Quality Management in Clinical Research

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- **What is Quality?**

"The act of overseeing all activities and tasks needed to maintain a desired level of excellence. This includes creating and implementing quality planning and assurance, as well as quality control and quality improvement. It is also referred to as total quality management (TQM)."

Keys to Quality Management

- Success requires the participation of all project team members
- Quality should be planned, designed, and built in: the cost of preventing mistakes is generally less than the cost of correcting mistakes
- Project Roles in Quality Management
- Project Manager assures all staff are in compliance with quality procedures
- Quality Manager(s) Develops quality procedures for subject areas such as data management, site monitoring, specimen collection, and document review and measures compliance
- Other Team Members follow quality procedures
- Quality Reporting
- Project Team Members complete and sign checklists and other documents indicating they are following quality procedures.

QualityManagement

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results.

Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection.

Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

- The quality management system should use a risk-based approach as described below.

- *5.0.1 Critical Process and Data Identification*
- During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

- *5.0.2 Risk Identification*
- The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, and informed consent process).

- *5.0.3 Risk Evaluation*

- The sponsor should evaluate the identified risks, against existing risk controls by considering:

(a) The likelihood of errors occurring.

(b) The extent to which such errors would be detectable.

(c) The impact of such errors on human subject protection and reliability of trial results.

- ***Risk Control***
- The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk.

- Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

- Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results.

Risk Communication

The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

Risk Reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, section 9.6 Data Quality Assurance).

- **Quality Assurance and Quality Control**

  5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

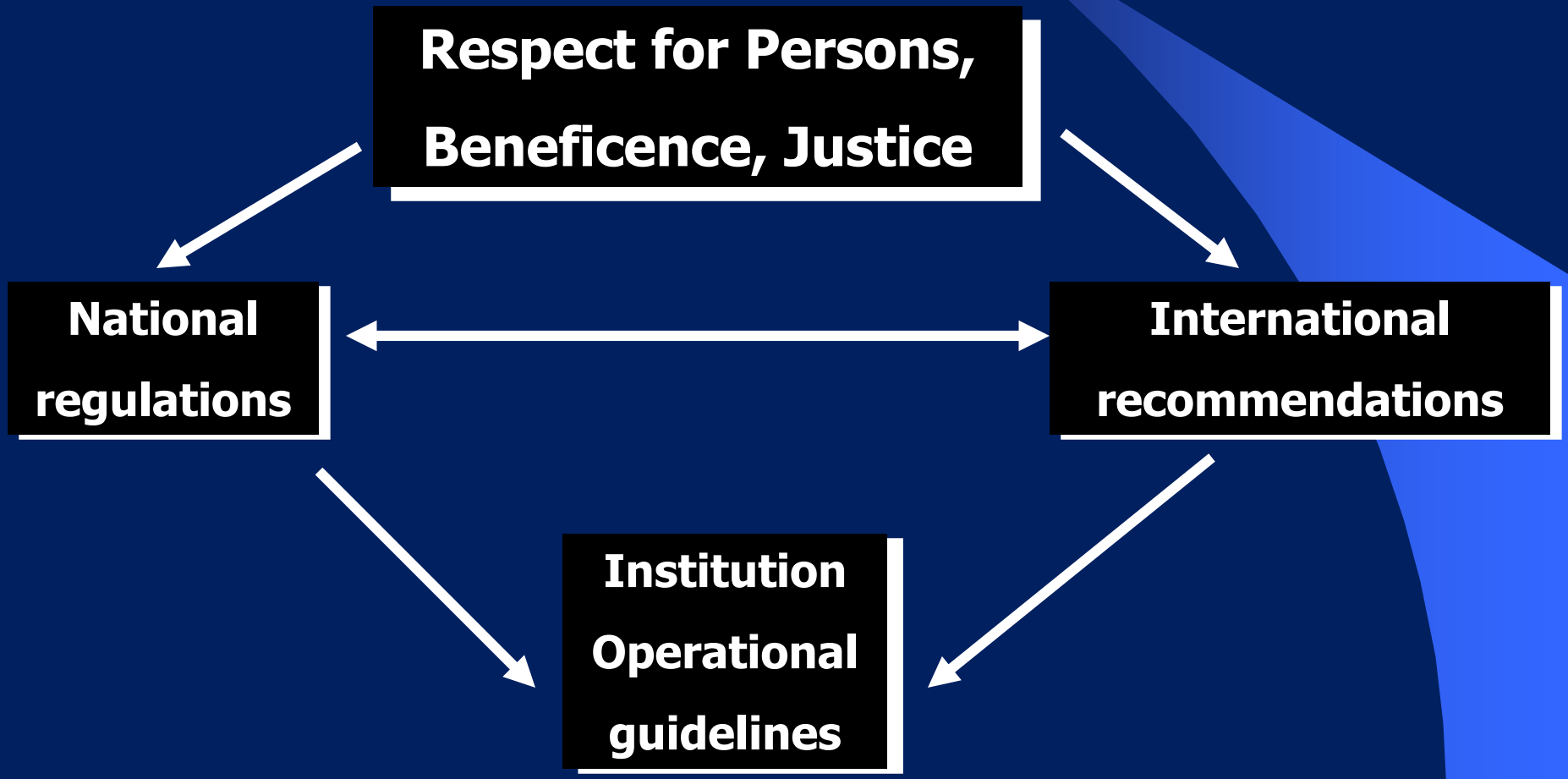
  5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see section 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

- 5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

- 5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

SOP (Standard Operating Procedures)

- Detailed, written instructions to achieve uniformity of the performance of a specific function applying Basic Biomedical Research Principles in every step of research process



- Clinical Study Proposal Writing ***(Design)***
- Application for approval of study (Technical + Ethical)
- Planning - Recruitment of research resources (man, money, material and method)
  - Training
  - Pilot Study
- Implementation of the Study ***(Conduct)***

  - Data (Sample) Collection, Appropriate Consent taking, systematic recording (of cases,, Equipment and materials used, etc.) ***(Record)***
  - Data Analysis, Evaluation and Conclusion
- Report Writing including lessons learnt and limitation of the study and results. ***(Report)***
- Dissemination of Results

•Electronic Records and Signatures

Computer systems utilizing electronic records and signatures must ensure accuracy, reliability, and consistent performance. Standard operating procedures (SOPs), audits, testing, and training are required.

Computer systems must use and maintain secure, computer-generated, time-stamped audit trails independently recording the date and time of entries and actions that create, modify, or delete electronic records.

Computer systems must use system checks to ensure that only those individuals authorized to use the system are allowed access to the system (and access to only those parts of the system they have authorization to use), alter records, and perform operations.

- Procedures must be established to ensure that records are retained for a duration of time, in an appropriate format, and that minimally they meet FDA requirements.

Training

(1) Training of research team members (investigators, project staff, etc.)

(2) Training on study methods (including consent taking, GCP, data collection and procession, laboratory techniques, data entry , etc.

(3) Training on Research Methodology

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through an up-to-date curriculum vitae **(CV)** and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authority(ies).

- Investigators may delegate responsibilities to appropriately qualified persons. This must be documented in writing. The investigator is still ultimately responsible for the conduct of the study, and is responsible for supervising and/or training any individual to whom he/she delegates tasks (ICH [2016] 4.2.5).

- Maintain study team training logs.

Research Monitoring

Definition of Monitoring

Monitoring is an intermittent (regular or irregular) series of observations in time, carried out to show the extent of compliance with a formulated standard or degree of deviation from an expected norm.

Hellawell (1991), modified by Brown (2000)

http://jncc.defra.gov.uk/page-2268

Elements of Monitoring

- Monitoring is the regular observation and recording of activities taking place in a project or programme. It is a process of routinely gathering information on all aspects of the project.

- To monitor is to check on how project activities are progressing. It is observation; — systematic and purposeful observation.

Elements of Monitoring

- Monitoring also involves giving *feedback about the progress of the project* to the donors, implementers and beneficiaries of the project.

- Reporting enables the gathered information to be used in making decisions *for improving project performance*.

Ways & means of Research Monitoring

- **Progress Report**
- **Final Report**
- **Adverse Events Report (Clinical Trials)**

Monitoring Process

- Part of the monitoring process includes the review of progress reports.

- Researchers are required to submit an Annual Report for each research project, initially 12 months after the approval date, and every 12 months thereafter, unless otherwise specified.

Source: *Metro South Health Service District Human Research Ethics Committee (MSHSD HREC), Australia*

- Based on information received in the progress report, the HREC may elect to undertake a Monitoring Visit.

- If a decision is made by the Principal Investigator to either suspend or cease a research project prior to the expected date of completion, a Final Report is to be forwarded to the HREC.

- A Final Report is to be submitted to the HREC on completion of the project on the expected completion date.

Monitoring a Clinical Trial

The act of **overseeing the progress of a** clinical trial, and of ensuring that it is *conducted, recorded, and reported* in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirement(s)

Purpose

- To improve quality & promote high standards
- To identify non-compliance
- To identify research misconduct/ fraud
- Ensures safety of trial participants
- To adhere to the regulations (Research Governance Framework, EU Directives)

Importance of Monitoring

- The rights and well-being of human subjects are protected
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of trial is in compliance with protocol, GCPs, and applicable regulatory requirements

Monitoring Plan

- A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.
- Extent and nature of monitoring
- Responsibilities of those involved
- Procedures for monitoring reports and for dealing with issues raised

Risk Assessment of a Project

- Systems should include a risk based programme of routine and random monitoring and audit.
- High risk may be assessed in terms of high volume of patients, or vulnerability of population (eg. Paediatric, mental capacity) or type of medicinal product/device

- Sponsor shall monitor progress of its studies (ICH 5.18.3)
- Where PI fails to comply with SOPs, protocol, regulatory requirements or GCP, prompt action to secure compliance is needed:

Monitoring visit

- **Eligibility of patients**
- **Consent & recruitment procedures**
- **Adverse events**
- **Investigational product accountability**
- **Other protocol requirements *eg. Sample collection, CT scans***
- **Review of site's Regulatory Documents**
- **Review Trial file; CRF verification:**
- **Comparison of CRF data *vs.* data in source documents (usually verify 100% of primary points)**
- **Data Query resolution**

- **Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)**

- An independent data monitoring committee that may be established by the sponsor *to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.*

Auditing

- **1.Audit**
- A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

2. Audit Certificate

- A declaration of confirmation by the auditor that an audit has taken place.
- **3. Audit Report**
- A written evaluation by the sponsor’s auditor of the results of the audit.
- **4. Audit Trail**
- Documentation that allows reconstruction of the course of events.

- **Audit**

  If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

- *5.19.1 Purpose*

  The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

- *5.19.2 Selection and Qualification of Auditors*

  (a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

  (b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

- *Auditing Procedures*

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

- **Noncompliance**

  5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

- Any time the randomization procedure is not followed or the code is broken, it raises a red flag during an audit or inspection.

- The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

- The investigator is required to make the records available to the monitor, auditors, the IRB/ERC, the FDA, and other regulatory authorities.

- **Quality Assurance (QA)**

  All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

- **1.47 Quality Control (QC)**

  The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

- **1.48 Randomization**

  The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

- **1.49 Regulatory Authorities**

  Bodies having the power to regulate. In the ICH GCP guidance, the expression “Regulatory Authorities” includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

- **1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

  Any untoward medical occurrence that at any dose:

  - Results in death,
  - Is life-threatening,
  - Requires inpatient hospitalization or prolongation of existing hospitalization,
  - Results in persistent or significant disability/incapacity, or
  - Is a congenital anomaly/birth defect.

  (See the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

STANDARD OPERATING PROCEDURES (SOPs)

S. No. List of SOPs

1. Writing, Reviewing, Distributing and Amending Standard Operating Procedures for ECs
2. Constituting an Ethics Committee
3. Confidentiality Agreements
4. Conflict of Interest Agreements
5. Training Personnel and EC Members
6. Selection of Independent Consultants
7. Procedures for Allowing a Guest of Observer
8. Categorization of Submitted Protocols for Ethics Review
   a. Initial Full Committee Review of New Research Protocols
   b. Expedited Review of Research Protocols
   c. Exemption from Ethics Review of Research Protocols
9. Agenda Preparation, Meeting Procedures and Minutes
10. Review of New Medical Device Studies

11. Review of Resubmitted Protocols
12. Review of Protocol Amendments
13. Continuing Review of Protocols
14. Review of Final Reports
15. Review of Serious Adverse Events (SAE) Reports
16. Review of Study Completion Reports
17. Management of Premature Termination, Suspension, Discontinuation of the Study
18. Waiver of Written of Verbal/oral Informed Consent

19 Site Monitoring Visits

20 Dealing with Participants' Requests and Complaints

21 Emergency Meetings

22 Communication Records

23 Maintenance of Active Study Files

24 Archive and Retrieval of Documents

25 Maintaining Confidentiality of EC's Documents

26 Reviewing Proposals involving Vulnerable Populations

27 Review and Inspection of the EC

28 Audio Visual Recording of the Informed Consent Process

(National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, Indian Council of Medical Research, 2017)

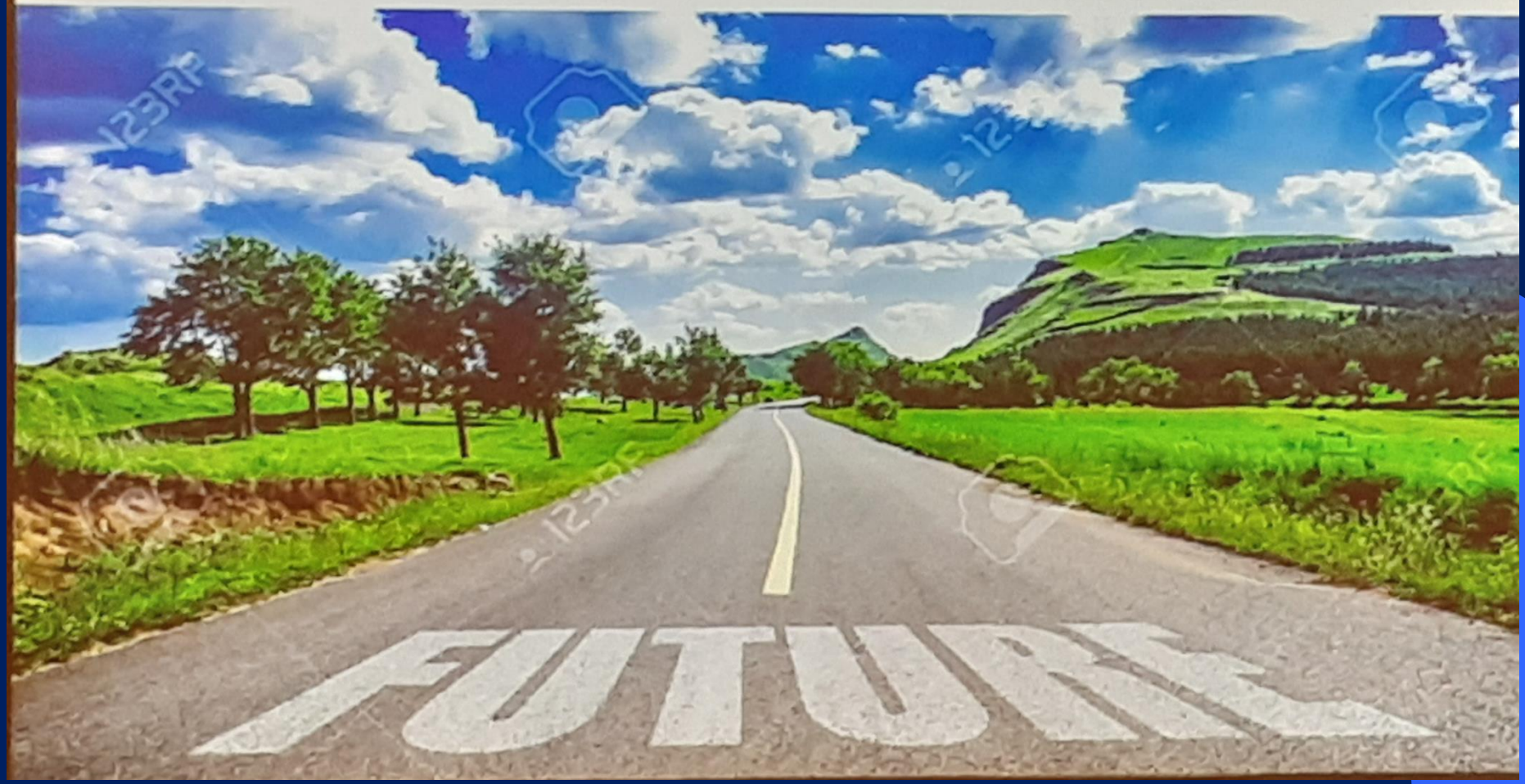
References

1. *International Council for Harmonisation of technical requirements for Pharmaceuticals for human use (ICH), ICH harmonised guideline, Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2) , Current Step 4 version dated 9 November 2016*
2. *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), March 2018, OMB Control No. 0910-0843 Expiration Date 09/30/2020*
3. *FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures-Scope and Application* in 2003 and *Guidance for Industry: Computerized Systems Used in Clinical Investigations* in 2007) *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures-Scope and Application*.
4. *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, Indian Council of Medical Research, 2017*

   www.icmr.nic.in

The Road Forward

Thank you



THE PRINCIPLES OF ICH GCP

2.I 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).

2.2 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.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
2.7 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.
2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.
2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.