Review Article

The revamped Good Clinical Practice E6(R3) guideline: Profound changes in principles and practice!

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Abstract

The International Council for Harmonisation has released a draft version E6(R3) of the Good Clinical Practice Guideline for public consultation. The objective of the revamped guideline is to make the new provisions applicable across diverse clinical trial types and settings and to remain relevant as technological and methodological advances occur. E6(R3) includes profound changes in the structure and content of E6(R2) version, which will impact all the trial conduct processes from planning to reporting. This guideline's focus on principles, digital technology, ethics, and quality will increase the responsibilities of the ethics committees, the investigator, and the sponsor. This brief review discusses the impact of the guideline on trial conduct and the challenges of implementation in India.

Keywords: Digital technology, E6(R3), Good Clinical Practice, quality

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INTRODUCTION

International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance version E6(R1), released in 1996 and revised in 2016, is undergoing a major makeover. ICH E6(R2) revision was a response to increase in the scale and complexity of evolutions in the technology of clinical trials and risk management process. This supplement just amended some GCP sections.[1] In contrast, ICH has expanded key concepts of quality in the design and trial conduct, discussed factors critical to the quality of the study, and described the management of risk to quality in the revamped GCP guideline.[2,3] E6(R3) version impacts all the trial conduct processes – planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting activities.[3] This article reviews major amendments in GCP guidelines and their impact on the conduct of clinical trials.

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E6(R3) SIGNIFICANT CHANGES

The revamped R3 version includes significant changes in the structure and the content of GCP guidelines.

New structure is:

- Introduction
- Principles
- Annex 1:
  1. Institutional review board/independent ethics committee (IRB/IEC)
  2. Investigator
  3. Sponsor
  4. Data governance – Investigator and sponsor.
- Glossary
- Appendices:

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A. Investigator's Brochure
B. Clinical trial protocol and protocol amendment (s)
C. Essential records for the conduct of a clinical trial.

Focus of key modifications in the contents is:

- Guiding guidelines
- Primacy of principles
- Thrust on technology
- Quest for Quality
- Elaboration of ethics
- Rising responsibilities.

GLOSSARY

This section includes modifications of E6R2 definitions and new additions.

- GCP definition is modified
  - E6R2 GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected
  - In the E6R3 GCP definition the description of clinical trial processes and aspects to be assured are changed. GCP is a standard for the planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety, and well-being of trial participants are protected.
- Trial participant replaces subject
- Clinical trial is any interventional investigation
- Source records, which replace source documents and data, are original documents or data (which include relevant metadata) or certified copies of the original documents or data, irrespective of the media used. This may include trial participants' medical/health records/notes/charts; data provided/entered by trial participants (e.g., electronic patient-reported outcomes [ePROs]); health-care providers' records from pharmacies, laboratories, and other facilities involved in the clinical trial; and data from automated instruments, such as wearables and sensors.

New terms added to the glossary are assent, audit trail, data acquisition tool, metadata, Reference Safety Information, signature, and Suspected Unexpected Serious Adverse Reactions (SUSAR).

GUIDING GUIDELINES

ICH recommends that E6(R3) guidelines should be read in conjunction with other ICH guidelines relevant to the design and conduct of clinical trials, including multiregional trials. This new guideline refers to other ICH guidelines in the following areas:

- Introduction – E8(R1) General Considerations for Clinical Studies
- Clinical trial/study reports – E3 Structure and Content of Clinical Study Reports
- Safety reporting – (1) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (2) E19 on a selective approach to safety data collection in specific late-stage preapproval or postapproval clinical trials
- Reference Safety Information – E2F Development Safety Update Report
- Statistical programming and data analysis – E9 Statistical Principles for Clinical Trials
- Data governance – Investigator and sponsor – E8(R1), E9
- Serious adverse event – E2A
- Clinical Trial Protocol and Protocol Amendment(s) – E8(R1), E9, E9(R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.

PRIMACY OF PRINCIPLES

In the E6(R3) guidelines, the principles have a place of prominence as they are intended to apply across diverse types of clinical trials and to remain relevant as technological and methodological advances occur.[3] Annex 1 provides information on how these flexible principles can be appropriately applied by the responsible stakeholders – IRB/IEC, investigator/institution, and sponsor to support efficient approaches to trial design and conduct.

The E6(R3) principles [Table 1] include well-known E6(R2) principles – protection of rights, safety, and well-being of participants; informed consent, IRB/IEC approval, and protocol conduct by qualified individuals; investigational product management (IP); new E6(R3) principles-robust science, quality, and risk management; and reliability of results, roles, and responsibility of sponsor and investigator. This guideline explains each principle and indicates how it can be put into practice. The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results.[3]

THRUST ON TECHNOLOGY

E6(R2) was amended to encourage the implementation of technological advances to improve and make clinical

Table 1: Principles of E6(R3)

Sr.no.	Principle	Practice
1	Rights, safety, and well-being of participant	Prevail over interests of science and society Require periodic review of new safety information Need to balance risks and benefits to participants and society Selection of participants representative of the anticipated population Qualified physician responsible for medical decisions and care Protection of confidentiality of participant's identity
2	IC	Freely given IC before clinical trial participation Information adequate to make informed decision about participation Focus on critical aspects of trial protocol
3	IRB/IEC approval	Conduct of trial in compliance with IRB/IEC approved protocol Periodic review of the trial by the IRB/IEC
4	Scientific knowledge	Adequate preclinical and clinical information on IP Scientifically sound clinical trial design based on state of art and current knowledge Periodic review of current scientific knowledge and approaches
5	Qualified individuals	Designed and conducted by individuals qualified by education, training, and experience
6	Quality in design and conduct	Quality and information generated supportive of good decision Quality by design with focus on factors fundamental to the protection of participants, the reliability and interpretability of the trial results Strategies implemented to avoid, detect, and address serious noncompliance with GCP, the trial protocol, and applicable regulatory requirements
7	Participant risk and importance of data	Trial processes proportionate to the risks to human protection and data reliability Emphasis on the risks to participants beyond those associated with standard medical care Prospective management of risks critical to quality factors
8	Protocol	Well-designed for human protection and data reliability Scientific objectives explicit Clear, concise, feasible protocol, plans, or documents
9	Results	Quality and information generated supportive of good decision Data capture, management and analyses, and quality of the information fit for purpose and proportionate to the risks Operationally feasible processes to support key trial objectives Computerized systems focus on factors critical to quality Efficient and well-controlled documentation for accurate reporting, interpretation, and verification Secure retention of records for the required period Transparency-registration of trials and posting of results
10	Roles and responsibilities of the sponsor and the investigator	Responsible for respective activities–tasks, duties, or functions Responsible for conduct, quality, and data integrity for activities transferred to service providers Responsible for appropriate oversight of the activities
11	IP	Manufacture in accordance with GMP Measures to retain quality of IP Use of IP in accordance with the protocol and trial documents Manufacturing, handling, and labeling of IP to ensure blinding Labeling of IP in compliance with regulatory requirements Adequate measures to ensure handling and shipping

IC=Informed consent, IRB/IEC=Institutional review board/independent ethics committee, IP=Investigational product, GMP=Good manufacturing practice, GCP=Good Clinical Practice

trial conduct efficient. E6(R3) has upgraded the guidelines for employing state-of-the-art technologies in managing clinical trials [Table 2]. The approach of this guideline is media-neutral to facilitate the use of different technologies for the purposes of documentation.[3] The guidelines recommend that the use of technology in the conduct of clinical trials should be adapted to fit the participant attributes and the specifics of trial design.[3] This guideline's thrust on technology would impact all aspects of trial conduct, quality, ethics, and responsibilities of stakeholders.

QUEST FOR QUALITY

ICH E6(R3) aims to foster a quality culture by proactively designing quality into clinical trials and drug development planning.[3] This guideline recommends that quality by design should be implemented to identify the data and processes that are crucial in ensuring trial quality, the risks that have the potential to compromise the integrity of those factors, and the reliability of the trial results. In all sections, the guideline emphasizes need for ensuring quality. Key activities of the clinical trial – monitoring and data management are considered essential quality control activities. The use of novel technologies has raised the bar for quality and enhanced the responsibilities of the stakeholders.

EXPANSION OF ETHICS

E6(R3) guidelines include ethical issues described in E6(R2), which have been the foundation of GCP, and current

Table 2: International Council for Harmonisation E6R3 critical changes

Theme	Content
Thrust on technology	Data acquisition - EHR, eCRF, source records, wearable devices, sensors, and social media
	Patient interaction – PROs and COAs
	Consent process - electronic, video
	Computer systems - validation, audit trails, metadata, user, management, backup, disaster recovery, and IT security
Quest for quality	Quality by design and fit for purpose
	Quality management system and risk management
	Quality of computer systems/technology
	QA and control of trial conduct
	QC focus - monitoring and data management
Expansion of ethics	Transparency - registration of trials and posting of results
	IC - electronic, images and video, telephonic, text in different formats, telephone, video conferencing, and remote
	Ethical review of protocol, documents, measures, and technologies to obtain and document IC if not possible in emergency research
	Process - reconsent, minor assent, and withdrawal of consent
	Conflict of interest - investigator, investigator site staff, and/or sponsor not to participate in EC review and decision
	Submission of protocol and relevant documents by sponsor
	Review of SUSARs
	Privacy, confidentiality, and data protection
Rising responsibilities-EC	Interpretation of principles to ensure ethical conduct
	Review of protocol procedures-PROs, COAs, and digital health
	Review of technology in consent documents and process
	Ensuring privacy, confidentiality, and transparency
	Review of safety information and updates
	Continuing periodic oversight
Rising responsibilities - Investigator	Oversight and quality of conduct for activities delegated to service provider/SMO
	Integrity and security of data irrespective of media used
	Transparency - sharing results and treatment with participant
	Timely access and review of data impacting participant eligibility, treatment, or safety
	Ensuring privacy, confidentiality, and transparency
	Computerized systems - quality, validity, and security
	Data governance
Rising responsibilities - Sponsor	Implement risk - proportionate processes for human protection and reliability of the trial results
	Oversight on QA/QC of the trial-related activities of investigators and service providers
	Ensuring privacy, confidentiality, and transparency
	Computerized systems - quality, validity, and security
	Data governance - data integrity, traceability, and security
	Criteria for the essentiality of records

EHR=Electronic health records, eCRF=Electronic case record form, PROs=Patient-reported outcomes, COAs=Clinical outcome assessments, IT=Information technology, QA=Quality assurance, QC=Quality control, IC=Informed consent, EC=Ethics committee, SUSARs=Suspected Unexpected Serious Adverse Reactions, SMO=Site Management Organization

ethical considerations [Table 2] based on new technological approaches for trial design and conduct. The guideline's focus is on ensuring the participant's rights in diverse conditions e.g., emergency research, electronic consent, on transparency of clinical trial and sharing of results, and protecting privacy and confidentiality. Integration of ethical requirements in the principles would facilitate the clinical research professionals in ensuring appropriate ethical practices when faced with new ethical challenges. Expansion of ethics would increase the burden of the ethical review.

RISING RESPONSIBILITIES

The current revamp of ICH E6(R2) is intended to facilitate clinical trial conduct in step with scientific and technological advances. This would lead to significant changes in the management of all processes throughout the life cycle of the clinical trial. Adoption of robust scientific knowledge in the design of trials, application of digital tools in study procedures, and the emergence of new ethical challenges would increase the burden of compliance to new GCP standards for all stakeholders [Table 2]. The EC should ensure the protection of the rights, safety, and well-being of participants in different types of trials. The investigator should be ready to face the challenges of complying with novel ethical, scientific, technological, and quality requirements. The sponsor's overarching responsibility of implementation of challenging compliance requirements to contemporary benchmarks of new GCP guidelines has increased enormously.

IMPACT OF REVAMPED GOOD CLINICAL PRACTICE GUIDELINE

New renovated E6(R3) is a major effort in updating and modernizing postpandemic changes in clinical trial design and conduct. It includes innovations in clinical trial designs

and technology and new operational approaches in trial conduct, which were rapidly adopted during COVID-19. During the COVID-19 pandemic, clinical research professionals – investigator site team, EC members, and sponsor teams – adapted to new ways of trial conduct with little systematic training. The conduct of COVID-19 clinical trials was fraught with the ethical challenges of obtaining voluntary informed consent from vulnerable participants.[4] Some of the observed deviations in trials conducted during the pandemic e.g., inadequate study oversight, missed critical protocol deviations, lack of source documents, lack of accuracy and completeness of data collected, lack of regular review data entered in the ePRO devices, and limited or no on-site monitoring, could have serious consequences for the protection of participants and the integrity of data.[5] Many such procedural or protocol adjustments to clinical research practices considered acceptable during the pandemic could be considered serious noncompliance in post-E6(R3) era. Hence, there is an urgent need for all clinical research professionals to develop competence in trial conduct procedures recommended by renovated GCP guidelines. Training workshops should focus on:

- Principles – Interpretation of principles to facilitate compliance with GCP
- Ethics – Current ethical concepts of protection of clinical trial participants
- Technology – Innovative technological approaches for data capture
- Science – Novel scientific designs for clinical trials
- Guidelines – ICH guidelines for the design and conduct of clinical trials
- Quality – Systems and processes to ensure compliance with quality standards
- Regulations – Regulatory requirements and expectations vis-à-vis new GCP.

These GCP update workshops should be tailored to the specific new responsibilities of the key stakeholders.

IMPLEMENTATION CHALLENGE IN INDIA

The main objective of modernized ICH GCP guideline is to provide a unified standard for the facilitation of the mutual acceptance of clinical trial data for ICH member countries and regions by applicable regulatory authorities. However, implementation of E6(R3) would be difficult in India as the Indian GCP is the only legal guideline as per the New Drugs and Clinical Trials Rules 2019 (NDCTR 2019). Indian GCP, which was released in 2001, has not yet been harmonized with E6(R2). Hence, the Indian GCP does not include current concepts such as quality management system, risk-based monitoring, and the use of computer systems in clinical trial conduct. Indian drug regulatory authorities did permit modifications in scientific, ethical, and technological aspects of trial conduct during the pandemic. NDCTR 2019, or Indian GCP has not been updated to include new developments in scientific, ethical, and technological aspects of clinical trials. Unless Indian GCP is modernized with ICH E6(R3), conduct of Indian clinical trials would not meet international GCP quality standards. As India aims to be an important player in global drug development, it is crucial to harmonize Indian GCP in step with renovated ICH GCP.

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Conflicts of interest

There are no conflicts of interest.

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