

African Vaccine Regulatory Forum (AVAREF)

GUIDE FOR THE INSPECTION OF CLINICAL TRIALS

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GUIDE FOR THE INSPECTION OF CLINICAL TRIALS

Background and introduction

To further harmonization in the inspection of clinical trials, the African Vaccines Regulatory Forum (AVAREF) initiated the preparation of a guide for the inspection of clinical trials. This guide, primarily based on the World Health Organization (WHO) and other guidelines, is the outcome of a global consultation process.

This guide provides for a set of harmonized recommendations to conduct an inspection of clinical trials in all phases including bio-equivalence studies; thereafter collectively referred to as clinical trials. Further objectives include ensuring that there is a basis to assure ethical and scientific integrity of clinical trials, and data integrity. It may be used by inspectors from a National Regulatory Authority (NRAs), as a monitoring tool by the Ethics Committees (ECs), or in joint inspections as appropriate. It can support mutual recognition of inspections of clinical trials between countries that apply the same standards and procedures of inspection. Where relevant, an understanding such as a mutual recognition agreement between inspectorates may be considered.

An inspection needs to cover all aspects, as appropriate, for a clinical trial and as provided for in various WHO guidelines. If there are relevant areas for inspection for which the WHO has not published a guideline, reference may be made to current international guidelines. The areas for the inspection, include but are not limited to, data and information relating to regulatory approvals, ethics review committee approval, protocols, case report forms, clinical trial reports, patient and patient data, sponsors, investigators and personnel involved in the trial, and laboratory data.

This guide can be used to perform an inspection at any stage of a clinical trial. It can also be used after the completion of a clinical trial, ie once the reports have been submitted to the NRA, to verify that the reports reflect true and accurate data and information. This guide is complemented by an inspection checklist that can be considered during the conduct of an inspection.

Scope

This guide covers inspection of clinical trials including bio-equivalence studies. It contains points to review and aspects to verify in areas such as a clinic or clinical pharmacology unit (CPU), pharmacies, and documentation. It includes the review of clinical laboratories and bio-analytical laboratories.

Glossary

See AVAREF, WHO, and the ICH guidelines for the definition of the terms used in this guide.

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Acronyms

| | |
|----------|--|
| ALCOA | Attributable, legible, contemporaneous, original, accurate |
| ALCOA+ | ALCOA plus complete |
| AVAREF | African Vaccines Regulatory Forum |
| CIOMS | Council for International Organizations of Medical Sciences |
| COA | Certificate of analysis |
| CPU | Clinical pharmacology unit |
| CRO | Clinical research organization |
| EC | Ethics committee |
| GCP | Good clinical practices |
| GxP | Good practice |
| HPLC | High-performance liquid chromatography |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical requirements for Pharmaceuticals for Human use |
| IMP | Investigational medical product |
| IRB | Investigational review board |
| LC-MS.MS | Liquid chromatography-tandem mass spectrometry |
| NRA | National regulatory authority |
| WHO | World Health Organization |

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Inspection team

An inspection needs to be conducted by a team of two or more inspectors who have appropriate qualifications and experience in inspecting clinical trials. The agency responsible for the inspection should appoint the inspection team.

The team will have a lead inspector responsible for coordinating the inspection, collating the information from team members, and finalizing the inspection report.

Preparation for and announcement of the inspection

All members of the inspection team should be provided with the relevant information about the scope of the inspection, the site of the inspection, and clinical trial(s) to be inspected, to enable them to appropriately prepare for the inspection. Each team member should become familiar with all the relevant documents, including the study protocol(s), clinical trial report(s), case report forms, adverse event reports, trial site information, and other related documentation.

The inspection may be announced. The announcement may be done a few weeks prior to the inspection together with an inspection agenda. This will ensure the availability of people at the site and to allow for all the source documents to be retrieved from the archives. The inspection team should decide in advance who will be responsible for any specific part of the inspection or review of data and information.

Conduct of the inspection

The inspectors should present proof of their identity at the start of the inspection. During the opening meeting, inspectors and trial site personnel should introduce themselves. The trial site representatives may give a brief overview of the trial site and the clinical trial to be inspected. The inspection team should clarify the purpose of the inspection and define the scope of the inspection.

After the introduction, the inspection begins. The inspectors assess whether the clinical trial was conducted in accordance with all the appropriate GxP guidelines; Declaration of Helsinki; CIOMS guidelines; and the approved protocol. If available, the clinical trial report submitted should be verified against source data.

Data and information to be verified in general, include, but are not limited to:

- Licensing requirements for the site conducting clinical trials
- Regulatory requirements and approvals for the conduct of the clinical trials
- Ethics approval
- The protocol and amendments
- Approvals relating to the protocol and amendments
- Case report forms and raw/source data

Clinical trial data and information are still generally recorded on paper. However, it is highly recommended to encourage the use of validated computerized systems to generate data and results.

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Data integrity

Decisions made, based on the outcome of clinical trials, rely on the integrity of the results and data obtained during the study. It is important that data and results are reviewed during an inspection to ensure that the data and information are comprehensive, complete, and reliable. The data should be complete, attributable, legible, contemporaneous, original and accurate, commonly referred to as “ALCOA+.” This applies to all data and information as reflected in manual records and electronic data from computerized systems.

Protocol

Clinical trials should be conducted in accordance with the provisions of the study protocol. Given that the protocol is approved prior to the inspection, the following should be verified during the inspection:

- That the correct protocol, as approved by the NRA and EC (number and version), was followed
- That all patients enrolled, met the inclusion and exclusion criteria
- That dosing, meals (fed and fasting), sample collection were done as stipulated
- That there is compliance with the requirements such as randomization, product information, reporting of serious adverse events, and preparation of reports
- That no deviations occurred that were not approved and justified
- That violations to the protocol were reported
- That the agreement signed between the investigator and the sponsor, confirming that the investigator has read and understood the protocol, and that will work according to it and good clinical practice, is available
- That reporting of results was done as required

Ethics approval

The ECs or other board responsible for reviewing the trials ensures the protection of the rights and welfare of human patients participating in clinical trials. Verify the relevant records relating to the work of the EC, for example:

- Composition of the EC is in compliance with national requirements, eg legislation with regards to the number of people, qualifications, and employment
- That all EC members including the chairperson, secretary are free from bias in relation to the clinical trial and sponsor as required by national legislation. This information may be given in the form of declaration of interest posted on the website or make available upon request
- That the EC operates in accordance with standard operating procedures (SOPs) defining frequency of meetings, notice of meetings, distribution of documents, and preparation and distribution of minutes of the meeting. This information may be available on the website or upon request That approval

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for the clinical trial was given prior to the start of the trial. This is done by reviewing the attendance sheet and minutes of the meeting related to the clinical trial, dates and contents on the letter of approval referring to the protocol. For the informed consent and related documents verify numbers, dates, signatures, agenda, and minutes of the EC meeting

- Approval was given for any advertisement and recruitment of trial patients, compensation, payments, and screening
- Reports were submitted to the EC as required, as well as reporting of any serious adverse events occurring during the trial

Regulatory approval

All parties involved in a clinical trial are expected to comply with the current requirements defined in the national legislation. The inspection will consist of a comparison of the procedures and practices carried out by the investigator with those set out in the protocol and reports submitted to the NRA. Verify:

- That regulatory approval was granted in writing to conduct the trial prior to its initiation. This includes the revision of the contents of the approval such as date of communication versus trial start date, signature on the approval letter, conditions imposed, whether the reference and clinical trial number match, protocol number, informed consent number and version, and any other information
- Conditions of approval and responsibilities, and compare with the content of the pre-trial agreement between the sponsor and investigator(s) such as application for approval, amendments to the trial protocol, reporting of all adverse events
- That any revisions and changes to the protocol and related documents were granted approval prior to implementation
- Whether serious adverse events and other reports were submitted to the NRA as required

Site

The site has to be suitable to conduct clinical trials. Its different areas should be inspected and assessed against the trial records. If the site underwent changes since the last inspection, the new changes have to be reviewed.

Verify whether the site is licensed, or authorized by another means, to conduct clinical trials in accordance with national legislation. This includes verification of the authenticity of the document issued by the relevant body in the country of conduct of the trial, referencing the correct address, validity period issued prior to the trial and valid beyond the trial date, and signatures and stamps as appropriate. This can be verified against the registration of the site, company, organization or business as required in terms of the local legislation.

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Verify that the site is in accordance with what is described either in the contract research organization master file or other document. Depending on the activities undertaken by the site, areas such as a clinic or CPU, pharmacy and laboratories should be available. It is expected that they have enough space, the required number of beds, appropriate equipment and instruments, storage for investigational medicinal products (IMPs) with controlled access, and other services as appropriate.

Clinic

The clinic or CPU should have areas where the different activities relating to the conduct of the trial can be performed. It is expected that the following will be available:

- Registration and screening area(s)
- Area for physical examination equipped with the required and calibrated instruments
- The required number of beds
- Areas for recreation during stay
- Areas for dosing, sample collection, sample preparation equipped with the required equipment and instruments such as centrifuges, freezers
- Equipped kitchen and dining area
- Emergency room with equipment, egoxygen, defibrillator, and emergency medication as required
- Emergency medication within their shelf life, with records of stock and administration
- Toilet facilities

Pharmacy

Sites usually have a pharmacy where IMPs are stored and dispensed under appropriate conditions. Verify:

- That access is controlled and that access records reflect entry and exit against the clinical trial activities such as dates for receiving and storage of IMPs, dispensing, issuing, returns, and cleaning;
- SOP content for the various activities including receiving, checking, storage, dispensing, labelling and reconciliation of IMPs. Verify the related records to ensure compliance with the protocol and SOPs
- SOP and records to monitor the conditions under which the IMPs are stored. Verify the labelling requirements against the room limits and records. The records should reflect the conditions such as temperature and relative humidity observed from the calibrated devices. If there values outside the specifications, verify if they were investigated and if any prospective impact on the IMPs was assessed
- Records relating to the IMP, such as import license or import authorization, proof of purchase, shipping letter, storage conditions during transport, receipt at the site, COA(s), stock card, and dispensing record including dates, quantity, and signatures

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- For dispensing, verify the SOP and records for line clearance, preparation of labels, dispensing, signatures and dates for dispensing. Cross check the records such as label sheets, randomization, CRFs, and reconciliation record for the IMPs
- Whether dispensing was done in the presence of another responsible person eg investigator or quality assurance personnel
- Whether IMP labels contain the correct information such as the study number, “for clinical trial use only”, patient number, period, randomization, dosage form, and route of administration, as appropriate
- Whether dosing or administration of IMP was done as required the protocol. Review the dosing or administration sheet against the case report form, randomization sheet and protocol; IMP management record, eg “Stock card” or other by checking the number of dosage units received, quantity dispensed, quantity dosed or administered, quantity returned to stock, quantity on hand, and quantity returned to the sponsor or disposed of
- SOP for safe disposal of waste

Documentation

Quality system

The trial site should have a quality system. The quality system consists of various documents describing policies, organization, management, responsibilities, formats, contracts, and procedures to follow including SOPs. Documentation has to be prepared and controlled with care. The quality system also covers the management of deviations, violations, risk management principles, and corrective and preventive actions.

The unit responsible for quality assurance has to ensure that the quality management system is followed and that the records are maintained.

To assess the quality system, verify the following:

- That the authorized organizational chart and job descriptions reflect the reporting lines and responsibilities of personnel for the conduct, control, and oversight of the trial(s)
- That the curriculum vitae of key personnel are current
- SOP and records for the qualification and training of employees and contracted personnel. The training records have to reflect recent and updated internal or external training
- Signatures of study personnel, signature list, against the signatures in the source documents, eg CRFs, dosing sheets

Contracts

There has to be a current and valid contract between the sponsor and the investigator. In cases where the trial site makes use of sub-contracted staff, eg clinical research associates, nursing staff, custodians, phlebotomists or other personnel, verify if there is

a current contract in place, and whether the sub-contracted personnel have the required qualifications, experience, and training. This can be done by selecting names at randomly from the list of personnel, and verifying the records for these personnel.

Archiving

The site needs to have archiving facilities with sufficient space to ensure the protection of records from damage, eg fire, water, humidity, and deterioration. The site has to have procedures and records to place and retrieve documents and trial data. During the inspection, verify SOPs and records to archive electronic data and electronic records.

Sponsor, investigator, and personnel

The contract between the sponsor and the investigator has to clearly define the responsibilities of each party. The declarations of interest have to be signed and dated. Verify that:

- The contract is valid, ie dated, period covering the trial, signatures by all parties, responsibilities indicated including obtaining, transport, storage, use, safe disposal or return of IMPs; monitoring of the trial, quality assurance, reports
- The scope of insurance, regardless of fault, is defined, provided for and current
- Product information was provided by the sponsor in a timely manner

The sponsor is responsible for providing the IMP and information, monitoring and compliance with legal, ethical, and regulatory principles.

The investigator is responsible to ensure that the conduct of the trial is in compliance with the protocol and regulatory and ethical requirements. Verify:

- Qualifications, eg degree, as required by national legislation
- Experience as stated in the curriculum vitae and training records
- Unbiased selection of patients, eg no preferential selection of family members, friends, and staff
- The signed statement committing to comply with GCP and the protocol to conduct the trial
- That full information relating to the IMP was given to the investigator before and during the trial including an annual update
- Preparation and signing of the final report was done

Trial personnel need to have appropriate qualifications, experience, and training. Verify that:

- A record reflects delegation of tasks, eg delegation log
- A list of signatures is available. Compare the signatures against the source data for the trial being inspected including, but not limited to, signatures in

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training records relating to the trial, recordings in case report forms, dosing charts, and sample collection forms

- The number of employees was appropriate to conduct the trial, such as the number of phlebotomists versus the number of patients and sample collection points
- Qualifications, training records, and curriculum vitae are available

Monitor(s) and monitoring reports

A sponsor has to ensure that the trial site is able to conduct the trial, and that the trial is conducted appropriately. A monitor should prepare reports following a visit to the trial site.

Verify whether the monitoring reports reflect the site review and trial progress. The report should include a revision of compliance with the protocol, data integrity, case report forms, and IMP management.

Quality assurance

The trials have to be conducted in compliance with quality assurance principles. Ensure that those responsible for the quality assurance review are independent of the conduct of the trial.

Any quality assurance reports reflecting the review of the data and information before, during, and after the conduct of the trial should be available at the site.

Patients

Patients should be protected from harm from the time of recruitment, during participation in the trial, and thereafter in accordance with the principles of GCP, the Declaration of Helsinki, and CIOMS guidelines. Verify that:

- There is an approved procedure for recruiting, and that the procedure and any recruitment materials, eg advertisements, were approved by the EC. Write down the dates, and version numbers
- There is an approved procedure to keep records, eg electronic or paper versions, of all patients, and that there is a system to ensure that patients are not participating in different trials, at the same time, or sequentially, eg one trial after the other, within the period of time defined in the protocol
- Patients are allocated a unique number to ensure identification of each patient, and that their participation in a trial is recorded. A complete record of participation in a trial has to be available
- Unless justified, vulnerable groups were not included in a trial
- Whether the following is available: proof of the date of birth, eg birth certificate, address, contact details
- For bio-equivalence study, ensure that there is a justification for the number of patients enrolled in the trial

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- Compare the signatures of patients, eg receiving payment against those in the informed consent form (ICF)

Informed consent forms

The patients have to be informed of the advantages and disadvantages of participating in a trial. This includes information on the IMP, possible adverse events, insurance, and other issues. Verify that:

- There are records to confirm that the required information was presented to the patient, verbally and in writing, eg ICH
- Each patient signed the ICF prior to participating in the trial. The ICF may be general or trial-specific, In both cases check the dates and signatures
- ICFs contain all the required information that should be communicated to the patient in a manner and language that the patient understands. The explanations and details usually include the following:
 - Aims, benefits, risks, and inconveniences when participating in the trial
 - Details of the IMP to be administered
 - The patient has the right to withdraw voluntarily from the trial at any time
 - Details on remuneration including pro-rata remuneration where necessary
 - What will the insurance cover
 - Confidentiality statement, eg information will be kept confidential but may be shared with regulatory authorities
 - Provision for access to treatment when needed
 - An explanation that termination can be done by the investigator if needed
- Correct version of the ICF was signed and dated prior to participating in the trial. If the patient consented to participate by verbal assent or a fingerprint, the ICF should be signed by an independent witness
- The contact details of the investigator or secretariat were given to the patients
- There were provision to allow patients to ask questions relating to the study prior to consenting

Randomization

Trials often have more than one type of treatment. This may require a randomization process to ensure that there is no bias in allocating the IMPs to be administered to the patient. Verify that:

- There is a procedure to describe how the randomization is done. Corroborate whether randomization was done according to the clinical trial protocol and the corresponding SOPs for the trial undergoing inspection. The records should reflect the date, time, software, and version used

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- IMPs were dispensed and dosed to patients, in accordance with the randomization schedule for the trial. Compare the randomization list against the dispensing sheets, dosing labels, and case report forms

Case report forms

Trial-related data and corresponding information has to be recorded in the case report form. Verify that:

- The results and data recorded are the same as those reflected in the source documents, eg laboratory reports. If corrections were made when the data were entered, ensure that the results are accurate and reliable, and that the reason for the change was given, signed, and dated
- That the following was done as defined in the study protocol: blood, urine and/or other samples taken; chest X-ray or other tests were done. Verify whether the results from these tests/analyses are within the specified ranges. Review the investigator's comments for all the results that were out of range
- The protocol was followed where it refers to the trial being conducted under fasting or under fed conditions. Where meals were to be provided, check that these were prepared and served at the correct times, correct caloric content, and that the amount or volumes consumed by each volunteer was recorded
- Other source data as recorded in the case report form, including, but are not limited to:
 - Inclusion and exclusion criteria
 - Age
 - Administration of the correct IMP
 - Sample collection time
 - Blood pressure values, pulse rate, respiration, temperature
 - Recording of adverse drug events
 - Recording of concomitant medication
 - Recording of the number of samples taken against number of samples transferred for preparation or storage and analysis

Laboratory and analysis

Laboratories should be able to analyze samples as specified in the protocol.

When testing is outsourced, the contracts should define the responsibilities and scope of each party including sample transport, storage, preparation, methods to be used, and reporting of results. The laboratories have to operate in compliance with GxP. Review the contracts during the inspection.

Clinical laboratory

Verify the following when reviewing data and results from the clinical laboratory:

- Supplier qualification and procurement procedures, eg approved vendor list, are done according to the SOPs

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- Laboratory staff is competent to perform tests as required
- Procedures and records for the qualification and calibration of the laboratory equipment and instruments are maintained
- Equipment log books are maintained
- Current normal ranges and values of the measures are specified
- There are procedures in place to receive, store, and handle certified reference materials, chemicals and reagents. Check that expired stock is not used, and that storage conditions are maintained
- COAs of materials are available
- There are procedures available to handle hazardous materials, eg live viruses
- Environmental monitoring of test areas is done
- Test methods are verified or validated as appropriate
- There are procedures for retesting, as required
- The printouts of the test results comply with ALCOA principles
- Procedures and records for the safe disposal of the laboratory waste are followed

Bio-analytical laboratory

The laboratory should have the necessary resources to perform the required analysis, including, but not limited to, premises, personnel, equipment, instruments, and documentation. Where licensing is required by national legislation, verify the validity of the license, eg name, registration, date, and scope of activities approved.

Ensure that there are designated areas for sample receiving and storage, sample preparation, analysis, and other activities as required. All the areas have to be clean and well maintained, access-controlled, and operate according to the conditions required by the study, eg temperature, light, and relative humidity.

Verify personnel qualifications, experience, and training records.

Verify whether the required equipment and instruments are available. And if so, whether they are qualified and calibrated. Examples include freezers, balances, centrifuges, pH-meters, micropipettes, high performance liquid chromatographers, liquid chromatography-tandem mass spectrometry equipment (LC-MS/MS).

Inspect the aspects specified above as they pertain to the trial. Review the source data specific for the trial and sample analysis. Follow the sample flow from receipt to storage, processing, analysis, and results processing and reporting.

Sample management

Procedures and records should be available to reflect the sample transfer from the CPU to receipt in the bio-analytical laboratory. Verify:

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- The details of the procedure and records, eg dates and number of samples transferred to the bio-analytical laboratory, against the data and information in the case report form, freezer logs, and transfer sheets (number of patients, periods, number of samples collected, and samples processed)
- Whether the samples were stored at the temperature defined in the study protocol, eg -20 or -70 degrees Celsius, until analyzed. Verify the temperature records for the storage period. In the case of any excursion, review the investigations and impact analysis
- Whether the freezers used to store samples were qualified. Check the availability of protocols and reports as well as procedures for the installation, operation and performance of the freezers, temperature mapping, source data, and calibration certificates, eg sensors
- Whether the procedures and records for the placement and withdrawal of samples are accurate

Equipment and instruments

Write down the identification and reference numbers of instruments reflected in the report and source data reports. Then, verify the records for those instruments and equipment. Verify whether the qualification and calibration status were valid at the time of use for method validation and sample analyses for those used for the trial for the following: balances, pipettes, micro-pipettes, and high performance liquid chromatography and liquid chromatography-tandem mass spectrometry equipment.

Method of analysis

Any method used to analyze samples has to be validated. For example, in the case of blood plasma samples, review the bio-analytical method used for sample analysis, and review whether the method was validated before it was used to analyze the samples. Review the following:

- Method development: procedure, scientific publications, records
- Method validation: procedure and records for all parameters, including full validation, partial validation, and cross validation. Review the raw data against the report, including electronic results for authenticity, audit trail, date, changes, and data integrity, eg chromatograms
- Sample and solution stability procedures and records
- Reference materials used: CoA, usage record, batch number used against data, expiry date, weights, preparation of solutions, dilutions and calculations

Sample analysis

Compare the data from the reports against the source data. Verify whether all the samples were analyzed according to the number of patients. To do so, compare the number of patients enrolled in the trial, all the periods, sampling times, samples

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transferred from the CPU to the bio-analytical laboratory, samples prepared, back-up samples, and select results from the report for verification against the electronic data. For electronic data verification, verify at least the following:

- Corroborate whether the instruments used were qualified and calibrated at the time of sample analysis, eg chromatographers, mass spectrometers
- Select printed records of data, eg chromatograms, and compare them against the electronic data for the sample set. Verify the date of analysis, time, analyst identification, system audit trail, changes, peak areas, integration and other related information for accuracy and reliability (ALCOA+)
- Verify whether the sample set met the requirements, eg calibration curve, quality control samples
- Corroborate whether there any analysis was repeated. And if so, whether this was done according to an SOP
- Corroborate whether an incurred sample analysis was done according to an SOP and whether the results were acceptable

Statistical analysis

Review the qualification of the biostatistical experts involved before and throughout the entire clinical trial procedure, as mentioned in the protocol. This includes, but is not limited to, study design, randomization, case-report forms, completion of the final report, and/or publication of the results. Review the data whenever possible.

Study report

The sponsor has to prepare a report reflecting the conduct and outcome of the study after its completion, and make it available for inspections. Whenever possible, the format of the report format should follow the ICH guidelines, eg ICHE3.

During the inspection, review the report to ensure that the results, data and information presented in the report are a true reflection of the trial.

Verify:

- Whether all demographic data, criteria, results, deviations, protocol violations, and adverse events are accurately documented in the report
- Whether the report is signed and dated by all responsible trial personnel including the investigator

Multicenter trials

A multicenter trial is usually conducted simultaneously by several investigators at different sites following the same protocol. During the inspection, review the procedures and administrative arrangements in place to ensure that the study was planned and conducted according to GCP and in accordance with the protocol.

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Verify the following during the inspection:

- Written proof of the protocol's acceptance, including annexes and amendments, by all investigators
- Whether the protocol and any amendments were approved
- Records for any meeting between the parties involved in the trial
- Records for randomization, IMP distribution and storage, and training; similarly to what is done to single center trials
- Standardization of methods to evaluate and analyze laboratory and diagnostic data
- Adherence to the protocol, monitors and reports
- Whether there was a means of centralized data management and analysis
- Compliance with procedures, e.g. preparation of the final report
- Whether the trial results were published
- Whether safety reports were provided to the investigators from all sites involved in a multicenter trial

Summary

At the end of the inspection, the inspectors should have verified compliance with at least the following:

- GxP principles
- Declaration of Helsinki and CIOMS guidelines
- Clinical study protocol
- Requirements from the EC
- Requirements set by the National Regulatory Authority
- Data integrity principles

It is expected that at the end of the inspection the following will have been reviewed:

- Master lists for the patients
- Documentation relating to the IMPs, including COAs, accountability, reconciliation, and dispensing records
- Laboratory results and source data including electrocardiograms and X ray films
- Logs, registers, and records
- Training procedures and records
- Lists of staff for each study
- Screening records including general screening forms and data)
- Master list with the signatures of volunteers
- Meal records including the correspondence between the dietician and caterer where applicable
- Custodian reports
- Sample transfer records
- Adverse drug event reports
- Concomitant medication records

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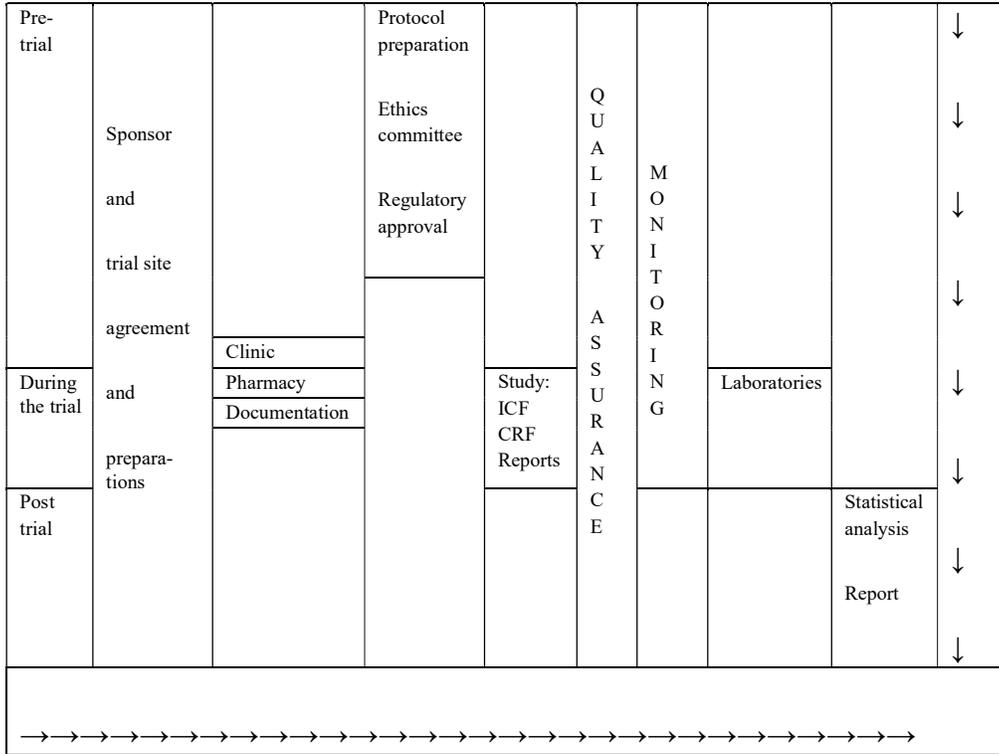
- ICFs
- Documented justification for the number of volunteers for the study
- Demographic data recorded versus those reported
- IMP dispensing records
- Product administration / dosing records
- Blood sample collection records
- Case report forms

References

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, World Health Organization WHO Technical Report Series, No. 850, 1995, Annex 3
2. Guidelines for the preparation of a contract research organization master file, World Health Organization WHO Technical Report Series, No. 957, 2010 Annex 7
3. Guidance on good data and record management practices, World Health Organization WHO Technical Report Series, No. 996, 2016 Annex 5
4. Good Laboratory Practices. Handbook. World Health Organization. 2009. <http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
5. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016
6. Guideline on bioanalytical method validation, EMA, 2012
7. Bioanalytical Method Validation Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM) May 2018

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Flow chart



The guide follows steps relating to general stages for the preparation of documentation, approvals, and the conduct of a trial. This flowchart is an example of the process flow, and not a requirement.