with periodic review of critical to quality factors to determine whether adjustments to risk control mechanisms are needed, since new or unanticipated issues may arise once the study has begun.
- Pay special attention to studies designed to include adaptations and/or interim decision points during the study.

Risk Control Mechanisms

Periodic Review

Special attention on Adaptations, Interim Decision

- These will require proactive planning and ongoing review and adjustment of critical to quality factors, and risk management.

Proactive Planning and Ongoing Review and Adjustment of CtQ Factors, and Risk Management

3.3 Approach to Identifying the Critical to Quality Factors (Summary)

Establishing a Culture that Supports Open Dialogue

Focusing on Activities Essential to the Study

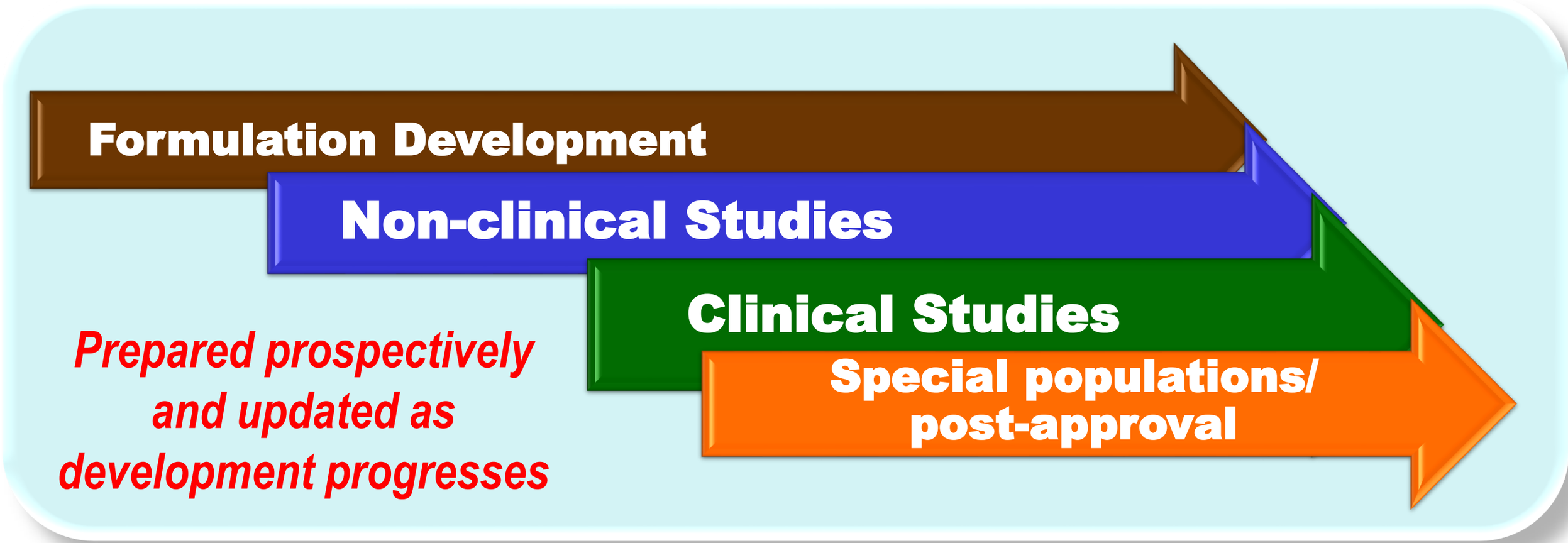
Engaging Stakeholders in Study Design

Reviewing Critical to Quality Factors

4 Drug Development Planning

Efficient Development

- Usually requires appropriately planned interactions with regulatory authorities throughout development.
- This is particularly important for multiregional studies to ensure the study design is aligned with regional regulatory requirements.



4 Drug Development Planning

Multi-Regional Clinical Trials

- With increased **globalisation** of drug development programmes there is a need to consider factors that impact quality of a protocol when it is conducted in more than one region (see ICH E17).
- **Early engagement with regulatory authorities to understand local/regional requirements** is encouraged and will facilitate the ability to design quality into the study protocol.
- The results of a study are often used in regulatory submissions in multiple regions, and the design should also consider **the relevance of the study results for regions other than** the one(s) in which the study is conducted.

4.1 Non-Clinical Studies

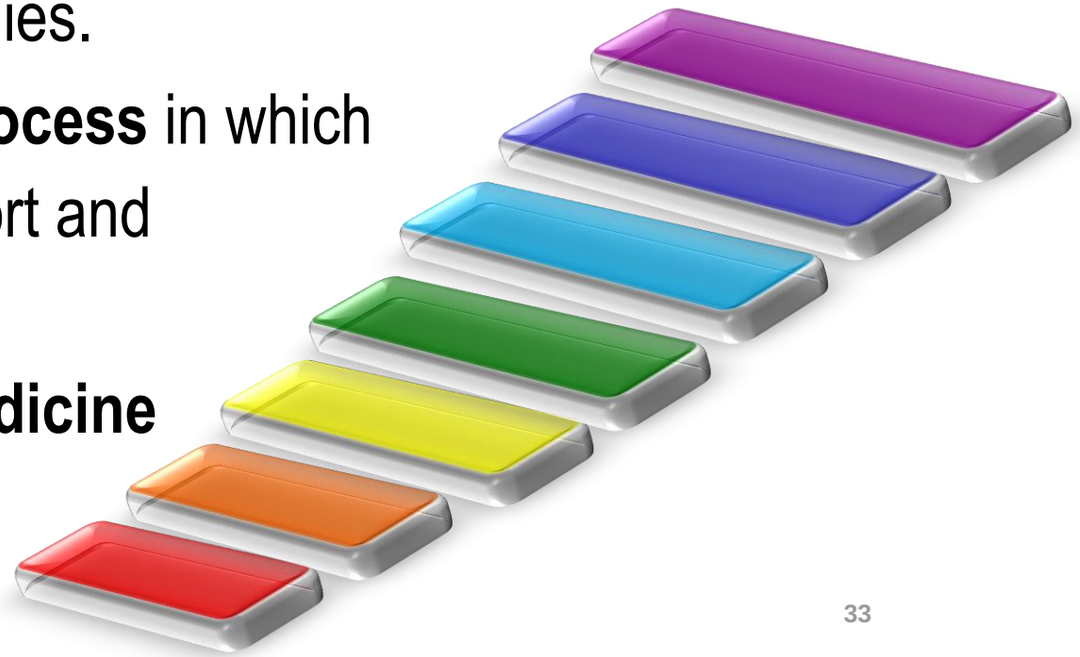
- Non-clinical information may include toxicology, carcinogenicity, pharmacology, and pharmacokinetics to support clinical trials (e.g., ICH Safety Guidelines and M3 Nonclinical Safety Studies).
- **Important considerations for determining the necessary non-clinical studies, and their timing with respect to clinical studies, depend on the physiological and toxicological characteristics.**
- These characteristics can include the drug's chemical or molecular properties (e.g., small-molecule, biologic/cellular/gene therapy, complex drug, and vaccine); pharmacological basis of principal effects; route(s) of administration; absorption, distribution, metabolism, and excretion (ADME); physiological effects on organ systems; dose/concentration-response relationships; half-life; duration of action; and indication.
- Use of the drug in special populations may require additional toxicological assessments.

4.2 Quality and Formulations of Investigational Medicinal Products

- Quality of investigational products is an important consideration in planning a drug development programme and is addressed in the ICH quality guidelines.
- Of particular importance in transitioning from non-clinical to clinical studies is the quality of the product formulation to be taken into clinical development.
- Formulations should be well characterised, including information on bioavailability.
- The formulation should be appropriate for the stage of drug development.
- Links between formulations, established by bioequivalence studies or other means, are important in interpreting clinical study results across the development programme.
- Age-appropriate formulation development is a consideration when clinical studies are anticipated in paediatric populations (ICH E11).

4.3 Clinical Studies

- Clinical drug development is **conducted in a sequence** that builds on **knowledge accumulated from previous studies**.
- Although clinical drug development is often described as consisting of four temporal phases (Phase 1-4), it is important to appreciate that the phase concept is **not a set of requirements.**
- Studies may be better categorized by other **design elements** such as study objective.
- Temporal phases do **not imply a fixed order** of studies.
- Drug development is ideally a **logical, step-wise process** in which information from small early studies is used to support and plan later larger, more definitive studies.
- It is essential to **identify characteristics of the medicine in the early stages** and to plan an appropriate development based on this profile.



4.3 Clinical Studies

Short-term Safety and Tolerability

Pharmacodynamic and Pharmacokinetic

Confirmatory, Larger, Longer, Diverse Study Population

Dose response may be obtained at any stage

ICH E4 Dose-Response Studies

4.3.2 Exploratory and Confirmatory Studies

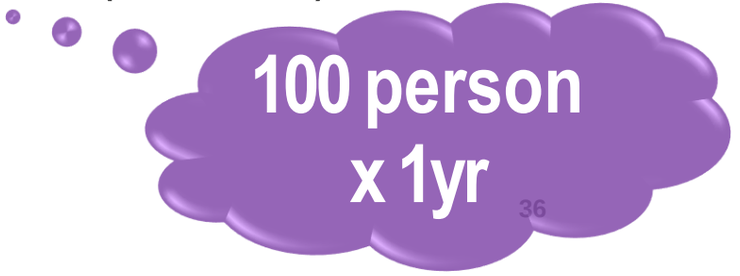
Exploratory Studies

- Exploratory studies support clinical proof of concept.
- These evaluations may aim to refine the effective dose(s) and therapeutic regimens (including concomitant medication) for subsequent studies, refine the definition of the target population.
- Initial exploratory studies may use a variety of study designs, including concurrent controls, comparisons with baseline status, and adaptive dose-finding.
- Other studies may involve modelling early or intermediate outcome data to predict clinical outcomes and thereby inform the design of the follow-on, larger confirmatory studies.

4.3.2 Exploratory and Confirmatory Studies

Confirmatory Studies

- Intended indication and recipient population.
- Adequate basis for marketing approval, and to support adequate instructions for use.
- Larger population of patients with or at risk of the condition or disease.
- More accurately represent patients, and may include subgroups of patients (e.g., cardiovascular, diabetes, hepatic and renal impairment).
- Further explore the dose-response or explore use in different stages.
- For a long period use, extended exposure should be conducted (ICH E1).
- Often randomised parallel designs.
- May use complex adaptive or innovative designs.



4.3.3 Post Approval Studies

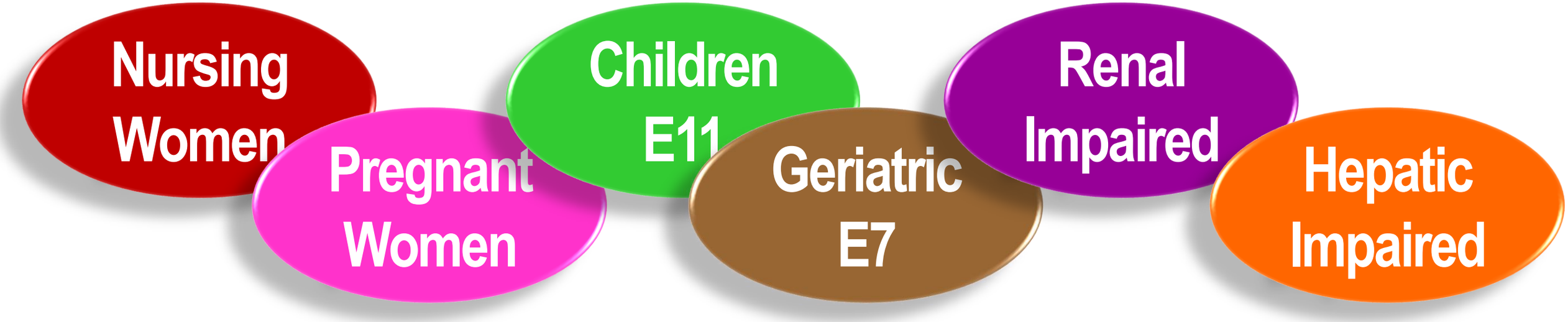
Post approval studies

may be performed for a variety of reasons

- (Hard endpoint while) being approved with surrogate.
- to demonstrate effects on clinical endpoints.
- Special populations, such as paediatric and elderly populations.
- To refine the understanding of potential risks.
- Long-term follow-up or with comparisons.
- Encompass a range of designs and data sources.

4.3.5 Consideration in Special Populations

- may require special study because they have unique risk/benefit considerations.
- ICH E5 provides a framework for evaluating ethnic factors.
- Non-clinical safety studies to support human clinical studies in special populations may be needed (ICH S5, S11, M3).



- E6/E11: Particular attention should be paid to the ethical considerations related to informed consent in vulnerable populations.

4.4 Feasibility

- During development, the **feasibility** of the individual studies should be assessed.
- The foundation of a successful study is a protocol that is both **scientifically sound** and **operationally viable**.

Scientifically Sound and Operationally Viable

- A detailed feasibility assessment includes consideration of study design and implementation elements that could impact the successful completion of a clinical development programme or study from an operational perspective in a particular geographical region.

4.4 Feasibility

Consideration of C-t-Q factors on Feasibility

- ✓ availability of qualified investigators/site personnel with experience in conducting a clinical study
- ✓ availability of equipment and facilities
- ✓ availability of the desired patient population
- ✓ ability to enroll sufficient participants as determined by the power analysis
- ✓ ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for paediatric studies; and regional standards of care.

⇒ can inform study design and enhance quality implementation

4.4 Feasibility

- An important aspect of study feasibility is understanding the view of **potential study subjects** about protocol elements that could impact their willingness to enroll or continue participation in the study (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes).
- The retention of study subjects and the follow-up of subjects who have withdrawn from treatment are key critical to quality factors.
- It is important to not underestimate the **value that appropriate and early consultation with patients** will have on the feasibility of the study, adherence to the protocol, and, more essentially, **relevance (or suitability) for patients of the drug approval** based on the accumulated knowledge and experience from the clinical studies.

Quality by Design

Identify Critical to Quality Factors

Speaker Change