DIRECTORATE GENERAL OF DRUG ADMINISTRATION
CLINICAL TRIAL INSPECTION

GUIDANCE ON CLINICAL TRIAL INSPECTION

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ABBREVIATIONS	
AE	Adverse events
CRO	Clinical Research Organisation
CRF	Case Record Form
CT	Clinical Trial
CV	Curriculum Vitae
EC	Ethics Committee
ICF	Informed Consent Form
IP	Investigational Product
SOP	Standard Operating Procedure
DGDA	Directorate General of Drugs Administration

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CLINICAL TRIAL INSPECTION PROGRAMME:

1. **Objectives** :

The aims of the programme are:

a. To verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial.
b. To verify the credibility and integrity of clinical trial data generated.
c. To verify the compliance with various regulatory provisions as per Drugs Act, 1940 and Rules their under, The Drugs (Control) Ordinance 1982 & it's amendment.

The purpose of this programme is to provide direction to inspectors/DGDA officers for conducting inspection of site of clinical trial, sponsor / CRO's facilities involved in clinical trial and information to investigators, sponsor/ CRO's about procedures for inspection and follow up of action.

2. **Scope and extent of the programme**:

Clinical trial inspection programme covers all clinical trial sites and sponsor / CRO's facilities involved in clinical trial of drugs including biological and medical device covered under Drugs Act, 1940 and Rules their under, The Drugs (Control) Ordinance 1982 & it's amendment.

3. Planning for Inspection:

Inspection can be conducted before, during or after a clinical trial is completed.

3.1 **Selection of studies**:

Inspection can be carried out as a routine surveillance or for any specific cause(s).Study may be selected for inspection based on, but not restricted to the following criteria:

3.1.1 Nature of study

3.1.2 For regulatory decision based on clinical trial data

3.1.3 Data irregularities

3.1.4 Complaints

3.1.5 Vulnerability of subjects

3.1.6 Number of CT including number of subject enrolled at a particular site

3.2 **Inspection assignments**:

DGDA will issue instruction to the officers /Inspectors to conduct the inspection identifying the Clinical trial, name, address, contact number of clinical trial site, sponsor / CRO's facilities to be inspected. It may also identify the type and purpose of the inspection and provide background materials like study protocol, CRF etc.

3.3 **Preparing for inspection**:

The inspector shall go through the information provided by DGDA and develop a plan for conducting the inspection.

3.4 **Scheduling the inspection**:

Inspection of clinical trial site would generally be pre-announced to ensure availability of the Investigator / Sub- Investigator and other personnel along with study records at the time of the inspection. The date of inspection and other arrangements would be finalised by the DGDA Officers / Inspector(s) in coordination with the investigator /sponsor/ CRO. Under some specific circumstances unannounced inspection of clinical trial sites can be carried out as per the direction of DGDA. Inspection of CRO/Sponsor can be conducted without prior notice.

4. **Conducting the inspection:**

4.1 **Clinical Trial Sites:**

The inspection includes verification of essential documents to determine whether the trial related activities were in accordance with the protocol, GCP guidelines published by DGHS, Govt. of Bangladesh and Drugs Act as well as other applicable regulatory requirements. When inspection is carried out after completion of the clinical trial, it will include comparison of data generated by the sponsor with source documents at the clinical trial sites and Case Record Form (CRF) in the investigator's files. If it is a routine surveillance or "for cause" inspection of an ongoing clinical trial, the comparison will generally include source documents and CRF.

4.1.1 Opening interview:

Inspector should meet investigator / key person of Sponsor and present his / her identity card. The inspector should provide verbal summary of methods and procedures to be followed during the inspection.

During opening interview following main activities should be carried out:

4.1.1.1 Investigator prior education and GCP experience, GCP training provided by the sponsor.

4.1.1.2 Who did what, when, where and how with respect to following:

- Obtaining Informed consent of subjects,
- Screening and admission of subjects to the study,
- Receipt, handling, administration, return of investigational product,
- Collection and analysing of data,
- Recording, transcribing and reporting of data to sponsor,
- Archiving the data

4.1.1.3 How did the investigator identify the subjects for the study,

4.1.1.4 Date of enrolment first and last subject

4.1.1.5 About Ethics Committee the site is using

4.1.1.6 Whether the investigator has copies of protocol, permission from DGDA, undertaking by the investigator etc.

4.1.1.7 Information about unexpected and serious adverse events (if any) occurred at the site,

4.1.1.8 Information about monitoring/auditing of the site by sponsor/CRO.

During the interview other relevant facts may also be found out.

4.1.2 ***ORGANIZATION & DELEGATION OF RESPONSIBILITIES:***

Inspector shall verify / obtain following:

4.1.2.1 Brief about study site.

4.1.2.2 Status of the study.

4.1.2.3 Investigator has agreement with sponsor for the study.

4.1.2.4 Financial & Confidentiality agreement with Investigator and concerned laboratory (ies) in place.

4.1.2.5 In Investigator undertaking protocol title, Investigator's name, address, telephone no of site, qualification, Name & address of laboratories, Name of Sub-Investigator etc are in-compliance with Drugs Act.

4.1.2.6 Obtain list of all clinical trials performed by investigator.

The list should have information such as
- Protocol Number
- Protocol Title
- Name of Sponsor/CRO
- Study date

4.1.2.7 Determine whether authority for conducting various Clinical trial related activities were delegated properly by the Investigator to the competent personnel so that investigator was able to supervise the study adequately. Obtain a list of personnel with delegated activity.

4.1.2.8 Documents following;
- Date of EC / IEC approval including initial review of protocol, amendment the ICD etc.
- Date of screening of first subject,
- Date of signing ICF by the first subject
- Date of first administration of IP,
- Date of last follow up of any subject,

4.1.2.9 List the name and address of facilities involved in laboratory test required by protocol. Verify accreditation status and adequacy of these facilities to perform the specified test,

4.1.2.10 Obtain a copy of site enrolment log,
4.1.2.11 Determine whether SOP's for various activity are established and documented,

4.1.3 Study Protocol

4.1.3.1 Determine if, there are any difference between protocol provided to DGDA and the protocol in the Investigator's file with respect to following:

- Version number and effective date
- Eligibility of Subject (Inclusion/ Exclusion Criteria)
- No of Subject
- Dosage
- Route of administration
- Frequency of dosage
- Randomisation & Blinding process
- Verify whether Investigator follow the protocol as approved
- Version number and EC approval of amendments

4.1.4 Subject record & Informed consent:

4.1.4.1 Review the Informed Consent Form (ICF) signed by the subjects. If the number of subjects at site is relatively small (e.g.20 or less) 100% of the ICF can be reviewed.

Determine the following:

4.1.4.2 whether ICF have all the elements enlisted in Drugs Act or WHO guidelines,

4.1.4.3 whether IC has been obtained from each subjects prior to participation of the subject in the study,

4.1.4.4 whether signature/thumb impression of the subjects have been affixed with date,

4.1.4.5 whether in case of illiterate subjects or illiterate representative of a subject, there are signature and details of an impartial witness,

4.1.4.6 Have witness/ signature being personally dated,

4.1.4.7 Have patient/witness signature been personally dated?

4.1.4.8 Has the dated signature of the designated person for administering informed consent (IC) been affixed?

4.1.4.9 Is the designated person for administering IC medically qualified?

4.1.4.10 If IC has been administered by a designated person who is not medically qualified, is there evidence that subject's queries of a medical nature were answered by a medically qualified person or the investigator?

4.1.4.11 Is the completed ICF signed and dated by the investigator?

4.1.5 Source Documents and Case Record Form

4.1.5.1 Verify condition, completeness, legibility, accessibility of the investigators source data file.

4.1.5.2 Determine whether subjects who were enrolled and /or completed the study meet inclusion and exclusion criteria;

4.1.5.3 Determine whether subject received the test drug with respect to dose and frequency specified according to the protocol;

4.1.5.4 Determine whether safety/ efficacy end point data was collected and reported in accordance with the protocol;

4.1.5.5 Does medical record mentions subject ID/ name /hospital registration number / and indication that subjects are participating in a clinical trial

4.1.5.6 Whether all adverse events were reported in CRF;

4.1.5.7 Compare the source document with CRF and determine whether source data have been correctly transcribed in CRF;

4.1.5.8 Verify whether all SAE's have been reported to the sponsor (within 24 hours) and EC (within 7 working days);

4.1.5.9 Verify whether adequate medical care have been given to the subject especially in the event of inter current illness, adverse events including abnormal lab parameters;

4.1.6 Ethics Committee (EC) / Independent Ethics Committee (IEC):

4.1.6.1 Identify the name , address of the EC/ IEC in the approval letter and compare it with that with the one stated in investigators undertaking ;

4.1.6.2 Verify if IEC approval letter mention study code , Protocol title and version number of the protocol, list of other documents reviewed, list of members present at the meeting, quorum of five members as specified in Drugs Act, Office Orders and as per relevant WHO guidelines are satisfied, date, time , venue of the meeting, signature and date of member secretary / Chairman;

4.1.6.3 In case the site does not have an IEC, verify whether following are in place:

- Statement of the investigator / institution that approval granted by another IEC would be abided by statement from the approving IEC that they would take responsibility for ongoing supervision of the site;

- Has the investigator submitted reports of all SAEs to the IEC and apprised the EC/IEC about the trial progress?

4.1.7 Sponsor:

4.1.7.1 Verify whether a clinical trial Investigators agreement has been signed for this study with the sponsor;

4.1.7.2 Whether investigator maintain copies of all reports submitted to the sponsor;

4.1.7.3 Whether all SAE are reported to sponsor within 24 hours;

4.1.7.4 Whether all CRFs were submitted to sponsor after completion of study;

4.1.7.5 Determine whether all dropouts and reasons thereof were reported to sponsor;

4.1.7.6 Determine the method and frequency of monitoring the progress of the study by the sponsor;

4.1.7.7 Whether a log of onsite monitoring visit is maintained at the site;

4.1.7 Test Drug Accountability:

4.1.8.1 Review individual subject record to verify the correct dose administration with respect to dose, frequency, route of administration;

4.1.8.2 Determine whether unqualified /unauthorised persons administered/dispensed the test drug.

4.1.8.3 Determine whether adequate record of qty. of test drug received , dispensed/ destroyed/returned is maintained ;

4.1.8.4 Determine whether storage condition/monitoring method are as per protocol/recommendation;

4.1.8.5 Whether trial medication are maintained under controlled access;

4.1.8.6 Have un-used trial medications been returned to the sponsor or disposed of

according to protocol? In case of destruction at site, is a certificate of destruction on file?

4.1.8.7 Are the drugs dispensing records being maintained properly?

4.1.8.8 Are the records for reconciliation of all IPs received from the sponsor maintained?

4.1.9 Record retention:

4.1.9.1 Is adequate space available at the site for retention of documents

4.1.9.2 Determine whether documents are maintained properly and for the period as specified and necessary measures have been taken for accidental and premature destruction;

4.1.9.3 Determine who maintained custody of the documents and means for assuring prompt action;

4.1.10 Concluding the Inspection:

The inspector should conclude the inspection with final discussion with the Investigator. During discussion the inspector should explain inspection finding .The inspector may also issue a list of observation at the conclusion of inspection.

4.2 **Inspection of CRO/Sponsor**

The inspection includes verification of essential documents to compare practice and procedure followed by the CRO/Sponsor to that committed in the clinical trial application and GCP guidelines published by Govt. of Bangladesh, Drugs Act and as well as other applicable regulatory requirements as per latest WHO guidelines. Inspection of CRO/Sponsor can be conducted without prior notice.

During inspection following aspects may be verified.

4.2.1 Documents submitted to DGDA and regulatory approvals obtained.

4.2.1.1 Clinical Trial application and DGDA approval letter

4.2.1.2 Import license application and import licence obtained. Copy of license

4.2.1.3 Export NOC for biological samples

4.2.1.4 List of investigators

4.2.1.5 Investigator Undertaking

4.2.1.6 Investigator's brochure

4.2.1.7 Protocol and Protocol amendments

4.2.1.8 Patient Information Sheet and Informed Consent Form

4.2.1.9 Case Record Form

4.2.1.10 Ethics Committee approval and notifications to DGDA

4.2.1.11 Unexpected and Serious Adverse Event Reports

4.2.1.12 Study report

4.2.2 Organisation and personnel:

4.2.2.1 Company profile and overall structure,

4.2.2.2 Organization chart for management of the clinical trial Structure and responsibilities for all activities involving investigational products Departments, functions, and key personnel responsible for Protocol development Investigator's brochure, Case Record Form Informed consent form (ICF), translations and amendments. Selection of investigators Regulatory approval, Ethics Committee (EC) approval, Monitoring Quality assurance Adverse Event (AE) Reporting, Data Management , Statistical Analysis Electronic Records/Clinical Database, Clinical Supplies-Investigational Products (IP) Archival.

4.2.2.3 Identify and determine the personnel responsible for following:

- Authority to review and approve study documents
- For final evaluations and decisions in the review of study
- For obtaining & reviewing adverse events and reporting to DGDA
- Monitors/CRO's with job descriptions and qualifications
- Job description of key stake holders
- Verify clinical personnel training record
- To obtain a list of external service providers and contractors and documentation of the service they provide.
- Verify the SOPs followed for various responsibilities and clinical trial related –activities.

4.2.3 Selection and monitoring of investigators

4.2.3.1 Obtain list of all investigators along with Investigator Undertaking, Signed Investigator Agreements

4.2.3.2 Criteria for selection of sites

4.2.3.3 Information provided to sites viz.

4.2.3.4 Informed consent form, Protocol, Reports/publications of previous trials, Investigator's Brochure, Product labelling, Training, All versions and updates etc.

4.2.3.5 Investigator's non-compliance (If any)

- Deviations from DGDA regulations
- Deviations form protocol
- How sponsor handles serious deviations from approved protocol or Drugs Act or WHO guidelines.

4.2.3.6 Steps for correction:

- Verify whether any investigators terminated? Review monitoring reports reported to DGDA,
- Any Non-compliant investigator /terminated? Reasons?

4.2.3.7 Selection of monitor:

- List all monitors for study duration
- Selection criteria for monitors
- Job descriptions/responsibilities
- Qualifications
- Training Records and CVs
- Reporting structure
- Monitoring SOP Frequency, scope and process, Obtain a copy of SOP and check compliance, If no SOPs, interview monitors to check how monitoring was done, Monitoring Plan, Monitoring Reports.

4.2.3.8 Review the Pre trial and periodic trial visit report in respect of following content:

- Process of verifying compliance to protocol
- Process of verifying investigator responsibilities
- Ethics Committee Approvals Amendments/Re-approval Communication-progress reports/SAEs etc Validity/Completeness
- Informed Consents Confirmation of consent and process of consent.
- Use of IEC approved forms.
- Adequacy of consent documentation, Completeness
- Which CRFs were compared to source docs? When and who verified CRFs against source data (hospital records, office charts, laboratory reports,etc.) at the study site. Form for data verification
- Check copy of any SOPs and guidelines for data verification

- Data correction handling, Compliance to Monitoring Plan, Frequency, Follow up etc.

4.2.4 Quality Assurance (QA):

4.2.4.1 Verify SOP for QA audits and operation of quality assurance unit

4.2.4.2 Describe how the audit and monitoring are separated

4.2.4.3 Obtain list of audited trial

4.2.5 Adverse events reporting:

4.2.5.1 Verify sponsor's method for following up of adverse events and for dissemination of AE information to others Investigators

4.2.5.2 Obtain list of SAE reported, Including death.

4.2.5.3 Verify the timeline for reporting the SAE to DGDA and other Investigators /EC;

4.2.6 Data collection and handling

4.2.6.1 Study tabulations: List of all studies for marketing Authorization

4.2.6.2 Data Tabulations: Number of subjects. Verify if number in CT application same as marketing Authorization application(compare to CRFs submitted)

4.2.6.3 If any subjects not included in the marketing Authorization application? Why not included?

4.2.6.4 Review of SOPS to verify compliance to assure the integrity of safety and efficacy data collected from clinical investigators

4.2.6.5 Verify that the SOPs were followed and document any deviations

4.2.6.6 Deviations/Data queries resolutions

4.2.6.7 Statistical processes

4.2.6.8 Primary endpoints compare the tabulations with CRFs and source documents

4.2.6.9 Record retention

4.2.7 Electronic Record and Clinical database:

4.2.7.1 Person responsible for designing and developing data base

4.2.7.2 Can it be modified, or has it been modified? If so, by whom?

4.2.7.3 If the clinical investigator can modify it, how would the sponsor be aware of any changes?

4.2.7.4 Validation :Person responsible, Process, Documentation of process

4.2.7.5 Error logs maintained for errors in software and systems?

4.2.7.6 Do error logs identify corrections made?

4.2.8 Data collection:

Following aspects may be verified:

4.2.8.1 Responsibilities : Authorization to access the system, to enter data and to change Data.

4.2.8.2 Use of electronic data capture or data transcription from paper CRFs into an electronic record

4.2.8.3 Audit trail : to record Changes to electronic records, Person Responsible for the change and Time of the change

4.2.8.4 Process of data transmission from the clinical investigator to sponsor or CRO

4.2.9 Computerized System Security:

Following aspects may be verified:

4.2.9.1 Management of system access e.g. access privileges, authorization/de-authorization procedures, physical access controls

4.2.9.2 Records of authorized personnel, Names, Titles. Description of their access Privileges

4.2.9.3 Access methods e.g., identification code/password combinations, tokens,

biometric signature, electronic signatures, digital signatures

4.2.9.4 Data security in case of disasters, e.g., power failure

4.2.9.5 Contingency plans and backup files

4.2.9.6 Controls in place to prevent data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software

4.2.10 Investigational Product (IP):

Following aspects may be verified:

4.2.10.1 Transferred data from central lab to sponsor

4.2.10.2 Integrity Procedures to ensure integrity of IP from manufacturing to receipt by the clinical investigator.

4.2.10.3 If IP met required release specifications by review of the Certificate of Analysis?

4.2.10.4 Storage of IP and the conditions of storage

4.2.10.5 Process of verification of IP integrity during shipment to investigator.

4.2.10.6 IP label

4.2.10.7 If the test article was recalled, withdrawn, or returned?

4.2.10.8 Accountability:

Following aspects may be verified:

- Names and addresses of clinical investigators receiving IP Shipment, date (s), quantity, batch number.
- Final disposition of the test article.
- Detailed audit if serious violations are suspected.
- Sufficient records to reconcile IP usage (compare the amount shipped to the investigators to the amount used and returned or disposed of).
- Check whether all unused or reusable supplies of IP returned to the sponsor when either the investigator(S) discontinued or completed participation in the clinical investigation, or the investigation was terminated. If the test article was

not returned to the sponsor, describe the method of disposition and determine if adequate records were maintained.

6. Reporting of inspection

The Inspection should be documented in writing in both during and after inspection. After the inspection a narrative report containing details of inspection finding should be prepared and submitted to DGDA.