

GCP Irregularities in Conduct of Studies How Far Are We Compliant to GCP?

Mujtaba Hussain Naqvi Syed, Suresh Kamireddy and Mohd. Salman

Clinsync CRO, Hayathnagar, Hyderabad, India

Abstract: Clinical research is the key to the discovery of latest diagnostic methods and to develop modern drugs for treatment of diseases. Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Globalization of clinical research demands the studies to be conducted in compliance with GCP. In spite of regulatory stringent rules, irregularities occur in conduct of studies especially with regard to compliance with GCP. This article deals with the common irregularities observed in conduct of studies and recommendations to minimize such irregularities.

Key words: GCP • Compliance • Clinical Studies

INTRODUCTION

Quality of clinical trial rests on data integrity and safety of studied population[1]. The globalization of research and complexity of trials together with the regulatory turning stringent maintaining quality has become mainstay in conduct of studies. According to a study of over 10,000 protocols, Dr. Getz observed that between 1999 and 2005, the number of unique study procedures grew by 6.5% annually. During the same period, the average number of inclusion criteria increased nearly thrice. This caused a significant increase in the investigator site burden. The annual increase of the site burden was 10.5%. The length of CRF increased from an average of 55 pages in 1999 to 180 pages in 2005-a rise of 227%. Dr Getz concluded that such a significant increase in the investigator site burden would adversely impact the site performance [2].

The Indian Good Clinical Practices (GCP) based on the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) provide operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and reporting procedures and should be strictly adhered to while carrying out a trial. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and

recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki and ensures that clinical trial data are credible.

It has been widely recognized that India offers unique opportunities for conducting clinical trials in view of the large patient pool, well- trained and enthusiastic investigators and premiere medical institutes available in the country along with considerable low per patient trial cost, as compared to developed countries.

The Indian Good Clinical Practices (GCP) based on the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) provide operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and reporting procedures and should be strictly adhered to while carrying out a trial. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India[3].

The Principles of ICH GCP [4]: 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).

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.

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

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

Clinical trials should be scientifically sound and described in a clear, detailed protocol.

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

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.

Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s).

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

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

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

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

International Observations on Gcp Compliance in Studies: Annual report of the Good Clinical Practice Inspectors Working Group 2013 conducted by European Medical Agency, a total of 1052 deficiencies, comprising

64 critical (6%), 429 major (41%) and 559 minor (53%) were recorded for the 83 CHMP requested inspections conducted in 2013. The deficiencies were broadly divided as below[5].

General

Essential Documents:

- Lack of essential documents e.g. receipt of IMP shipment to site, records of blood samples shipment to the central laboratories
- Incomplete documentation e.g. incomplete screening list
- Lack of contemporaneous independent copy of the Case Study Report (CRF) filed on site Standard Operating Procedures (SOPs):
- Lack of evidence that sponsor SOPs have been followed and used
- SOPs not update as required
- Sponsor failure to implement an efficient quality management system

Source Documentation:

- Discrepancies between source data and data reported in the Clinical Study Report (CSR)
- Missing source documents
- Lack of document specifying location of source data

Qualification/training:

- Incomplete training documentation
- Lack of training of study personnel on trial related procedures

Organization and Personnel:

- Incomplete site personnel signature log
- Tasks performed by staff not authorised to do so

Trial Management

Data Management:

- Inappropriate system for reporting protocol violations
- Laboratory reports were submitted late to the site
- Data management activities were only undertaken after the clinical conduct of the trial was Completed.
- The decisions made by the DMSB were not communicated to the site

Monitoring:

- Monitor has not identified number of deficiencies on site
- Lack of escalation process to resolve issues identified by monitor
- Monitor not following monitoring plan
- Investigator's training was done over the phone

Document Control:

- Lack of version/date on the document
- Late introduction of amendments in the study

Investigational Site

Protocol Compliance (Selection Criteria):

- Violation of a number of inclusion criteria for some patients
- Final decision about eligibility not always documented in hospital records

Reporting in CRF/diary:

- Several discrepancies between source data such as medical history, concomitant medication etc. and the CRF for a sample of subjects
- Corrections on CRF not signed and dated
- Data not reported in CRF in a timely manner

Protocol Compliance (Others):

- IMP and concomitant medication protocol deviations
- Protocol visits were not performed within the visit windows specified in the protocol
- The sponsor established and used a system of prospectively accepting deviations from the protocol
- Insufficient maintenance of blinding of IMP

Protocol Compliance (Safety Reporting):

- Not all adverse events reported to the sponsor as required per protocol
- Instructions for SAE follow-up reports not followed
- Inadequate SAE documentation and reporting

Protocol Compliance (Assessment of Efficacy):

- Site did not strictly follow the protocol criteria that had to be used to assess the disease status

- The procedures for the primary end point assessment for patients were not always strictly followed as required by the clinical protocol.

Indian Scenario: Inadequate/inaccurate case histories form the second most commonly cited deficiency in US FDA inspections of clinical investigator sites. Similarly, source documentation issues ranked 5th among the top 10 findings from European Medicines Agency (EMA) inspections of investigator sites in 2009 and in some instances the findings were classified 'critical'. In one of the studies conducted on documentation by medical students It was found that 77.8% of the participants had low knowledge about medical records documentation and 54.1% of them did not have good attitude about completion of medical records the significance and value of medical records documentation in treatment, education and research. Results of this study indicate that delinquencies of medical records at the university-affiliated hospitals are due to lack of awareness of the students towards the method of medical records documentation.⁶ Not surprisingly, clinical trial monitors and auditors also report documentation issues as a frequent area of GCP concern.

To ensure that the bio-availability and bio-equivalence (BA/BE) studies are performed strictly in accordance with the applicable regulatory provisions and prescribed guidelines in the country, the Drugs Controller General of India (DCGI) has started auditing of all the clinical research organisations (CROs) in the country.⁶

Common GDP Irregularities

Informed Consent Process:

- Name on consent form and screening not matching.
- Date of Birth and age is not matching.
- Sufficient time is not given for reading patient information sheet.
- Inconsistency in signature of volunteer
- Signature of investigator is not done.
- List of eligible volunteer's not filed in the ICF File.
- ICF Distribution and Presentation Record not documented properly.

Ae Recording

- AE reporting form is not complete.
- Concomitant medication given but AE is not reported.
- AE not reported to sponsor or IEC.

Case Record Form

- Date and time of activities not entered correctly.
- Blanks left out for observations. E.g. subject number not entered.
- Finding cannot be traced with source data.
- Deviations were not documented.

Operational Errors

Delegation

- Delegation of duties not documented properly or not followed accordingly.
- Delegation done by unrelated personnel.
- The delegated personnel do not receive protocol training.
- The delegation was given to one personnel but documentation was done by different personnel.

Drug Dispensing

- Study Drug Dispensing and Accountability Record errors.
- Pharmacy entry and exit log error
- Batch no. is not matching

Drug Dosing

- Absence of PI/CI/Physician during dosing activity
- Restrictions not followed
- Unauthorized access to clinics

Recommendations to Minimize Irregularities in Studies:

- Regular GCP training and documentation maintained by departments.
- Workshops and training in good documentation practice to be conducted regularly by project management team.
- Quality Assurance to report irregularities observed to Investigators for appropriate corrective measures to prevent them in future.
- Completeness of documentation to be checked by quality control before starting of study.

- Principal investigator to ensure protocol training is given to all delegated staff of study and a questionnaire to assess the level of understanding on vital aspects of protocol can be implemented.
- Training on study specific SOPs to be given before study by the personnel delegated by principal investigator.
- Independent monitor delegated by quality assurance to overview consent process and documentation.
- Medical monitors to assess inclusion of subjects and safety aspects before and during the conduct of study.
- Project managers to ensure that monitors have a checklist of aspects to be checked at the site during monitoring visit.
- Training and updates on changing regulatory requirements in different regions to be given to study staff by the quality assurance.

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