



Ethiopian Food and Drug Authority (EFDA)

Guideline for Medical Devices Good Clinical Practice

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Acronyms

CIP	Clinical Investigation Plan
CRF	Case Report Form
DMC	Data Monitoring Committee
EC	Ethical Committee
EFDA	Ethiopian Food and Drug Authority
GHTF	Global Harmonization Task Force
IB	Investigator's Brochures
IRB	Institutional Review Board
NREC	National Research Ethical Committee
DSMB	Data and safety monitoring board
DSMC	Data and safety monitoring Committee
USADE	Unanticipated serious adverse device effect
GHTF	Global Harmonization Task Force
IVD	In Vitro Diagnostics

1. Introduction

Clinical Investigation on medical device is necessary to establish the clinical performance or effectiveness and safety of medical devices used in health care system as well as individual users. Much of what is known today about the risk and benefits of specific devices has come from randomized controlled clinical trials that are designed to answer important scientific and health care questions.

According to article 27 of Food and Medicine Administration Proclamation 1112/2019, the medical device clinical trial on human beings should be conducted as per the relevant requirements set in the proclamation and regulation issued to implement it. The same proclamation requires the clinical trial protocol (Clinical Investigation plan) to be evaluated and accepted from scientific, legal and ethical perspective prior to the trial conduct. This guideline is therefore developed to provide guiding principles to medical device developers, manufacturers, and other research organizations to determine if the clinical investigation for their device is mandatory. It then sets regulatory requirements including ethical considerations, responsibilities of principal investigator, monitor, sponsor and other critical actors, clinical investigation plan contents, practices and monitoring of clinical investigation conduct, and clinical investigation report.

The guideline provides regulatory and scientific requirements on the conduct of clinical investigations using medical devices to support scientific justification on clinical effectiveness and safety of medical devices in support of the marketing authorization.

2. Definition

Effectiveness is achievement of a clinically significant intended result in a defined portion of the target population when the investigational medical device is used within its intended uses and according to its instructions for use, the investigator's brochure and CIP, as determined by documented scientific evidence.

Adverse device effects is adverse events related to the use of an investigational medical device. The definition includes events resulting from insufficient or inadequate instructions for use, development, installation, or operation, or any malfunction and event resulting from use error or from intentional misuse of the investigational medical device.

Adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Audit is systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, according to the CIP, standard operating procedures, this International Standard and applicable regulatory requirements.

Case report forms (CRFs) is set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the CIP.

Clinical investigation is systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device. "**Clinical trial**" or "**clinical study**" are synonymous with "clinical investigation".

Clinical investigation plan (CIP) is document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. The term "protocol" is synonymous with "CIP".

Clinical performance is behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s).

Comparator is medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation.

Coordinating Investigator is an investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial

Contract research organization (CRO) is person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.

Coordinating investigator is investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation

Data monitoring committee (DMC) is independent committee that may be established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation. E.g. Data and safety monitoring board (DSMB), data and safety monitoring Committee (DSMC) etc.

Deviation is instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP.

Device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. It includes malfunctions, use errors, and inadequate labelling.

Primary Endpoint(s) or principal indicator(s) is used for assessing the primary hypothesis of a clinical investigation.

Secondary Endpoint or indicator(s) is used for assessing the secondary hypotheses of a clinical investigation.

Ethics committee (EC) is independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation.

Informed consent is documented by means of a written, signed and dated informed consent form.

Informed consent process is process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation.

Investigation site is institution or site where the clinical investigation is carried out. It is synonymous with "investigation centre".

Investigational medical device is medical device being assessed for safety or performance in a clinical investigation.

Investigator is individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions.

Investigator's brochure is compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.

Malfunction is failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

Major amendments is an amendments to the clinical investigation where they are likely to have a significant impact on the safety or physical or mental integrity of the participants; the scientific value of the trial; the conduct or management of the clinical investigation; or the quality or safety of any investigational device used in the clinical investigation.

Minor Amendment is Amendment to the clinical investigation where they do not involve a more than minimum risk for participants or the conduct of the clinical investigation and do not have significant impact on the scientific value of the clinical investigation; the conduct or management of the trial or safety of investigational device used in the clinical investigation.

Monitor is an independent body or person assigned by the sponsor to conduct the monitoring of clinical investigation at the investigation site to confirm the compliance of the site, investigation team to CIP, EC and regulatory standards.

Principal investigator is qualified person responsible for conducting the clinical investigation at an investigation site.

Randomization is process of assigning subjects to the investigational medical device or comparator groups using an established recognized statistical methodology to determine the assignment in order to reduce bias.

Serious adverse device effect (SADE) is adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious adverse event (SAE) is adverse event that

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 1. a life-threatening illness or injury, or
 2. a permanent impairment of a body structure or a body function, or
 3. in-patient or prolonged hospitalization. Or
 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress. foetal death or a congenital abnormality or birth defect

Source data is all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

Source document is printed, optical or electronic document containing source data.

Sponsor is individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation.

Unanticipated serious adverse device effect (USADE) is serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Use error is act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. It includes slips, lapses, and mistakes.

Vulnerable subject is individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

3. Objectives

The objective of this guideline is to provide guidance on the requirements for good practices during conducting of clinical investigations of medical devices on human beings to

- Protect the rights, safety and well-being of human subjects
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results
- Define the responsibilities of the principal investigator
- Assist sponsors, investigators, ethical committees, and other bodies involved in the conformity assessment of medical devices

4. Scope of the guideline

This guideline is applicable to clinical practice of all medical devices other than Invitro diagnostics (IVD) clinical investigation including pre-and post-market studies carried on human beings.

5. Ethical Consideration

5.1.General

Clinical investigations should be conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki. These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and should prevail over interests of science and society. These principles should be understood, observed, and applied at every step in the clinical investigation.

Clinical investigation studies on medical device must be reviewed and receive prior written approval from National Research Ethical Committee (NREC) and/or Institutional Review Board (IRB) prior to enrolment of study participants. Such approval may be conditional or unconditional and sponsor should strictly adhere to any conditions prior to the enrolment of study participants.

The sponsor generally assumes responsibility for obtaining IRB and NREC review of the study Clinical investigation plan. The approval letter of the NREC and/or the IRB is required for all clinical trials. Hence, such approval letter(s) with copy of the approved protocol should be hold at the clinical investigation site and provided for review as requested by the Authority.

5.2.Improper influence or inducement

The sponsor should avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in or contributing to, the clinical investigation.

All investigators should avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

5.3.Compassion and Additional Health Care

Compensating subjects for costs resulting from participation in the clinical investigation (e.g. transportation) may be appropriate but the compensation should not be so large as to unduly encourage the subject to participate. Evidence such arrangements should be reflected in the CIP and the records.

Arrangements for standard health care for subjects who suffer from an adverse event as a result of participating in the clinical investigation should be made and documented. This should be reflected in the CIP.

5.4.Responsibility

All parties (investigators, sponsor, monitor, research organization, investigation site) involved in the conduct of the clinical investigation should share the responsibility for its ethical conduct in accordance with their respective roles in the clinical investigation.

5.5.Vulnerable Populations

Clinical investigation should be conducted in vulnerable populations only when they cannot be carried out in non-vulnerable populations. These clinical investigations should be designed specifically to address health problems that occur in the vulnerable population and offer the possibility of direct health-related benefit to the vulnerable population.

The precaution implemented should be indicated.

5.6.Informed Consent

5.6.1. General

Written informed consent should be obtained from the subject and the process should be documented before any procedure specific to the clinical investigation is applied to the subject.

The informed consent form consists of an information form and an informed consent signature form. These two forms can be combined in one document or separated in to two documents.

5.6.2. Process of Obtaining Informed Consent

The general process for obtaining informed consent should be documented in CIP and should:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation.
- Avoid any coercion or under improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive the subject's rights
- Use native non-technical language that is understandable to the subject,
- Ensure the existing of witness for those subjects which unable read the informed consent form
- Provide ample time for the subject to read and understand the informed consent form & to consider participation in the clinical investigation,
- Include personally dated signatures of the subject & the principal investigator or an authorized designee responsible for conducting the informed consent process
- Provide the subject with a copy of the signed and dated informed consent form and any other written information
- Show how informed consent will be obtained and recorded in special circumstances where the subjects is unable to provide it him-or herself, and
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation

The above requirements should also be applicable to informed consent obtained from the subject's legally authorized representative.

6. Clinical Investigation Planning

6.1.General

All parties participating in the conduct of the clinical investigation should be qualified by education, training and experience to perform their tasks and this should be documented appropriately. Such documented evidence should be available at investigation site and be part of CIP.

6.2.Risk Evaluation

Risks associated with the investigational device should be estimated in accordance with latest version of ISO 14971 prior to conducting a clinical investigation. The risk analysis should include or refer to an objective review of published and available unpublished medical and scientific data. A summary of risk analysis, including an identification of residual risks, should be included in the investigator Brochure (IB).

The decision to embark upon the clinical investigation of a medical device requires that the residual risk(s) to the subject associated with the clinical procedure required by the CIP be balanced against the anticipated benefits to the subjects.

This risk analysis should also be used as a basis for identifying anticipated adverse effects characterized by their nature, incidence, severity and outcome.

The anticipated adverse device effects should be documented in the CIP, the IB and the informed consent form. This enable compliance with any reporting requirements for anticipated and unanticipated serious adverse device effects (SADEs).

6.3.Justification for the design of the clinical investigation

There should be a justification for selected design of clinical investigation. The justification for the design of the clinical investigation should be based on the evaluation of pre-clinical data and the analysis of a clinical evaluation.

The clinical evaluation includes an assessment and analysis of clinical data concerning safety or performance of the investigational device or similar devices or therapies. The evaluation should be relevant to the intended purpose of the investigational device and the proposed method of use. This is a scientific activity that should be done with rigour and objectivity according to scientific standards using the principles of Global Harmonization Task Force (GHTF) clinical evaluation.

The results of the clinical evaluation should be used to determine and justify the optimal design of the clinical investigation. They should also help identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of comparator (s).

6.4. Clinical Investigation Plan (CIP)

There should be clinical investigation plan for the conduct of medical device clinical investigation. The CIP should include the information specified in Medical device Clinical investigation authorization guideline.

The CIP and all subsequent amendment to the CIP are agreed upon between the sponsor, the coordinating investigator and all principal investigators, and are recorded with a justification for each amendment. Amendments to the approved CIP should be notified to and get approval from the Authority before being implemented.

6.5. Investigator's Brochure (IB)

The investigator should retain an IB that provides the investigators with sufficient safety or performance data from pre-clinical investigations and/or other clinical investigations to justify human exposure to the investigational device specified in the CIP.

The IB should be updated throughout the course the clinical investigation as significant new information becomes available (e.g. a significant change in risk, etc)

The principal investigator(s) should acknowledge the receipt of the IB and all subsequent amendments and should keep all information confidential. However, as deemed necessary by the request of the Authority.

6.6. Case Report Forms (CRFs)

An approved CRF should be available and used at clinical investigation site. The CRFs should capture the data for each enrolled subject as required by the CIP. The CRFs should include information on the condition of each subject upon entering, and during the course of, the clinical investigation, exposure to the investigational device and any other therapies.

A procedure should be in place to ensure, that when it is necessary to amend the CIP, the Sponsor should review the CRFs to determine if an amendment of these forms is also necessary.

6.7. Monitoring Plan

There should be a monitoring plan developed by the sponsor based on assessment of the extent and nature of monitoring appropriate for the clinical investigation, including the strategy for source data

verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoint of the clinical investigation. The monitoring activities should be conducted as per the monitoring plan.

6.8. Investigation site selection

An investigation site selection report comprising adequacy and appropriateness of the site as well as availability of qualified investigator should be documented or retained. The rationale for selecting an investigation site should be documented. The rationale can be based on prior experience of the sponsor with the investigation site.

6.9. Agreement

There should be a valid agreement between the sponsor and the principal investigator(s) /investigation site(s) and between any other relevant parties (e.g. investigators, CRO(s) and core laboratories), which defines the responsibilities of each party in the clinical investigation. All agreements should be recorded in writing and signed and dated by all parties involved.

The agreement should indicate that, by participating in a clinical investigation, the parties may share some regulatory responsibilities with the sponsor.

6.10. Labelling

The investigation device labels, the instructions for use or the packaging should indicate that the investigational device is exclusively for use in a clinical investigation. For post approval clinical investigation of medical device, the labelling requirement “for investigational use only” may not be applicable. For detail labelling requirement please consult the guideline for labelling requirements of the authority.

6.11. Data Monitoring Committee (DMC)

There should be a procedure for establishing DMC whose primary function should be described in the CIP. The sponsor should establish a DMC prior to starting the clinical investigation.

The decision to establish a DMC should be guided by the risk analysis, taking into account both the risks associated with the use of the investigational device and the risk associated with subject’s participation in the clinical investigation.

The responsibilities of the DMC should be detailed in written in the procedures to establish the frequency of meetings, handling of emergency situations and documentation of such meeting.

7. Clinical Investigation Conduct

7.1.General

The clinical investigation should be conducted in accordance with this guideline and the authorized CIP by the Authority.

The clinical investigation should not be commenced until written approval from the EC and Authority have been received.

7.2.Investigation site Initiation

Documented information should be retained, by the sponsor or monitor, for an initiation visits and/or an investigator meeting for each participating investigation site at the beginning of the clinical investigation. A log should be initiated identifying names, initials, signatures, functions, and designated authorizations for the principal investigator and members of the investigation site team.

7.3.Investigation site monitoring

The conduct of the clinical investigation should be monitored according to the monitoring plan.

In general, there is a need for on-site monitoring before, during, and after the clinical investigation. However, in exceptional circumstances, the sponsor may determine that remote monitoring (without visiting the investigation site), in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication, can assure appropriate conduct of the clinical investigation. In such circumstances, the sponsor should provide a justification for omitting the source document verification.

7.4.Adverse events and device deficiencies

7.4.1. Adverse Events

All adverse events should be documented in a timely manner throughout the clinical investigation and should be reported. Serious adverse events should be reported within 48 hours and all other adverse events should be reported in an interim or final report of the clinical investigation.

7.4.2. Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device should be documented throughout the clinical investigation and appropriately managed by the sponsor.

Device deficiencies that do not cause an adverse event but could have led to a medical occurrence

- a) If either suitable action had not been taken,
- b) If intervention had not been made, or
- c) If circumstances had been less fortunate

7.5. Clinical Investigation Documents and documentation

7.5.1. Amendments

Any amendment made to IB, CIP, CRFs, informed consent form and other subject information, or other clinical investigation documents with their justification statement, throughout the clinical investigation should be communicated and get approval for major amendments from the authority and EC before being implemented.

Proposed amendments to the CIP should be agreed upon between the sponsor and principal investigator, or approved by the EC. The version number and date of amendments should be documented.

7.5.2. Subject Identification log

Each investigation site should maintain a log of all the subjects enrolled in the clinical investigation, assigning an identification code that is traceable to their names, alternative subject identification or contact information. The names, alternative subject identification or contact information should remain confidential to the code assigning person.

Depending on the clinical investigation design, a log should be maintained that identifies everyone who has been pre-screened for potential enrolment in the clinical investigation.

7.5.3. Source documents

Source documents should be created and maintained by the investigation site team throughout the clinical investigation.

7.6. Additional members of the investigation site team

New members of the investigation site team may be added from time to time at new or existing sites. New personnel should receive adequate training including GCP and critical investigation requirements before they start their assignment and this training should be documented. The names, initials, signatures, functions, and designated authorizations of new personnel should be documented.

7.7. Subject privacy and confidentiality of data

Confidentiality of data should be pragmatically maintained by all parties involved at all times throughout the clinical investigation. All data should be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information should be preserved in reports and when publishing any data.

The principal investigator or institution should provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and the authority inspections.

As required, the principal investigator or institution should obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

7.8. Document and Data Control

7.8.1. Traceability of documents and data

All documents and data should be controlled and maintained in a way that assures their traceability. Where relevant, the accuracy of translations should be guaranteed and documented. All documents, and subsequent versions, related to a clinical investigation should all be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation.

The investigator should assure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. Where copies of the original source document as well as printouts of original electronic source documents are retained, these should be signed and dated by an authorized member of the investigation site team with a statement that it is a true reproduction of the original source document.

If assignment to a treatment group is blinded/masked in any way, it should be safeguarded throughout the clinical investigation, including data entry and processing. In such instances, procedures for decoding blinded/masked clinical investigations should be established and strictly followed.

7.8.2. Recording of data

The data reported on the CRFs should be derived from source documents and be consistent with these source documents, and any discrepancies should be explained in writing. The CIP should specify which data can be recorded directly in the CRFs. The CRFs should be signed and dated

by the authorized site team member and principal investigator or his/her authorized designee(s). Any change or correction to both written and electronic data reported on a CRF should be dated, initiated and explained if necessary, and should not obscure the original entry (i.e. an audit trail should be maintained).

7.8.3. Electronic clinical data systems

When electronic clinical databases or remote electronic clinical data systems are used, written procedures should be established and implemented to:

- a) establish and document requirements for the electronic clinical data system to receive and process data,
- b) verify and validate that the requirements for the electronic clinical data system can be consistently met,
- c) ensure attributability, completeness, reliability, consistency and logic of the data entered,
- d) ensure accuracy of reports,
- e) ensure that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail),
- f) maintain a security system that prevents unauthorized access to the data, both internally and externally,
- g) maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user,
- h) ensure that all completed CRFs are signed by the principal investigator or authorized designee,
- i) maintain adequate backup, retention and retrievability of the data, and
- j) train users on proper use of the system.

7.9. Investigational device accountability

Access to investigational devices should be controlled and the investigational devices should be used only in the clinical investigation and according to the CIP.

The sponsor should keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

There should be written procedure for recording keeping of investigational device. The principal investigator or an authorized designee should keep records documenting the receipt, use, return and disposal of the investigational devices in accordance with this procedure, which should include:

- a) The date of receipt
- b) Identification of each investigational device (Device name, intended use, manufacturer, batch number/serial number or unique code),
- c) The expiry date, if applicable,
- d) The date or dates of use
- e) Subject identification,
- f) Data on which the investigational device was returned/explanted from subject, if applicable and
- g) The date of return of unused, expired or malfunctioning investigational devices, if applicable

7.10. Accounting for subject

All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) should be accounted for and documented.

If a subject withdraws from the clinical investigation, the reasons(s) should be recorded. If such withdrawal is due to problems related to the investigational device safety or performance, the investigator should ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

The subject's preference on follow up on his/her status or condition outside the clinical investigation should be documented and records of such follow up by the subjects should be retained.

7.11. Auditing

Audit of the clinical investigation may be conducted by the sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedures, this guideline and other applicable regulatory requirements. These audits may cover all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions.

An audit is useful:

- a) As a routine part of the sponsor's quality assurance programme
- b) To assess the effectiveness of monitoring system
- c) Whenever there are serious or repeated CIP deviations or suspicion of fraud
- d) To bring an investigation site in to "inspection readiness" i.e. to prepare the investigation site for a potential regulatory inspection

The auditors should be qualified by training and experience to conduct audits properly.

The auditing of clinical investigation systems should be conducted in accordance with the sponsor's written procedures or specific plan on what to audit, how to audit, the frequency of audit, the frequency of audit reports.

The sponsor's audit plan and procedures for a clinical investigation audit should be guided by the importance of the clinical investigation, the number of subjects in the clinical investigation, the type and complexity of the clinical investigation, the level of risk to the subjects and any identified problem(s). The audit results should be documented and communicated to relevant parties, if applicable.

8. Suspension, termination, and close-out of the clinical investigation

8.1. Suspension or premature termination of the clinical investigation

8.1.1. Procedure for suspension or premature termination

The sponsor, principal investigator, EC, or the authority may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

The investigator should have a procedure for possible conditions for suspensions and premature termination; and handling study subjects and on how to communicate relevant institutions when suspending or premature termination of the clinical trial investigation.

If suspicion of an unacceptable risk to the subject arises during the clinical investigation, or when so instructed by the EC or authority, the sponsor should suspend the clinical investigation while the risk is assessed. The sponsor should terminate the clinical investigation if an unacceptable risk is confirmed.

The sponsor should consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party should justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor should keep each other informed of any communication received from either the EC or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor should inform the authority as appropriate and ensure that the EC is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor should inform all other principal investigators.

If suspension or premature termination occurs

- a) The sponsor should remain responsible for providing resources to fulfil the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical investigation, and
- b) The principal investigator or authorized designee should promptly inform the enrolled subjects at his/her investigation site, if appropriate.

8.1.2. Procedure for resuming the clinical investigation after temporary suspension

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, ensures effectiveness of corrective actions and decides to lift the temporary suspension, the sponsor should inform the principal investigators, the authority and

where appropriate, the ECs of the rationale and provide them with the relevant data supporting this decision.

Concurrence should be obtained from the authority and where appropriate, ECs before the clinical investigation resumes.

If subjects have been informed of the suspension, the principal investigator or authorized designee should inform them of the reasons for resumption.

8.2.Routine Close-out

Routine close-out activities should be conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved and all parties are notified.

1. Completing the records includes ensuring that
 - a) All essential documents are complete and up to date
 - b) All CRFs are completed
 - c) All outstanding queries are resolved
 - d) The status of all ongoing adverse events is documented,
 - e) Arrangements are made for archiving and record retention, and
 - f) Documenting disposition of any
 - i. Investigational devices
 - ii. Remaining samples (e.g. blood or tissue)
 - iii. Other clinical investigation materials
2. Notification includes
 - a) Notification to the authority and
 - b) Notification to EC, if required

Notification the close out of the clinical investigation to the authority should be within 90 days of close out of the clinical investigation.

8.3.Clinical Investigation report

Periodic interim (progress) report of the clinical investigation should be provided biannually. Furthermore, after close-out of the clinical investigation, a report of the clinical investigation should be completed in accordance with this guideline and other relevant regulatory requirements of the authority, even if the clinical investigation was terminated prematurely.

The clinical investigation report should

- a) be in written form
- b) include identification of the device(s), a description of the methodology and design of the clinical investigation, any deviations from the CIP, data analysis together with any statistics and a critical appraisal of the aims the clinical investigation.
- c) take into account the data from each investigation site and for all subjects. No subject should be identifiable either from the clinical investigation report or the published results.
- d) Where applicable, be made available to the coordinating investigator and all principal investigators for review and comment. The sponsor should maintain records confirming that the clinical investigation report has been provided for review. If a reviewer does not agree with all or part of the clinical investigation report, his/her comments should be recorded and communicated to the other principal investigators.
- e) be signed by the sponsor and coordinating investigator including their agreement with the content of the clinical investigation report. If no coordinating investigator is approved, the signature of the principal investigator(s) should be obtained.
- f) be provided to the authority in accordance with applicable requirements.

8.4.Document retention

The sponsor and principal investigator should maintain the clinical investigation document (including electronic document) for five years after official close of the clinical investigation. They should take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

The list of essential clinical investigation documents to be maintained in sponsor and investigation site files should include (refer Annex I of this guideline)

Disposal of obsolete records and document after the retention period should be in way that ensure the confidentiality of individual subjects involved in the clinical investigation.

9. Responsibilities of the sponsor

9.1. Clinical quality assurance and quality control

Quality assurance and quality control principles should apply to the processes of the clinical investigation. The sponsor should:

- a) Establish, implement and maintain written clinical quality assurance procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded, reported and retained in compliance with this guideline, the CIP, any subsequent amendment(s), and any other applicable standards and other regulatory requirements,
- b) Maintain records to document the compliance of all parties involved in the clinical investigation,
- c) Justify and document significant exceptions to the requirements of this guideline. Clinical quality assurance and quality control may be integrated in the sponsor's overall quality system. (please refer latest version of ISO 13485 for further information).

9.2. Clinical Investigation Planning and conduct

9.2.1. Selection of clinical Personnel

Prior to commencement of the clinical investigation, the sponsor should:

- a) Define, establish and allocate all the roles and responsibilities related to the clinical investigation in one or more written agreements.
- b) Set selection criteria and select appropriately qualified principal investigators
- c) Set selection criteria and select a coordinating investigator, if appropriate, as in the case of a multicentre investigation
- d) Receive disclosures of conflict of interest from principal investigators and other investigators.
- e) Ensure the members of the investigation site team and their designated authorization(s) are identified in long with details

- f) Designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitor(s) and
- g) Ensure documentation of training, experience and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical investigation, including training, on:
 - 1. GCP
 - 2. The use of the investigational device(s)
 - 3. Device accountability procedures
 - 4. IB
 - 5. CIP
 - 6. CRFs and instructions for completion
 - 7. The written informed consent form and process as well as other written information provided to subjects, and
 - 8. Sponsor's written procedures and any other applicable regulatory requirements.
- h) Ensure that, in multicentre investigations, all investigators and all other parties involved are given instructions on uniformly assessing and documenting clinical and laboratory findings.
- i) Ensure that any clinical-investigation-related activities of sponsor representative (s) at the investigation site(s) are described in the CIP and the informed consent form, and that these activities occur in such a way that they do not bias the data integrity.
- j) Consider the need for a DMC and if appropriate, establish the committee.

9.2.2. Preparation of documents and materials

Prior to commencement of the clinical investigation, the sponsor should

- a) prepare the documents and ensure they are reviewed and approved by the relevant persons by dated signature. Copies should be provided to all parties involved.
- b) assure the accuracy of the translation, where relevant,
- c) ensure that a supply of investigational devices, is available in a timely manner for the clinical investigation; investigational devices should not be made available to the principal investigator until all requirements to start the clinical investigation are met,

- d) provide insurance covering the cost of treatment of subjects in the event of clinical-investigation-related injuries,
- e) document any financial arrangements between the principal investigator or the investigation site and the sponsor,
- f) submit all required application(s) to begin the clinical investigation to the authority for review, acceptance, or permission as per the recent guideline for authorization of clinical investigation.
- g) ensure that EC's approval/favourable opinion is obtained and documented, and that appropriate provisions are made to meet any conditions imposed by the EC, and
- h) ensure that any modification(s) required by the authority and/or EC are made and documented by the principal investigator and have gained the approval/favourable opinion of the authority and EC respectively.

9.2.3. Conduct of clinical investigation

The sponsor should be responsible for

- a) accountability of investigational devices throughout the clinical investigation,
- b) documenting correspondence with all parties involved in the clinical investigation, including ECs and the authority,
- c) ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation,
- d) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s),
- e) taking prompt action to secure compliance with all clinical investigation requirements, and
- f) submitting progress reports, including safety summary and deviations as required by the authority and ECs.

9.2.4. Monitoring

9.2.4.1. General

The purpose of clinical investigation monitoring is to verify that the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), this guideline, and the applicable regulatory requirement(s).

The sponsor should monitor the clinical investigation by himself or assign monitor with appropriate qualifications who performs the monitoring activities described in the following subsections (sections 9.2.4.2 to 9.2.4.7).

9.2.4.2. Qualifications of the monitor

Monitors should be:

- a) qualified in the field of GCP through training and experience as well as scientific or clinical knowledge;
- b) knowledgeable on the use of the investigational device(s) and relevant requirements, CIP and informed consent process;
- c) trained on the sponsor's clinical quality assurance and quality control system as well as any special procedures for monitoring a specific clinical investigation.

Training should be documented in the sponsor's files.

9.2.4.3. Assessment of the investigation site

The monitor should assess each investigation site to verify that the principal investigator has:

- a) adequate qualifications;
- b) adequate resources, including facilities, laboratories, equipment and a qualified investigation site team;
- c) access to an adequate number of subjects.

9.2.4.4. Initiation of the investigation site

The monitor should initiate each investigation site to ensure that the principal investigator and investigation site team

- a) have received training and understood the requirements and contents of
 - 1) CIP,

- 2) IB,
 - 3) the informed consent form and process,
 - 4) CRFs,
 - 5) the instructions for use,
 - 6) any written clinical investigation agreements, as appropriate,
- b) have access to an adequate number of investigational devices
 - c) have been trained in the use of the investigational device, and
 - d) are familiar with the responsibilities of the principal investigator.

In certain circumstances, the monitor may conduct a meeting with the principal investigator and the investigation site team instead of, or in addition to the on-site initiation visit.

9.2.4.5. Routine on-site monitoring visits

The monitor should perform routine on-site monitoring visits to verify that

- a) compliance with the CIP, any subsequent amendment(s), this guideline and other applicable regulatory requirements is maintained; deviations should be discussed with the principal investigator(s) or authorized designee, documented and reported to the sponsor, the Authority and as applicable to EC,
- b) only authorized individuals are participating in the clinical investigation,
- c) the investigational device is being used according to the CIP or instructions for use and that, where modifications are required to the device, its method of use or the CIP, these are reported to the sponsor,
- d) investigation site resources, including laboratories, equipment and the investigation site team, remain adequate throughout the duration of the clinical investigation,
- e) the principal investigator continues to have access to an adequate number of subjects and investigational devices,
- f) signed and dated informed consent forms have been obtained from each subject at the point of enrolment or before any clinical-investigation-related procedures are undertaken,
- g) source documents and other clinical investigation records are accurate, complete, up to date, stored and maintained appropriately,

- h) CRFs and queries are complete, recorded in a timely manner, and consistent with source documents,
- i) appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialled by the responsible person and verified by the principal investigator or by his/her authorized designee; the monitor should not make corrections, additions or deletions to the CRFs,
- j) all adverse events and device deficiencies are reported to the sponsor and the Authority.
- k) All serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor and the authority and if applicable to EC without unjustified delay,
- l) the storage and investigational device accountability are correct, and the traceability process is being followed,
- m) all other required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation,
- n) maintenance and calibration of the equipment relevant to the assessment of the clinical investigation is appropriately performed and documented, where applicable,
- o) current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required,
- p) subject withdrawal has been documented; the monitor should discuss this with the principal investigator or his/her authorized designee,
- q) subject non-compliance with the requirements stated in the informed consent has been documented; the monitor should discuss this with the principal investigator or his/her authorized designee,
- r) the principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation, and
- s) any corrective and preventive actions, as needed, have been implemented and are effective.

9.2.4.6. Close-out activities

The monitor should perform close-out activities as described in section 8.2 of this guideline.

9.2.4.7. Monitoring reports

All monitoring activities should be documented and reported to the Sponsor in a written form and should include:

- a) the date, investigation site identification, title of the clinical investigation, name of the monitor and name of the principal investigator or other individuals contacted, and
- b) a summary of what the monitor reviewed and his/her observation(s) with regard to the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

A copy of the monitoring report or a summary of key findings should be shared with the principal investigator in writing.

9.2.5. Safety evaluation and reporting

The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and should:

- a) review the investigator's assessment of all adverse events; and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor should communicate both opinions to concerned parties, as defined in c), d) and e) below,
- b) review all device deficiencies; and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor should communicate both opinions to concerned parties, as defined in c), d) and e) below,
- c) report to the Authority, within the required time period (i.e. 48 hours), all serious adverse events and device deficiencies that could have led to a serious adverse device effect,
- d) report or ensure the reporting, to the EC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the CIP or by the EC,
- e) report all relevant safety information to the DMC, if established, according to written procedures,

- f) in the case of a multicentre clinical investigation, inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their EC, if required by the CIP or by the EC, whichever is more stringent; this information should be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk analysis report,
- g) ensure that the authority and the EC are informed of significant new information about the clinical investigation, and
- h) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

9.2.6. Clinical investigation close-out

The sponsor should

- a) ensure all clinical investigation close-out activities are properly conducted as in section 8.2 of this guideline.
- b) provide a statistical analysis of the data,
- c) produce a clinical investigation report and submit it for review for principal investigators, participating investigators and other concerned bodies; and
- d) ensure that the clinical investigation report, whether for a completed or prematurely terminated clinical investigation, is provided to the authority and the EC.

9.3. Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation data should reside with the sponsor. All requirements in this guideline applying to a sponsor should also apply to the external organization in as much as this organization assumes the clinical-investigation-related duties and functions of the sponsor.

The sponsor should specify in writing any clinical-investigation-related duty or function assumed by the external organization, retaining any clinical-investigation-related duties and functions not specifically transferred to, and assumed by, the external organization.

The sponsor should be responsible for verifying the existence of and adherence to written procedures at the external organization.

9.4. Communication with the Authority

The sponsor should:

- a) Submit CIP and other supporting document and obtain authorization from the authority before the initiation of the clinical investigation in Ethiopia.
- b) Submit and obtain authorization of any major amendment from the Authority and notify the minor amendment to the Authority.
- c) report on the progress and status of the clinical investigation, and close-out report including premature termination of the clinical investigation and
- d) perform safety reporting.

10. Responsibilities of the principal investigator

10.1. General

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

If the sponsor contracts an institution to conduct the clinical investigation, the institution should appoint an appropriately qualified person to be the principal investigator.

10.2. Qualification of the principal investigator

The principal investigator should:

- a) be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with guideline; evidence of such qualifications of the principal investigator and key members of the investigation site team should be provided to the sponsor and be included in the CIP through up-to-date CVs or other relevant documentation,
- b) be experienced in the field of GCP and trained in the use of the investigational device under consideration,
- c) disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and

- d) be knowledgeable with the method of obtaining informed consent.
- e) Allocate sufficient time to conduct and manage the clinical investigation.

10.3. Investigation site Requirements

The principal investigator should be able to demonstrate that the proposed investigation site

- a) has the required number of eligible subjects needed within the agreed recruitment period, and
- b) has one or more qualified investigators, a qualified investigation site team and adequate facilities for the planned duration of the clinical investigation.
- c) Agree with the sponsor on the conduct of clinical investigation at the site.

10.4. Communication with the EC

The principal investigator should:

- a) provide the sponsor with copies of any clinical-investigation-related communications between the principal investigator and the EC,
- b) comply with applicable EC requirements,
- c) obtain the written and dated approval/favourable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments
- d) perform safety reporting and
- e) promptly report any deviations from the CIP that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the EC, CIP.

In particular circumstances, the communication with the EC can be performed by the sponsor, partly or in full, in which case the sponsor should keep the principal investigator informed.

10.5. Informed consent process

The principal investigator should:

- a) comply with the requirements specified in section 5.6 of this guideline.
- b) ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and

- c) ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

10.6. Compliance with the CIP

The principal investigator should:

- a) indicate his/her acceptance of the CIP in writing,
- b) conduct the clinical investigation in compliance with the CIP,
- c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
- d) ensure that the investigational device is used solely by authorized users and in accordance with the CIP and instructions for use,
- e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
- f) refrain from implementing any modifications to the CIP without agreement from the sponsor, and if required the authority and EC,
- g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
- h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
- i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
- j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,
- k) maintain the device accountability records,
- l) allow and support the sponsor to perform monitoring and auditing activities,
- m) be accessible to the monitor and respond to questions during monitoring visits,
- n) allow and support the authority and the EC when performing auditing activities,
- o) ensure that all clinical-investigation-related records are retained and
- p) sign the clinical investigation report.

10.7. Medical care of subjects

The principal investigator should:

- a) provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events, as described in the informed consent.
- b) inform the subject of the nature and possible cause of any adverse events experienced,
- c) provide the subject with the necessary instructions on proper use, handling, storage and return of the investigational device, when it is used or operated by the subject,
- d) inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
- e) provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,
- f) ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,
- g) if appropriate, subjects enrolled in the clinical investigation should be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers should be provided),
- h) inform, with the subject's approval if required by the authority, the subject's personal physician about the subject's participation in the clinical investigation, and
- i) make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

10.8. Safety reporting

The principal investigator should:

- a) record every adverse event and observed device deficiency, together with an assessment,

- b) report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information should be promptly followed by detailed written reports, as specified in the CIP,
- c) report to the Authority (if delegated by the sponsor) serious adverse events and device deficiencies that could have led to a serious adverse device effect, and
- d) report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by CIP or by the EC,
- e) supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

References:

1. *Clinical investigation of medical devices for human subjects- Good clinical practice (ISO 14155:20120)*
2. *Clinical investigation of medical devices for human subjects- Good clinical practice (ISO 14155:2011)*
3. *Guideline for Registration of Medical Devices, 3rd Edition, Ethiopian Food and Drug Authority, Sept 2014, Addis Ababa, Ethiopia*
4. *Guideline for Medicine Clinical Trial Authorization, 2nd Edition, Ethiopian Food and Drug Authority, June 2017, Addis Ababa, Ethiopia*

Annex I: Essential clinical investigation documents

S. No.	Title of documents	Documents handled at	
		Site file	Sponsor file
Essential clinical investigation documents prior to clinical investigation			
1	Investigator's brochure	X	X
2	Clinical investigation Plan (CIP)		
3	Sample of labelling attached to investigational device	-	X
4	Principal investigator's CV: Current, signed and dated	X	X
5	CV of key members of the investigation site team: Current, signed and dated	X	X
6	Log of principal investigator and key members of investigation site team at each investigation site	X	X
7	List of investigation sites	-	X
8	Ethics committee(EC) notification, correspondence and opinion/approval	X	X
9	EC voting list for the clinical investigation	X	X
10	Regulatory authority notification, correspondence and approval (where required)	X	X
11	Signed agreement between principal investigator(s) /investigation site(s) and sponsor	X	X
12	Signed agreements between sponsor and third parties e.g. CRO core laboratories	-	X
13	Financial agreements, if separate from agreements on responsibilities	X	X
14	Insurance certificate, if applicable	X	X
15	Shipping records for investigational devices	X	X
16	Shipping records for clinical investigation-related documents and materials	-	X
17	Sample of approved informed consent forms, information for the subjects and advertisements including translations	X	X
18	Randomization list for randomized clinical investigation	X	X
19	Decoding procedures for blinding/masked clinical investigations where applicable	X	X
20	Investigation site selection report	-	X
21	Clinical investigation initiation monitoring report	-	X
22	Follow-up letter further to clinical instigation initiation monitoring correspondence with the investigation site	X	X
23	Case report forms (CRF)	X	X
24	Adverse events forms	X	X
25	Device deficiency forms	X	X
26	Names/contact information of monitor(s)	X	X
27	Training records	X	X

28	Normal values/range for clinical laboratory test, if relevant to the clinical investigation	X	X
29	Confirmation of adequacy of equipment's, if relevant to the clinical investigation	X	-
30	Certification, accreditation or established quality control or external quality assessment or Other validation of the laboratory, if relevant to the clinical investigation or Identification and qualification of the laboratory director, if relevant to the clinical investigation	X	X
31	Disclosures of conflicts o interest	X	X
Essential clinical investigation documents during clinical investigation			
1	Amendments, if any	X	X
2	CIP amendments, if any	X	X
3	Sample of amendment to informed consent form	X	X
4	EC opinion/approval of any amendments	X	X
5	Notices or approvals to the Authority of any amendments where required	X	X
6	CV of new principal investigators	X	X
7	CV of new key members of the investigation site team current signed and dated	X	X
8	Shipping records and investigational device accountability records	X	X
9	Shipping records for clinical investigation-related document materials	-	X
10	Monitoring visit report	X	X
11	Correspondence related to the clinical investigation, including emails, letters, meeting notes and phone reports	X	X
12	Updated log of the principal investigator and key members of the investigation site team at each investigation site including signature, tittle, and responsibilities in the clinical investigation	X	X
13	Signed, dated and full executed informed consent forms	X	-
14	Source documents	X	-
15	CRFs, fully executed	X	X
16	Reports of adverse events adverse device effects and device deficiencies	X	X
17	CRFs corrections	X	X
18	Reports of adverse events or device deficiencies by sponsor to the Authority or by the principal investigator, where applicable	X	X
19	Reports of adverse events by principal investigator to EC or by sponsor, where required	X	X
20	Reports by sponsor to investigators of adverse events occurring at other investigation sites	X	X

21	Interim or annual reports by principal investigators to EC, where applicable	X	X
22	Subject screening Log	X	X
23	Subject identification log	X	-
24	Accountability Logs of investigational devices at the investigation site, where applicable	X	X
25	Updated names/contact information of monitor(s)	X	X
26	Updates to normal value (s)/ range(s) for clinical laboratory test, if relevant to the clinical investigation	X	X
27	Updates to confirmation of adequacy of equipment, if relevant to the clinical investigation		-
28	Updates of <ul style="list-style-type: none"> - Certification accreditation or established quality control or external quality assessment or - Other validation of the laboratory, if relevant to the clinical investigation or - Identification and qualification of the laboratory director, if relevant to the clinical investigation 	X	X
29	Updates of disclosures of conflict of interest	X	X
Essential clinical investigation documents after clinical investigation			
1	Investigational device accountability at each investigation site, where applicable	X	X
2	Documentation of investigational device return or disposal where applicable	X	X
3	Completed subject identification log	X	-
4	Audit certificate (if required or conducted)	-	X
5	Close-out monitoring report	-	X
6	Notification of clinical investigation close-out to EC by the principal investigators or sponsor, where required	X	X
7	Notification of clinical investigation close-out to the authority by the sponsor or principal investigators, where required	X	X
8	Sponsor's statistical analysis and clinical investigation report	X	X