Review Article

Audit Finding's on GCP Violations and it's Prevention

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ABSTRACT

This article summarizes regarding audit findings on GCP violations or on it's noncompliance and what are the aspects that a regulatory authority would find during an audit of clinical trial on violation of GCP and what are the measures to be taken in preventing them by the investigator, sponsor, clinical trial related staff and all others. if the GCP violations are not prevented it would ultimately lead to termination of clinical trial and imposition of fines/penalties by the regulatory authorities.

Keywords: Inspect, conduct, audit, report, compliance.

INTRODUCTION

As we all know ICH-GCP guidelines are the most important guidelines in a clinical research industry and all the clinical trials conducted globally should have their compliance with ICH GCP. [1]

The most common audit findings on GCP violation are as follows….

- Informed consent form
- Institutional review board/ independent ethics committee
- Protocol adherence.
- Reporting of SAE

Findings of Informed Consent form

Informed consent form is defined as voluntary consent given by the subject after listening to all the trial related risks and benefits of participation into the trail by the investigator. whICH is to be signed and dated by subject.

Informed consent form should contain all relevant information of objectives, methods of study, drug product, treatment regimen, available alternative treatment and all possible complications and discomforts, which may arise from participation in study.

Informed consent form is the responsibility of the investigator, who should prepare and get prior approval from IRB/IEC.

Informed consent form is used by the subject/legally accepted representative/impartial witness.

Regulatory authority would inspect if subject has obtained ICF prior to the participation of trail.

- They would inspect whether study staff is qualified enough to obtain ICF.[2]
- They would inspect whether legally accepted representative present is valid or invalid.
- They would inspect if the given ICF has been approved by IRB/IEC.
- They inspect whether the patient has signed full ICF.
- They inspect if ICF has amendments and if they have their approval/favorable opinion by IRB/IEC.
- They inspect whether the consent has been conducted in conductive environment.
- If ICF has been translated into preferred language of the subject by the translator, the regulatory authority would inspect if the translator is qualified enough or not.
- They also inspect if substantial amendment to ICF is approved.
- They would inspect if translated consent signed and dated by a non-English speaking patient/study registration/enlistment and also check if it contains required signatures.
- They would also inspect if consent used was the current IRB/IEC version at time of patient registration or not and if outdated consent was used
- They would inspect If reconsent not obtained as required consent of ancillary/advanced imaging studies not executed.
- They would inspect If consent of ancillary/advanced imaging studies is not executed.

Quality Control findings of Informed Consent Form

They would inspect for various quality control findings of informed consent form such as if consent form has been signed by participant but signature of investigator or witness is not dated.

They would inspect if whiteout is used to correct an error on consent form.

Findings of Institutional Review Board/Independent Ethics Committee

As per ICH GCP guidelines, right, safety and well being of trial subjects are the most important considerations and should prevail over the interests of science and society.

As we need an external person to review independently whether ICH GCP guidelines has been followed or not which has to be performed by IRB/IEC.

IRB/IEC should be independent of investigator and sponsor.

They inspect the following….

- If information requested by regulatory authority regarding written procedures (sop) and membership lists is been refused or accepted.
- If they meet minimum eligible criteria of composition as we are aware that it is about 5 members. Which includes the following….

Physician

Physician should be the first person in ethics committee.

The clinical trial which has been designed if it is relevant and if meets all the applicable requirements or not is been checked by the physician.

Pharmaceutical Scientist

Pharmaceutical scientist is responsible for reviewing of drug products.

Social Activist

He/she is the person who is works for society and well being of society.

They would talk about the benefit of society.

Retired Judge

He/she would review for any of those legal obligations on conduction of clinical trial.

Laymen

Persons who does'nt involve in review of clinical trial are not responsible for review of clinical trial.

They would review regarding compensation of subjects.

All the 5 members are responsible for voting and give approval only when clinical trials are performed based on ethics.

- They would inspect if any of them are missing in the composition.[3]
- They inspect if work has been taking place according to the written procedures like sop and if sop's are available or not.
- They also inspect if all the submitted reports like serious and unexpected and related have been taken care or neglected.
- They also inspect for presence of relevant records which should be retained for at least 3 years.
- They would inspect if there is any documentation is missing.
- They would inspect for reapproval of expedited reporting.
- They would inspect if there are any major changes for approved protocol that would increase the risk to subjects were given expedited approval only.
- They would also inspect expedited reapproval for situations other than approved exceptions.

Findings of Protocol Adherence

- Protocol is a document that describes the objective, design, methodology, statistical considerations and organization of a trial.
- The protocol usually also gives the background and rationale for the trail, but these could be provided in other protocol referred documents throughout the ICH-GCP guidelines.
- A written description of changes to formal classification of a protocol is called protocol amendment.
- Protocol is prepared by the sponsor.
- Investigator/institution should conduct the trail in compliance with protocol.
- Adherence to study protocol is the most critical. because any deviation to the protocol is considered as non-compliance or violation of protocol irrespective of study sponsor's acceptance on deviation.[6]
- So a regulatory authority would inspect the following…

Omission

If they have met the requirements in the protocol or not.

Addition: They inspect if we perform an activity which is not specified in the protocol.

Deviation: They inspect if there is any change in particular procedure as specified in the protocol.

- ❖ They would inspect if amendment is documented, dated, and if maintained with the protocol.

- ❖ They would also inspect if any change to the protocol has been performed by investigator and if it is been reported to the sponsor by investigator or not.
- ❖ They would also inspect if the amendment is been approved by IRB/IEC and regulatory authority prior to implementation.
- ❖ Auditor would firstly find evidence for deviation from protocol and review the following…..
- ❖ They would inspect what are the reasons for deviation.
- ❖ They would inspect if the patient fails to complete scheduled visits as required by the protocol.
- ❖ They would inspect if list in final study report matched the protocol deviation log for the site.

FINDINGS OF REPORTING OF SAE

Serious Adverse Event (SAE)

Any noxious, unintended event which falls under the following criteria..

- ➢ fatal/death.
- ➢ life threatening.
- ➢ inpatient hospitalization/prolongation of inpatient hospitalization.
- ➢ congenital animalia or birth defect.
- ➢ persistent disability.
- ➢ other medically insignificant event.
- ➢ All grades, types, duration of SAE should be accurately recorded.[5]
- ➢ We should obtain the required protocol baseline studies needed to effectively assess toxicity.
- ➢ reporting of SAE plays an important role in ICH GCP as the safety and well being of trial subjects are the most important considerations.
- ➢ they inspect if SAE have been reported at correct time or not as it is very critical.
- ➢ they inspect documents related to SAE'S.
- ➢ they inspect 1) charges
  2) study notes[1]
- ➢ they inspect for any laboratory abnormalities.

Prevention of GCP violations

GCP violations can be prevented by following the below considerations. if these preventive measures are not taken the clinical trial would most likely be terminated and fines are imposed by the regulatory authority.

Prevention of informed consent form violations

- ➢ We should always check if participant's informed consent documentation is completed before beginning study procedure.[8]
- ➢ We should never perform any study assessments before obtaining informed consent form from potential participants.
- ➢ We should always review study and consent form with the participant as soon as the failure is identified.
- ➢ We should document all steps to correct the situation and attach them to the signed ICF and notify our supervisor immediately.
- ➢ We should conduct consent interviews in a quiet, separate room.
- ➢ While reviewing a consent form with a participant, we need to focus on that task instead of distractions.
- ➢ The person who obtains a participant's consent must be present when consent form is signed. having the investigator sign the consent form later is unacceptable. We should never backdate a consent form.
- ➢ We should create and use check list in order to ensure every detail in ICF process is obtained.
- ➢ By following good documentation practices, if an error takes place during it's completion. good clinical practice or good medical record correction techniques can be used to correct it.
- ➢ We need to cross out the error without obstructing original entry, initial, date, and crossing out and enter correct information.
- ➢ When issues are identified, we should reconsent the participant using appropriate informed consent form and attach a memo identifying the issue and the corrective action to new consent form.
- ➢ When a new consent form is required to check on each participant of next visit to ensure that he/she has signed the new form.
- ➢ We need to device a system for flagging the files of participates who have not yet signed new consent forms.
- ➢ We should use a tracking spreadsheet.
- ➢ We must ensure documentation of consent form is in source notes.

Prevention of Institutional Review Board/Independent Ethics Committee violation:

- ➢ in order to prevent GCP violations in IRB/IEC may need to follow a few appeal of determinations which are as follows…
- ➢ no overrule should be permitted.[9]
- ➢ it should not allow a committee or a official to set aside or overrule a determination by IRB/IEC to disapprove modifications recommended by IRB/IEC .

- IRB/IEC should provide notice to investigator on disapproval. it should provide research investigator with a written statement of its reasons regarding its opinion of modification/ modification in proposed research and must give investigator an opportunity to respond in person or in writing.
- it should conduct ongoing monitoring, initiatives.
- the IRB/IEC should be responsible for reviewing of all audit findings or other reports.
- it should evaluate and determine whether if it requires corrective action or not.
- IRB/IEC should conduct self-assessments and monitoring.
- it also should conduct regular meetings to identify areas of review and operations whICH may require further enhancement and strengthening.
- whICH includes an evaluation of membership &composition of IRB's to ensure appropriate expertise relative for the portfolio of research conducted.
- IRB/IEC should review and approve research utilizing expedited procedures in accordance with regulatory authorities.
- It should conduct meetings in an orderly manner.
- It should appoint qualified IRB/IEC members to review and approve research utilizing expedited procedures in accordance with the regulatory authorities.
- during audit, all documents like written procedures, membership lists, requested by regulatory authorities should be given.
- documents should be maintained appropriately.
- works should be carried out according to written procedures like sop, and sop should be maintained properly.
- the reports like serious and unexpected submitted to IRB/IEC should be checked and relevant action should be taken.

Prevention of Protocol Adherence Violation

- we need to have thorough review and understanding of the protocol.[10]
- We should crosscheck and identify any procedures in the protocol that differ from standard practice at our establishment.
- It would be much better to conduct regulation initiation meetings and give relevant training to staff members.
- To implement and use a well-designed study specific forms for documentation including checklists.
- We can prevent most of the deviations by performing study required procedures and visits within the required window.
- Because of large number of out of window procedures/visits may indicate poor scheduling/planning.

During Navigation

We have to make sure eligibility criteria are clear and there is no subject to interpretation.

- predicting all the possible deviations during navigation itself and prior to IRB/IEC submission and creating contingency plans in the protocol would be more appropriate and advantageous.
- regular internal monitoring would also be favorable for preventing deviations.
- we should be careful during reviewal of amendments.
- We should use correct version of the protocol.
- the clinical trial should be conducted in accordance with protocol that has been prepared by the sponsor which have also received prior approval from IRB/IEC and regulatory authorities.
- no deviations should be implemented by the investigator without consulting or having agreement with sponsor and also without approval/ favourable opinion of sponsor.
- except in conditions such as…
  - immediate hazards to subjects
  - when subjects involves only logistical or administrative aspects of trail like..
  - if monitors are changed
  - telephone numbers are changed
- any deviation that has been implemented by investigator/ person designated by the investigator should be able to give proper explanation on deviation.
- violations occur due to human errors.
- if we intend to correct the violations such that explaining the cause of situation of violence. it is mandatory to document them and take their approval/favourable opinion from IRB/IEC.

Prevention of Reporting of SAE violation

- It should conduct follow up studies which are necessary to assess if AE is performed or not.
- There should be no delayed reporting of AE that would require filing an expedited AE report.
- There should be no recurrent under or overreporting of AE.[5]
- AE should be substantiated.

- All SAE should be reported by investigator to sponsor within 24 hours and to IRB/IEC within 7 days.
- Sponsor should report SAE to regulatory body immediately.
- The expeditated reports/immediate reports should have compliance with ICH clinical safety data management and should also comply with applicable regulatory requirements.
- All the safety updates, and periodic reports should be reported to the regulatory authorities as specified.
- SOP'S should be developed for handling of reporting of SAE.
- Monitor's should help in ensuring timelines of reporting from the site, ensure final reports are sent and reconcile total no of SAE'S.
- Trial monitors should review the patient's files and ensure that all the SAE'S were reported to regulatory body within required time frame and should update them to a stable status.
- Local safety monitor should provide real-time safety oversight.
- Local safety monitor should review SAE'S immediately after they occur and should follow the events until resolution.

CONCLUSION

Good clinical practice is the most important guideline which is to be followed by each and every individual involved in conducting a clinical trial. It's noncompliance can easily be easily found out in the inspections. most of the GCP findings on its violations include informed consent form, IRB/IEC, protocol adherence, reporting of SAE. So violations should be prevented by maintaining all the relevant documents, following sop, protocol, maintaining timelines for SAE reporting and all required GCP requirements.

REFERENCES

1. https://www.mastercontrol.com/gxp-lifeline/top-five-GCP-violation-0410/
2. https://centres.sg/wp-content/uploads/2017/10/BO1201_Ms-S-SACHIDANANDAN_02.pdf
3. http://fercit.org/SIDCER-FERCAP/Handout_10/2.%20Common%20findings%20related%20to%20IRB%20compliance%20to%20ICH%20GCP%20_Dr.%20Gunnar%20Danielsson.pdf
4. https://www.fda.gov/media/93884/download
5. Rajusama, Vijaya Lakshmi, Satish M, Audit of an investigator site-A Crucial task in clinical research to ensure a reliable clinical trial, Review of planning methodologies & techniques, International journal of research and development in pharmacy and life sciences,2016, volume-5,issue-4,(received May 13 2016, Accepted july 27,2016).
6. https://GCP.nidatraining.org/modules/6/pdf
7. Pooja Mahajan, Natasha D'souza, Arun Bhatt, Vipul Halbe, Richa Sharma, Shweta Narayana Swamy & Murtuza Bhughediwala, US Food and drug administration Indian site inspections: An Experience, Perspectives in clinical research,2012,April-Jun 3 (2):73-79 PMCID: PMC3371552 PMID: 22701824
8. Informed consent https://GCP.nidatraining.org/modules/2/pdf
9. https://www.dfhcc.harvard.edu/crs-resources/OHRS_Documents/02_-_Investigator_Resources/IRB_Policies_and_Procedures_for_the_Protection_of_Human_Subjects.pdf
10. http://heilbrunnfamily.rucares.org/assets/file/Protocol%20Deviations%20and%20Protocol%20Violations%20Made%20Simple%20DBRK%208%201%202013%20FINAL%20(2).pdfTEN
11. Habarugira Jean Marie Vianney, Antonia Agusti, Michael Makanga, Serious Adverse Event Reporting and follow-up requirements in the European developing countries clinical trials: current practice, J Pharmacovigil, Jan, volume-22, 2014. DOI: 10.4172/2329-6887.1000148.

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