



Review Article

AUDIT OF AN INVESTIGATOR SITE - A CRUCIAL TASK IN CLINICAL RESEARCH TO ENSURE A RELIABLE CLINICAL TRIAL: REVIEW OF PLANNING, METHODOLOGY AND TECHNIQUES

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ABSTRACT

Clinical trials for establishing the safety and efficacy of a drug can be among the most costly and time-consuming elements of product development. The success of any clinical trial is dependent on assuring that the data collected are of good quality. Clinical investigator site audits may be conducted at any medical facility or institution where clinical trials are conducted on human volunteers or subjects. Due to the increasing complexity of clinical trials and regulatory scrutiny, the components of a site audit program and the approaches taken towards designing and managing audits are constantly evolving. Audit forms an important part of a quality system to determine if clinical studies are being conducted in compliance with applicable statutory and regulatory requirements paying particular attention to subject rights, safety and well-being, and to provide verification of data integrity. Although auditing alone cannot transform a poorly planned, executed, monitored, or analyzed trial into a credible one, an active clinical trial audit program will point out potential problem areas early, so solutions can be found before it is too late. Used effectively investigator site audits can reduce costs, maintain project schedules, and ensure regulatory compliance. To make sure that these benefits will be realized, however, sponsors must develop a comprehensive auditing strategy.

Keywords: Clinical trials, Investigator site, Audit, Quality system, Regulatory compliance.

Abbreviations: ICH: International Conference on Harmonisation; GCP: Good Clinical Practice; SOP: Standard Operating Procedure; CRFs: Case Report Forms; CRO: Contract Research Organization; GMP: Good Manufacturing Practice; CV: Curriculum Vitae; CIOMS: Council for International Organizations of Medical Sciences; LAR: Legally Acceptable Representative; ICF: Informed Consent Form; IRB: Institutional Review Board; IEC: Institutional Ethics Committee; IMP: Investigational Medicinal Product; SDV: Source Data Verification; AE: Adverse Event; SAE: Serious Adverse Event; SUSARs: Suspected Unexpected Serious Adverse Reactions; CAPA: Corrective Action and Preventative Action plan; FDA: Food and Drug Administration; EMA: European Medicines Agency

INTRODUCTION

Clinical trials for establishing the safety and efficacy of a drug can be among the most costly and time-consuming elements of product development. If procedural errors render unusable the information gathered in a series of clinical trials, the time and expense required to conduct the studies again can easily terminate the entire development effort.

The investigative site, focusing on clinical research is where the subjects are identified and enrolled, where treatments are sought and tested, where assessments are made and data are collected and entered into case report forms.

Clinical investigator site audits may be conducted at any medical facility or institution where clinical trials are conducted on human volunteers or subjects. Typically, the following clinical investigator sites are audited:

Clinical investigator sites conducting Phase II–Phase III studies
Clinical investigator sites conducting Phase IV studies upon requirement of regulatory authorities

Clinical investigator sites, contract research organizations, or Phase I Units.

Clinical investigators who conduct human subjects' research with investigational/approved drugs are required to permit auditors to access, copy, and verify any records or reports

made by the clinical investigator with regard to, among other records, the disposition of the investigational product and subject's case histories [1].

Audit forms an important part of a quality system. The success of any clinical trial is dependent on assuring that the data collected are of good quality [2].

The fundamental principles of Good Clinical Practice (GCP) are protection of human subject's rights and safety as well as the validity and accuracy of data generated from clinical trials to support regulatory submissions. Trial sponsors are required by the International Conference on Harmonisation (ICH) guidelines to implement and maintain quality assurance and quality control systems to achieve these objectives.

ICH GCP defines audit as '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, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s) [3].

The way for sponsors to ensure that there will be no unpleasant surprises after clinical trials are finished is to plan for one or more independent investigative site audits during the trials to determine if clinical studies are being conducted in compliance with applicable statutory and regulatory requirements paying particular attention to subject rights, safety and well-being, and to provide verification of data integrity.

Investigator site audit, which is typically conducted no more than once or twice during the course of a clinical trial, encompasses many aspects of the study. An audit of a clinical trial provides the research sponsor with independent appraisal of the quality and completeness of the data generated by the trial. Although auditing alone cannot transform a poorly planned, executed, monitored, or analyzed trial into a credible one, an active clinical trial audit program will point out potential problem areas early, so solutions can be found before it is too late. Audits also provide the chance to review one clinical research system, such as control of a clinical trial, across several sites. In rare

instances, an audit can be used to investigate possible fraud. In such cases, data audits can show whether data in source documentation, such as medical records and laboratory reports, are consistent with entries on Case report Forms (CRFs) and data listings. Used effectively, therefore, audits can reduce costs, maintain project schedules, and ensure regulatory compliance. To make sure that these benefits will be realized, however, sponsors must develop a comprehensive auditing strategy. Sponsors must decide not only which sites and data will be audited and how often the audits will be performed, but also how the information generated from the audits will be used to improve procedures [4].

AUDITING PRINCIPLES

Adherence to these principles is a prerequisite for providing a reliable and relevant audit outcome. These principles relate to auditors:

Ethical conduct: Trust, integrity, confidentiality and discretion are essential to auditing. Actions that may influence the results of an audit should be avoided.

Impartial reporting: The obligation to describe truthfully and accurately the audit activities.

Due professional care: The application of diligence and judgement in auditing. Reasonable care in all matters and the completeness of the audit report avoiding errors that may jeopardize any of these auditing principles.

Two further principles relate to the audit process:

Independence: Auditors cannot audit work where a conflict of interest would arise. They must maintain an objective state of mind throughout the audit process to ensure that the findings and conclusions will be based only on the evidence.

Evidence: The rational basis for reaching reliable audit conclusions based on audit criteria.

CHOOSING AN AUDITOR

One of the first, and most important, decisions the Sponsor faces is choosing an auditor. Because they are sometimes not part of the sponsors' organizations, contract auditors can promote a spirit of objectivity and encourage investigators to communicate problems openly. Auditors can also be chosen from the sponsor's quality assurance organization or from any group not associated with direct management of the clinical trial.

Auditors should be selected based on the following qualifications/experience and training:

- a) Suitable experience and education
- b) Independence
- c) Formal regular appropriate training
- d) Understanding of the clinical trial process
- e) Up-to-date knowledge of ICH GCP guidelines and any country-specific guidelines or regulations, national laws and requirements related to Clinical research.
- f) Skills required: Communication, Writing, Language etc.
- g) Nature: Tenacity, Power of observation, analytical capability, decision, sense of ethics and maturity

Suitable experience and education

- It is desirable that auditors be educated to University level or have equivalent experience in medicine, pharmacy, pharmacology, toxicology or other related field. Experience in good manufacturing or laboratory practices is certainly a good qualification for auditors, but a strong background in the relevant clinical area and experience reviewing medical records is also essential. The level of education is required to allow for effective communication with persons involved in clinical trials.
- Auditors need to be familiar with the healthcare systems in the various countries and to be familiar with basic medical terminology.
- Auditors must have had training in auditing techniques either from attendance at a course(s) and/or by being accompanied and mentored by experienced auditors.
- Auditors must be provided with a job description to document their roles and responsibilities and any ongoing training requirements.
- Up to date records of qualifications, training and experience must be maintained.

Independence

- Auditors must report, at the highest level to the body that has sponsored the audit, usually the Appointing Body. Preferably they should not be in a reporting structure in which the Chair of the Clinical Operations is their superior.
- Auditors, if assigned from an external source (i.e., not directly working for the relevant Sponsor/CRO)

must initially sign a statement provided by the Sponsor/CRO to show they have no conflict of interest, any financial or other links with the Sponsor/CRO and parties to be audited so that they can be provided with full access to all auditable documents. The auditor should also sign a confidentiality agreement to be allowed full access to documents.

Formal regular appropriate training

- Auditors must undertake regular GCP training/updates which must be documented in their CV/training records. The number of hours on GCP training will vary depending on whether there have been significant changes to GCP regulations since the last training was completed. Training should be completed when any new GCP directives/guidelines or other documents are issued, either at a national or international level.
- It is desirable to have training on the relevant parts of the Good manufacturing practice (GMP) requirements.
- Other appropriate training and training needs must be assessed regularly. Auditors must take action to maintain and improve their skills.
- The level of training required must be sufficient to ensure competence and skills required for the planning, execution, reporting and management of audits. Ideally, the course agenda and training materials should be permanently filed.

Understanding of the clinical trial process

- Auditors must have knowledge of principles and processes that apply to the development of a medicinal product and clinical research.
- It is recommended that auditors should have at least 1-2 years' experience in GCP auditing. The clinical trial process should then be well understood.
- Additionally, regular training should also be documented in the Auditors CV/training records.
- Auditors need to be familiar with procedures and systems for recording clinical data, have a knowledge and understanding of current technology, IT systems, data handling and archiving techniques.

- Up-to-date knowledge of ICH GCP guidelines and any country-specific guidelines or regulations, national laws and requirements related to the conduct of clinical trials and the granting of a marketing authorisation.
- Training needs to be conducted on a regular basis or when any new regulations or guidelines are published.
- The course agenda and training materials must be filed in the auditor's training records.

SELECTING SITES FOR AN AUDIT

In a multi centric trial the selection of the sample of clinical investigator sites may be achieved by a risk-based algorithm, by following a pre-determined set of selection criteria, or according to the auditor's own judgment. In all of these approaches, the factors that affect site selection typically include some or all of the following criteria:

- Study phase.
- Number of subjects recruited or enrolled at the clinical investigator site.
- Status of the clinical study in the project.
- Type of Patient population.
- Complexity of the study.
- Trial criticality for regulatory submission.
- Concern that the Investigator is not fulfilling his/her obligations or is noncompliant with GCP, protocol, or regulatory requirements.
- Information relating to concern for subject safety.
- Parameters and/or procedures critical with regard to quality.
- Information relating to consistent CRF discrepancies or high query rates.
- At request of the study operational team (if accepted by Quality Assurance unit).
- Past audit experience.
- Past inspection experience.
- Geographical and logistical considerations.
- Use of contract suppliers.

The sample of investigator sites allows assurance that systems and procedures for running clinical studies are effective.

AUDIT PLANNING

Elements of planning for an audit can be incorporated into an audit plan. An audit plan should include:

- **Scope:** To identify the intent, purpose, location, date (if known) of the audit activities and any relevant study identifiers.
- **Contacts:** To identify the key personnel involved in conducting the audit (both auditors and auditees).
- **Agenda:** Outline of detailed activities e.g. facility tour, identification of interviewees.
- **Documentation to be reviewed:** To identify the documents to be available for review.
- **Audit History:** To outline the audit history as relevant to the auditor-e.g., describes past interactions.
- **Letter/Communication:** Auditees should receive a letter of introduction with a confirmation of the audit dates and brief synopsis of activities to be conducted.
- **Provision for Responses:** Description of how responses are to be made (e.g. inclusion of action plan) and the expectant timeframe [5-7].

AUDITING PROCEDURES AND METHODOLOGY

Audit preparation

In preparation for the audit, auditors will review key regulatory and essential documents from the trial master file and investigator file at the sponsor or CRO. Documents to be reviewed include, as appropriate:

- Protocol and amendments.
- Investigator Brochure.
- Regulatory/IRB/Ethics Committee approval documentation.
- Protocol agreement and other study contracts.
- Case Report Forms (CRF) and site-specific consent forms.
- Investigational Medicinal Product Documents (e.g. accountability, shipment).
- Monitoring Plan, Monitoring Visit Reports, project plans and manuals.
- Safety plans and safety reports (e.g. Council for International Organizations of Medical Sciences CIOIMS).
- Important correspondence (pertaining to safety, protocol deviation or key decisions).

- Investigator qualification documentation (e.g. curriculum vitae, medical licenses, Financial Disclosure Forms (if necessary)).

Audit conduct

Audit activities conducted at the investigator site include, but are not limited to:

- **Introductory meeting:** Meeting with the Principal Investigator, Sub Investigator and/or Study Coordinator to review the objectives of the audit and to obtain preliminary information regarding site practices and conduct of the study at the site.
- **Review of documents**
 - **Informed consent process:** Review informed consent source documentation and signed Informed Consent Forms at the site.
 - Verify that correct version of consent form/assent form was used to consent the patients.
 - Verify the date the consent form was signed and dated by delegated site personnel and patient.
 - Ensure no protocol specific assessment was conducted prior to consent (check subjects medical record, source documentation).
 - In case an updated approved consent form version is available—the subject has been re-consented as required.
 - Legally acceptable representative(s) and/or impartial witness may provide consent only when the subject and/or legally acceptable representative (LAR) are unable to provide consent respectively.
 - Review and monitor the details to be completed in the informed consent form (ICF) for appropriateness i.e., contacts details of investigator, study staff and Ethics Committee.
 - Verify whether subjects received a copy of the signed ICF.
 - **Review and verify regulatory/ethics/essential study documentation in the site file:**
 - All applicable documents exist and are current as of date of audit.
 - Regulatory documents (Ethics, competent authority including amendments).

- Regulatory/Institutional Board (IRB)/Institutional Ethics Committee (IEC) communication.
- All approved versions of the protocol and protocol amendments—including Signature pages.
- Investigator brochure-All versions.
- Consent form and patient information sheets and advertisements.
- Randomisation procedure.
- Final CRF.
- site personnel qualification and training documentation.
- Delegation of responsibilities Log.
- Lab normal ranges and accreditation certificates.
- Screening log/enrolment log.
- Adverse event log.
- Reporting of protocol deviations.
- Serious adverse events, and safety reports for regulatory submission.
- Subject identification code list.
- Sample label.
- Prescription template.
- Investigational Medicinal Product (IMP) handling instructions/IMP management plan.
- Unbinding procedure (including checking sealed envelopes for integrity).
- Financial disclosure documentation.
- Monitoring reports.
- **Investigational Medicinal Product (IMP):** Review the receipt, storage, security, and accountability processes and documentation.
 - Check expiry dates of IMP on site and ensure valid quantity available for patient treatment.
 - Check that IMP is stored under protocol specified conditions.
 - Verify that IMP is dispensed as per protocol requirements.
 - Verify the labels on the IMP comply with the applicable regulatory requirements.
 - Ensure pharmacy file is reviewed and document filed is current.

- **Source Data Verification (SDV):** CRF sampling ratio and Study criteria to verify is determined prior to audit.
- **Safety:** identification, documentation and reporting of AEs and SAEs. Medical management of adverse events.
 - Verify AEs, concomitant medications, and underlying illnesses are reported accurately on the CRFs, and in accordance with the protocol.
 - Ensure that all AEs documented in CRF are verifiable with source documentation.
 - Verify that any urgent safety measure undertaken was reported to the competent authority and the sponsor as soon as possible (within three calendar days).
 - Check any specific requirements for reporting of serious adverse events (SAEs)/Suspected Unexpected Serious Adverse. Reactions (SUSARs) to external organisations other than competent authorities (i.e., IMP supplier) are done properly.
 - **Study Conduct:** adherence to protocol and Good Clinical Practice.
 - Confirm patient medical history with documentation available in medical notes.
 - Verify that the patient meets the inclusion criteria for the trial and does not meet any of the exclusion criteria – check against patient medical history/notes and CRF.
 - Check the deviations/violations log for departures from processes and protocol.
 - Protocol waivers to eligibility criteria are not permitted. The auditors should note deviations from eligibility criteria, to ensure that is clear documentation explaining the departure.
 - **Laboratory procedures:**
 - Review the procedure for collection of specimens and ensure compliance with protocol/SOPs
 - Review the laboratory has relevant trial documentation such as protocol, authorisations and written green light to process the samples. It should be checked that the relevant staff have adequate knowledge of GCP, pertaining to the tasks that they are carrying out for the trial.
- **Monitoring:** Review of monitoring practice, SDV and adherence to the Monitoring Plan
 - Review CRFs for completion and are signed and dated appropriately.
 - Verify the source documents that were used to complete CRFs.
 - Check whether the data are reported accurately on the CRFs and are consistent with the source data/documents.
 - Check whether the patients (including withdrawals) are followed up adequately or not.
- **Facility tour** (e.g. Pharmacy, laboratory, archive or other relevant departments). Any laboratory and/or equipment used for generation of key efficacy/safety data, and associated records, will be inspected during the tour. Any freezers used to store biological sample that will be analyzed for key data should also be checked during the tour.
- **Debriefing or closing meeting:** Meeting with relevant site personnel to discuss audit observations, explain audit reporting process, and answer any questions. The auditor should confer prior to the closing meeting:
 - To review the audit findings, and appropriate information collected during the audit, against the audit objectives;
 - To agree on the audit conclusions, taking into account the uncertainty inherent in the audit process;
 - To prepare recommendations, if specified by the audit objectives, and;
 - To discuss audit follow-up, if included in the audit plan.

Reporting of audit findings

Following the completion of each site audit non-conformities should be reviewed with the auditee to obtain acknowledgement that the audit evidence is accurate, and that the non-conformities are understood then a comprehensive audit report will be generated, which describes the scope of the audit activities and key findings and observations. The audit report is strictly confidential and should be retained securely and only shared with the

auditor(s), auditee(s) and the Appointing Body. The audit report should reflect the execution of the audit. It should be dated and signed by the auditor and contain, at the minimum, the following items:

- Scope and objectives of the audit.
- Identification of the auditor (s).
- Identification of the auditee(s) and the representative(s) of the auditee.
- Audit plan.
- Identification of the facilities, persons interviewed, and the documents reviewed.
- Audit methodology.
- Findings of the audit.
- Recommendations for corrective actions or areas of suggested revisions in practice.
- Timeframe for responses.
- Audit report distribution list.
- Signature and date of the auditor.

Classification of audit findings

In accordance with the level of importance or degree of impact of the audit findings, audit findings are graded based on the grade classification.

Normally, audit findings are classified using three or four grades. As an example, a three- grading scale and the definition of each grade are provided below.

Critical: This applies when the audit findings are considered to adversely affect the rights, safety or well being of trial subjects and/or the quality and integrity of the clinical trial or trial data. A combination of multiple “major” audit findings may result in a “critical” systemic audit finding even though each of the findings is not “critical.”

- Critical observations are considered totally unacceptable.
- Possible consequences: rejection of data and/or legal action and/or regulatory action required.
- Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

Major: This applies when, if not managed appropriately, the audit findings has possibility to adversely affect the rights, safety or well being of the trial subjects and/or the quality

and integrity of the clinical trial or trial data. A combination of multiple “minor” audit findings may result in a “major” systemic audit finding, even though each of the finding is not “major.”

- Major observations are serious deficiencies and are direct violations of GCP principles.
- Possible consequences: rejection of data and/or regulatory action required.
- Remark: Observations classified as major may include a pattern of deviations and/or numerous minor observations.

Minor: This applies to a deviation from the quality management system and/or the principles of GCP, where conditions, practices or processes would not be expected to adversely affect the rights, safety or well being of the trial subjects and/or the quality and integrity of clinical trial and trial data.

- Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.
- Possible consequences: Observation classified as minor indicates the need for improvement of conditions, practices and processes.
- Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences

Once the audit report is issued, the monitor, study coordinator and any other key investigator site staff should discuss the audit findings and decide how to respond to each finding. The response should contain both corrective and preventative actions, as appropriate to the findings of the audit. The audit response is therefore often referred to as a Corrective Action and Preventative Action plan (CAPA). It is customary for a post-audit courtesy or thank-you letter to be sent to the investigator site following the audit. Audit findings are not normally included in this letter. An Audit Certificate is usually generated upon completion of the audit as a record that the audit has taken place.

The audit certificate should include the following:

- Name and affiliation of the auditor

- Name of the site audited
- Audited system (for example, general review or specific to a project or clinical trial)
- Audit dates

The classification of the audit findings is intended to help classify the severity of observations noted during auditing of clinical trials. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e., severity). The specific examples provided in this document is not an exhaustive list further they would apply to specific audited parties and should be interpreted case by case.

Critical Observations

Prohibition

- Country specific Clinical Trial Import License and Clinical Trial Exemption is not obtained.

General

- Use of a prohibited substance(s) without having received prior authorisation.

Application for authorisation

- Misrepresentation or falsification of data submitted to obtain authorisation to conduct clinical trials.

Authorisation

- Clinical trial ongoing after authorisation suspended or cancelled.
- Importation of a clinical trial drug when authorisation is suspended or cancelled.

Amendment

- Information contained in the application for amendment falsified, misleading, or deceptive.
- Failure to notify regulatory authority after amendment was implemented in cases where the clinical trial endangered the health of trial subject or other person.
- Failure to stop a clinical trial during a suspension or cancellation.

Good clinical practices

- Evidence of fraud such as “fabricating” subjects, falsification of study data.

Labeling

- Statement(s) on label is/are false or misleading.

Records

- Failure to report SUSARs which occurred inside and/or outside specific country.
- large number of major protocol deviations not reported.
- No records in respect of the use of a drug in a clinical trial.
- No records with respect to the enrolment of clinical trial subjects/Subject not registered prior to treatment.
- Information given at registration is inconsistent with actual data in medical records chart (wrong stage of disease, diagnosis, cell type, etc.).

Additional information and sample(s)

- Providing false, misleading or deceptive sample(s) of the drug or additional information relevant to the drug or the clinical trial.

Interpretation

- Voting members of the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) were not independent of the qualified investigator and/or the sponsor of the clinical trial.
- IEC/IRB membership did not include a minimum of 5 members or IEC/IRB membership and registered with regulatory authority.

Major observations

IEC/IRB deficiency descriptions

- Approvals of clinical trials without a quorum of members with the required representation.
- IEC/IRB membership did not include the entire representative required by the country specific/ICH Guidelines for Good Clinical Practice.
- IEC/IRB did not have written procedures in accordance with Good Clinical Practices.
- IEC/IRB approval of the clinical trial was not conducted as per their written operating procedures.
- IEC/IRB did not maintain adequate written minutes of meetings.
- IEC/IRB did not consider the qualifications of qualified investigators before approving trials.

- IEC/IRB did not conduct periodic reviews of continuing clinical trials.
- Initial IEC/IRB approval documentation missing.
- Initial approval by expedited review.
- Protocol never approved by IEC/IRB/Failure to obtain IEC/IRB approval of the protocol and/or the informed consent forms prior to initiation of a clinical trial.
- Major changes to previously approved protocol that increase health risks to subjects, were given expedited approval only.
- Implementation of an amendment(s) without obtaining authorisation from IEC/IRB.
- Failure to implement IEC/IRB approved amendment(s) at a clinical trial site.
- Expedited reapproval for situations other than approved exceptions.
- Registration and/or treatment of patient prior to full IEC/IRB approval.
- Reapproval delayed greater than 30 days but less than one year.
- Registration of patient on protocol during a period of delayed reapproval or during a temporary suspension (i.e., Request for Rapid Amendment).
- Missing reapproval.
- Expired reapproval.
- Internal reportable adverse events reported late or not reported to the IEC/IRB.
- Lack of documentation of IEC/IRB approval of a protocol amendment that affects more than minimal risk.
- Failure to submit or submitted after 90 days, any reportable external safety report to the IEC/IRB that is considered an unanticipated problem.

Application for authorisation

- Failure to report an IEC/IRB that previously refused to approve a trial as requested by regulatory authority.
- Failure to notify regulatory authority when changes were made to the chemistry and manufacturing information or to the approved protocol.

Good clinical practices

- Qualified investigator does not have the qualifications to conduct the clinical trial.
- Medical care and decisions related to the trial are not under the supervision of the qualified investigator.
- Protocols not amended; informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the clinical trial drug which endanger the health of the clinical trial subject or other person.
- Inadequate source data to substantiate clinical trial results.
- Clinical trial was not conducted in accordance with the protocol.
- Sponsor did not notify the qualified investigator of SUSARs that occurred at other sites.
- Qualified investigator did not notify the sponsor and/or IEC/IRB in a timely manner of SUSARs.
- No procedures in place for reporting new safety information to the qualified investigator.
- Significant clinical endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms.
- Inadequate systems in place for drug accountability.
- Storage or handling controls in place for drugs were inadequate.
- Source data was not verified for quality, completeness and integrity.
- System(s) and/or procedure(s) that assure the quality of every aspect of the clinical trial were not implemented.
- Inadequate monitoring of the clinical trial site by the sponsor.
- Individuals involved in the conduct of the clinical trial are not qualified by education, training or experience to perform their respective tasks.
- Incomplete documentation of protocol deviation.
- Lack of documentation that sponsor was informed of protocol deviations.

- Unacceptable frequency of required evaluation violations.

Records

- No security procedures in place for electronic records or electronic signatures.
- The electronic data system was not validated.
- Sponsor has no or incomplete records of all adverse events which occurred inside or outside Specific country.
- Incomplete records respecting the enrolment of clinical trial subjects.
- Incomplete records concerning shipment, receipt, use, disposition, return or destruction of the drug.
- Quantities of drug not accounted through the various stages of shipment, receipt, disposition, return or destruction of the lot of the drug.
- No signed/dated qualified investigator undertaking for each clinical trial site prior to the commencement of his/her responsibilities.
- Copies of the protocol/amendments and informed consents approved by the IEC/IRB does not retained for each clinical trial site.
- Absence of IEC/IRB attestation for each clinical trial site stating that it has reviewed and approved the protocol, the informed consent and that it functions in compliance with GCP.
- No edit trails for changes to electronic records in order to identify who made the changes or when.
- No provisions for retention of records as required by the regulatory authority Guidelines for Good Clinical Practice.
- Incomplete records in respect of the use of a drug in a clinical trial/Failure to document drug administration.

Suspected Unexpected Serious Adverse Reactions (SUSARs) reporting

- Sponsor failed to report SUSARs to regulatory authority.
- Sponsor did not comply with the prescribed timeline for reports of SUSARs.

- Sponsor did not submit, within the prescribed timeline, an assessment of the importance and implication of any findings made.

Discontinuance of a clinical trial

- Sponsor did not inform regulatory authority that the clinical trial was discontinued in its entirety or at a clinical trial site within 15 working days after the date of the discontinuance.
- Sponsor did not provide regulatory authority with the reasons for the discontinuance and its impact on the proposed or ongoing clinical trials.
- Sponsor did not inform all qualified investigator(s) of the discontinuance of a trial, the reason for the discontinuation or did not advise them in writing.
- Sponsor did not stop the importation of the drug as of the date of the discontinuance.
- Sponsor, after having discontinued a clinical trial, resumed importing the drug without having submitted the required information to regulatory authority.
- Clinical trial ongoing at one or more sites after Sponsor stated that the trial was discontinued at those sites.

Informed consent

- The informed consent did not contain all of the required information.
- Consent form not approved by IEC.
- Consent form document missing.
- Consent form document not signed and dated by the patient/study participant.
- Consent not obtained in a language fully understood.
- Translated consent or short form not signed and dated by a non-English speaking patient/study participant.
- Consent form not signed by patient prior to study registration/enrollment.
- Consent form does not contain all required signatures.

- Consent form used was not the current IEC/IRB approved version at the time of patient registration/Outdated consent used.
- Consent form not protocol specific.
- Consent form does not include updates or information required by IEC/IRB.
- Re-consent not obtained as required.
- Consent of ancillary/advanced imaging studies not executed.
- Informed consent not obtained from subjects before enrolment in the trial or after major amendments to the informed consent form.
- Informed consents not administered properly or not signed and dated.

Eligibility

- Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol.
- Documentation missing; unable to confirm eligibility.

Treatment

- Incorrect agent/treatment/intervention used.
- Wrong route in administration.
- Additional agent/treatment/intervention used which is not permitted by protocol.
- Dose deviations, modifications, or incorrect calculations (error greater than +/- 10%).
- Dose modifications/treatment interventions not per protocol.
- Treatment/intervention incorrect or not administered correctly, incorrectly calculated, or not adequately documented.
- Timing and sequencing of treatment/intervention not per protocol.
- Unjustified delays in treatment/intervention.
- Failure to report concomitant therapy.
- Failure to dose reduce in the face of severe toxicity.
- Failure to dose escalate on a dose-intensity study.

- Inappropriate dose reduction on a dose intensity study.
- Error in concomitant medications.
- Failure to administer an important medication.
- Failure to return unused investigational drug to pharmacy.

Adverse event

- Grades, types, or dates/duration of serious adverse events inaccurately recorded.
- Adverse events cannot be substantiated.
- Follow-up studies necessary to assess adverse events not performed.
- Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group.
- Recurrent under- or over-reporting of adverse events.
- Failure to obtain the required protocol baseline studies needed to effectively assess toxicity.

Disease outcome/response

- Inaccurate documentation of initial sites of involvement.
- Measurements/evaluation of status or disease not performed or not documented according to protocol.
- Protocol-directed response criteria not followed.
- Claimed response cannot be verified or auditor could not verify the reported response.
- Failure to detect disease (as in a prevention study) or failure to identify disease progression.

General data management quality

- Recurrent missing documentation in the patient/study participant records.
- Protocol-specified laboratory tests not reported or not documented.
- Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented.

- Protocol-specified research/advanced imaging studies not done or submitted appropriately.
- Frequent data inaccuracies.
- Errors in submitted data.
- Delinquent data submission (> 6 month delinquency is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency).

Minor Observations

Application for authorisation

- Sponsor did not maintain copies of previous investigator's brochures pertaining to the clinical trial drug.

Eligibility

- One or more criteria not documented in medical record.

Good clinical practices

- Delegation of tasks incomplete, signature log incomplete.
- Correction of data not initialed and/or dated.
- Minor errors in transcribing data from source documents to case report forms.
- Source data stored in unsecured location.

Labeling

- Labeling of the products not complying with regulatory requirements.

IEC/IRB deficiency descriptions

- Protocol reapproval delayed 30 days or less.
- Delayed reapproval for protocol closed to accrual for which all patients/study participants have completed therapy.

Informed consent

- Consents do not have unique subject identifiers on each page.

Pre-therapy

- Missing few minor tests.
- Date of birth, date of diagnosis, lab values or dates inconsistent.

On-Study Procedures

- Missing a small number of minor required evaluations or tests.
- Missing minor measurements.
- Missing one of several minor measurements used to assess response and scans.

AUDITING TECHNIQUES

Collecting information

The most intensive part of any audit process is where the information is assessed and recorded. For collecting information specific types of audit skills and techniques are useful. Various techniques include:

- Interviewing researchers
- Reading documents
- Reviewing manuals
- Studying records
- Reading reports
- Analysing data
- Observing activity
- Examining conditions
- Confirming interview evidence
- Documenting observations

Finding evidence

It is the auditor's primary role to collect evidences wherever possible of research practice and compare it against the requirements of Good Clinical Practice, Regulatory and SOPs. The auditor is responsible for documenting observations and conclusions, safeguarding audit documents, records and reports, assessing whether requirements are being met, and developing reports incorporating recommendations for change or adherence. Evidence can come from a range of areas. This list gives a good hierarchy for looking for evidence:

- Compliance with ICH-GCP guidelines and applicable Regulatory requirements like FDA, EMA etc...).
- Research findings, particularly systematic reviews.
- Local regulations, protocols and procedures.
- Conformity to contractual agreements.
- Quality, consistency, content, and completeness of the documentation.

Common indications of fraud

- Lack of any errors or corrections on CRFs.
- Participants who are perfectly compliant with study visits and evaluations.
- 100% of all participants who were screened, enrolled and completed the study.
- Study staff exhibiting lack of knowledge about the study, seeming lack of equipment or resources when compared to audited work.
- Abnormally large amount of work compared to the resources noted.
- Inconsistent sources of data.
- Lack of variation in handwriting, ink, or writing style.
- Study staffs that are guarded or suspicious [5,8-14].

SITE AUDIT CHECK LIST

Regulatory Documentation				
S.No		YES	NO	NA
1	Is the Site Study File available and is it updated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Is the most recent version of the protocol on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Are there previous versions of the protocol?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	If yes, are they on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Is this an FDA regulated study?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	If yes, is there a signed FDA 1572 on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Is the Clinical Investigator Financial Disclosure form on file for each investigator?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	Are there CVs of PI/Co-PI and all study staff on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Are CVs updated within the past one year?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	Are CVs signed and dated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	Is there a subject enrollment log?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	If yes, is subject enrollment log up to date?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	Is study site get audited previously	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	If yes, is there an audit log?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	Is audit log up to date?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16	How often is site audited?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17	Is there a staff signature log?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18	If yes, is staff signature log up to date?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19	Does the staff signature log include delegation of responsibility?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20	Are all versions of the Investigator Brochure on file or device manual?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21	Are lab tests required?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22	Is a copy of normal lab values on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23	Are samples are collected as per GCP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24	Are samples transported as per GCP guidelines	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25	Whether storage of samples are as per GCP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
IEC/IRB Documentation				
S.No		YES	NO	NA
1	Is all correspondence (signed/dated applications, responses,	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Is other correspondence (e.g., e-mails) to and from the IEC/IRB on	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Is the initial IEC/IRB approval letter on file?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Continuing Review	Date submitted	Date approved	IEC/IRB approval letter
				YES NO NA
Number of Continuing Reviews (CR)?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Was each CR submitted on time? (prior to expiration)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6	Was there any lapsed period(s) between expiration date and CR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Was any subject screened or enrolled during this lapse period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	If yes, was a protocol violation submitted to the IEC/IRB/?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Were any study procedures done during the lapse period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	If yes, were they approved by an IEC/IRB Chairman?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	Have there been any changes to the study?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	If there have been changes to the study, were the amendments approved by the IEC/IRB before implementation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Subject Recruitment Procedures

3.No		YES	NO
1	Are recruitment methods stated in the IEC/IRB approved protocol?	<input type="checkbox"/>	<input type="checkbox"/>
2	How are potential subjects identified? (check all that apply)	<input type="checkbox"/> Investigators <input type="checkbox"/> Medical record review <input type="checkbox"/> Database <input type="checkbox"/> Clinical practice <input type="checkbox"/> Treating physician <input type="checkbox"/> Subject response to recruitment materials <input type="checkbox"/> Other	
3	Is initial contact made in compliance with institutional requirements and the IEC approved protocol?	<input type="checkbox"/>	<input type="checkbox"/>
4	If recruitment materials are used, specify: (check all that apply)	<input type="checkbox"/> Advertisements (posted) <input type="checkbox"/> Flyers <input type="checkbox"/> Web posting <input type="checkbox"/> Letters <input type="checkbox"/> Pre-Screening form <input type="checkbox"/> No recruitment materials used; go to section 4 <input type="checkbox"/> Other	
5	Have all recruitment materials (including pre-screen been approved by the	<input type="checkbox"/>	<input type="checkbox"/>
6	Are all approved recruitment materials (original and all revisions) on file?	<input type="checkbox"/>	<input type="checkbox"/>
7	Were changes made to recruitment materials since last continuing review?	<input type="checkbox"/>	<input type="checkbox"/>
8	If yes, was an amendment submitted to IEC/IRB?	<input type="checkbox"/>	<input type="checkbox"/>
9	Is a pre-screening telephone interview conducted?	<input type="checkbox"/>	<input type="checkbox"/>
10	If yes, is there a copy of the pre-screening form used?	<input type="checkbox"/>	<input type="checkbox"/>
11	Is it approved by the IEC/IRB?	<input type="checkbox"/>	<input type="checkbox"/>

Informed Consent Process

1	How many versions* of the consent form are there?		
2	Provide the valid date and expiration date for each version of the consent form:	Valid date	Expiration date
3	Are all original copies of the IRB approved consent form on file?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
4	Randomly choose 5 or more subject files for review. Using each subject file complete the information below Add additional space as necessary to accommodate the number of subject files chosen.		
	Is consent given prior to study procedures?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
	If the protocol has been amended has re-consenting been undertaken and documented appropriately?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
5	Any invalid consent forms used? Invalid consent form includes, but is not	<input type="checkbox"/> YES	<input type="checkbox"/> NO

	limited to: consent form without IRB approval stamp; expired consent form; incorrect study population.		
6	If yes, was a protocol violation report submitted to the IRB?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
7	Did each subject sign his/her own consent form?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
8	How has the patient checked (initialed or ticked) each statement?		
9	Is all consent forms signed and dated by the person taking consent?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
10	Do the dates of the signatures between the patients and consent taker match?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
11	Is subject's receipt of a copy of the signed and dated consent form documented?	<input type="checkbox"/> YES	<input type="checkbox"/> NO

Subject Selection Criteria: Using the study files for subjects chosen for review complete the following. Add additional space as necessary to accommodate the number of chosen subjects.

S.No		YES	NO
1	Is there an eligibility checklist containing inclusion/exclusion criteria?	<input type="checkbox"/>	<input type="checkbox"/>
2	Does each subject file indicate whether the subject was included/excluded appropriately?		
	Subject #1:	<input type="checkbox"/>	<input type="checkbox"/>
	Subject #2:	<input type="checkbox"/>	<input type="checkbox"/>
	Subject #3:	<input type="checkbox"/>	<input type="checkbox"/>
	Subject #4:	<input type="checkbox"/>	<input type="checkbox"/>
	Subject #5:	<input type="checkbox"/>	<input type="checkbox"/>
3	If any subjects that did not meet eligibility criteria were enrolled, was a protocol violation submitted to the IRB?	<input type="checkbox"/>	<input type="checkbox"/>

Adverse Event (Ae)/Serious Adverse Events (Sae) Reporting

S.No		YES	NO
1	Have any AEs occurred in this Trial?	<input type="checkbox"/>	<input type="checkbox"/>
2	Have any SAE/SUSARs occurred in this Trial?	<input type="checkbox"/>	<input type="checkbox"/>
3	Are reported AEs/Serious Adverse Events verifiable against patient records (i.e., adequately recorded in the source documents)?	<input type="checkbox"/>	<input type="checkbox"/>
4	Have all AEs/SAEs been reported according to protocol and regulatory guidelines?	<input type="checkbox"/>	<input type="checkbox"/>
5	How many SAEs have been reported to the EC since last continuing review?		
6	SAE	Date of event	Date of report
7	Any serious adverse events NOT reported to the IEC since last continuing review? <input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, reason(s) for not reporting:	
8	Are the reports and IEC submissions on file?	<input type="checkbox"/>	<input type="checkbox"/>
9	Have all AEs/SAEs been reported to the sponsor?	<input type="checkbox"/>	<input type="checkbox"/>

Protocol violations/deviations

Violations & Deviations	Date occurred	Date reported	Date of IEC Notification	IEC\IRB notification on file	
				YES	NO
1 Number of deviations reported to IEC?				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>
2	Any violations not reported to the IEC?			<input type="checkbox"/>	<input type="checkbox"/>
3	Any sponsor approved protocol deviations			<input type="checkbox"/>	<input type="checkbox"/>

Drug dispensing accountability					
S.No		YES	NO		
1	Is there documentation of drug used for each subject?(ex. dispensing log)	<input type="checkbox"/>	<input type="checkbox"/>		
2	Who is responsible for dispensing?				
3	Are there shipping/receiving receipts?	<input type="checkbox"/>	<input type="checkbox"/>		
4	Who is responsible for drug/device storage? <input type="checkbox"/> PI <input type="checkbox"/> PI designee				
5	If site is responsible, are appropriate logs (temperature) maintained?	<input type="checkbox"/>	<input type="checkbox"/>		
6	Have there been any drug related errors to date?	<input type="checkbox"/>	<input type="checkbox"/>		
7	Is there appropriate documentation for the return or destruction of drugs?	<input type="checkbox"/>	<input type="checkbox"/>		
Data collection & source documents					
1	Is Data collection complete for each subject?	YES	NO		
	Subject #1:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #2:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #3:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #4:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #5:	<input type="checkbox"/>	<input type="checkbox"/>		
If data collection is not complete, please explain:					
		YES	NO		
2	Is source documentation available to support data entry for each subject?				
	Subject #1:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #2:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #3:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #4:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #5:	<input type="checkbox"/>	<input type="checkbox"/>		
If no/missing source documentation, please explain:					
		YES	NO		
3	Do the source documentation/CRFs for each subject include dated signature/initials of the person obtaining the information for each subject?				
	Subject #1:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #2:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #3:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #4:	<input type="checkbox"/>	<input type="checkbox"/>		
	Subject #5:	<input type="checkbox"/>	<input type="checkbox"/>		
4	Are changes/cross-outs (if any) in subject files routinely initialed and dated?	<input type="checkbox"/>	<input type="checkbox"/>		
5	Has the investigator or person designated by the appropriate investigator made appropriate corrections, additions, or deletions that are dated and initialed by the investigator or person designated by the investigator?	<input type="checkbox"/>	<input type="checkbox"/>		
6	Do Case Report Forms and other study documents such as data collection sheets contain any entry error, omission or illegibility?	<input type="checkbox"/>	<input type="checkbox"/>		
7	Is all study hard copy documentation stored in a restricted area?	<input type="checkbox"/>	<input type="checkbox"/>		
8	Is access to electronic study records and files password protected?	<input type="checkbox"/>	<input type="checkbox"/>		
Allocation of responsibilities					
1	Who delegates :	PI	Co-PI	Study Staff	Other
	Amendment applications?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Continuing review application?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	SAE/AE reports?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Violation/Deviation reports?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Of the subjects chosen for review, how many consent forms are signed by:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Can appropriate allocation of responsibilities be substantiated? (e.g. licensure, certification, training, etc.)	<input type="checkbox"/> Yes		<input type="checkbox"/> No	

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